REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 547 DEL 31/03/2023

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO dott.ssa MICHELA CONTE

DIRETTORE SANITARIO dr. ANTONIO DI CAPRIO

DIRETTORE DEI SERVIZI SOCIO – SANITARI dott. EDDI FREZZA

OGGETTO: AUTORIZZAZIONE ALLA SPERIMENTAZIONE CLINICA FOR PROFIT DAL TITOLO "STUDIO DI FASE 3, RANDOMIZZATO, IN DOPPIO CIECO, PER VALUTARE L'EFFICACIA E LA SICUREZZA D'IMPIEGO DI IANALUMAB (VAY736) VERSUS PLACEBO NEI PAZIENTI CON ANEMIA EMOLITICA AUTOIMMUNE CALDA (WAIHA) CHE HANNO FALLITO ALMENO UNA LINEA DI TRATTAMENTO (VAYHIA) – CVAY736O12301"

IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott. Carlo Bramezza

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2023 Numero Proposta: 431/23

Il Dirigente, Direttore dell'U.O.C. Affari Generali, nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Cristiano Galizian

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Il Direttore dell'U.O.C. Affari Generali relaziona quanto segue.

Premesso che:

- con deliberazione n. 316 del 31/03/2017 si è provveduto ad istituire, ai sensi della deliberazione della Giunta Regionale del Veneto n. 2174 del 23/12/2016, recante "Disposizioni in materia sanitaria connesse alla riforma del sistema sanitario regionale approvata con L.R. 25 ottobre 2016 n. 19", il Nucleo per la Ricerca Clinica (N.R.C.) dell'Azienda ULSS 7 Pedemontana;
- la citata DGRV n. 2174/2016, Allegato L, richiama l'applicazione della disciplina regionale in materia di sperimentazione clinica (DGR n. 1066/2013 e DGR n. 925/2016), che prevede l'istituzione di un N.R.C. per ciascuna Azienda ULSS della Regione;
- la DGR n. 1066/2013 (Allegato B) prevede che il N.R.C. sia istituito preferibilmente "presso il Servizio di Farmacia Ospedaliera ovvero Servizio Farmaceutico territoriale ovvero Servizio di Farmacologia delle istituzioni sanitarie, fermo restando i criteri di indipendenza e di assenza di conflitti di interesse" e sia composto "da professionalità multidisciplinari appartenenti all'ambito sanitario, epidemiologico –statistico, etico-giuridico e organizzativo –gestionale";
- con deliberazione n. 1477 del 05/08/2022 è stato approvato, in aggiornamento della disciplina aziendale regolata con la deliberazione n. 453 del 28/5/2014, il Regolamento aziendale sulla gestione delle sperimentazioni cliniche profit e no-profit, comprensivo anche della regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi;
- con deliberazione n. 1684 del 09/09/2022 sono stati aggiornati i componenti del Nucleo per la Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23/12/2016.

Rilevato che:

- con nota del 26/10/2022 pervenuta al ns. prot. n. 2492/2023, la società Opis s.r.l., in qualità di Contract Research Organization (C.R.O.) di Novartis Farma S.P.A., la quale a sua volta in virtù di delega è autorizzata ad agire, per la realizzazione dello Studio nel territorio italiano, in nome e per conto del Promotore Novartis Pharma AG, ha richiesto al Comitato Etico di Vicenza la pertinente autorizzazione ad effettuare, presso l'U.O.C. Oncoematologia dell'Ospedale di Bassano, la sperimentazione clinica dal titolo "*Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di Ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (Waiha) che hanno fallito almeno una linea di trattamento (VAYHIA) – CVAY736O12301":*

SCHEDA STUDIO CLINICO

Titolo	Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di Ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (Waiha) che hanno fallito almeno una linea di trattamento (VAYHIA)"
Protocollo	CVAY736O12301
EudraCT	2022-001773-31
Strutture interessate	U.O.C. Oncoematologia – Ospedale Bassano U.O.C. Laboratorio Analisi – sede Ospedale Bassano U.O.C. Farmacia - sede Ospedale Santorso U.O.C. Cardiologia – Ospedale Bassano
Sperimentatori	Dr Eros Di Bona Direttore U.O.C. Oncoematologia –

	Ospedale di Bassano;
Co – sperimentatori	Dr ssa Mariangela Brogna– Dirigente Medico Dr.ssa Stefania Fortuna - Dirigente Medico Dr.ssa Anna Artuso – Dirigente Medico
Promotore	Novartis Pharma AG - , Lichtstrasse 35 CH- 4056 Basel (Svizzera) che ha incaricato Novartis Farma S.P.A. sede Milano di eseguire le attività e i servizi dello studio in Italia
CRO	OPIS srl via Matteotti, 10 Desio (MB)
Centro Coordinatore	Azienda Ospedaliera "S. Giuseppe Moscati" di Avellino

- è stato individuato, quale Responsabile della sperimentazione clinica presso questa Azienda, il dr. Eros Di Bona, –Direttore dell'U.O.C. Oncoematologia – Ospedale di Bassano;
- con nota del 28/10/2022, il dr. Eros Di Bona ha chiesto la valutazione e l'autorizzazione allo svolgimento dello studio suddetto.

Tenuto conto che:

- il N.R.C. Aziendale, nella sua composizione prevista dalla deliberazione n.1684 del 09/09/2022, ha verificato la fattibilità locale della ricerca sopra citata, considerata la regolarità della documentazione presentata dallo sperimentatore, nonché delle integrazioni trasmesse, anche dalla CRO, in particolare il parere AIFA del 23/01/2023, agli atti;
- il N.R.C ha pertanto trasmesso, una volta raccolta tutta la suddetta documentazione, con nota del 6/02/2023 al prot. 10669, al Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC), la richiesta di valutazione dello studio;
- il Comitato Etico per le sperimentazioni Cliniche della Provincia di Vicenza (CESC) in occasione della prima seduta del 14/02/2023, nota ns prot. 19860 del 6/03/2023, ha espresso, esaminata la documentazione, il proprio parere favorevole alla conduzione dello studio clinico in oggetto, presso l'U.O.C. Oncoematologia, alla seguente condizione *"che nell'informativa e consenso v. 02.04.00 del 7/10/2022 venga specificato che nel momento in cui il Promotore dello studio dovesse utilizzare le informazioni personali e i campioni biologici del paziente, prelevati durante lo studio, per condurre ricerche future, verrà richiesto specifico parere al Comitato Etico e il paziente verrà ricontattato per la sottoscrizione di un nuovo consenso informato specifico per la nuova indagine"*;
- in seguito, in occasione della seduta del 14/03/2023 il CESC, viste le integrazioni pervenute dal Promotore, ha avuto modo di sciogliere la riserva sollevata nella seduta del 14/02/2023, esprimendo il proprio definitivo parere favorevole come segue : "…*In data 13 marzo il Promotore ha inviato alla segreteria una nota comunicando che il centro non parteciperà alle ricerche supplementari e modificando a tale fine, il documento "informativa e consenso" alla v, 02.04.00 del 07/03/2023.*

  Pertanto si sciolgono le riserve e si esprime parere favorevole all'unanimità" (vd nota al ns. prot. 24665 del 21/03/2023);
- -trattasi di uno studio fase 3, for-profit, randomizzato, doppio cieco, multicentrico, internazionale (partecipano oltre 20 centri), a 3 braccia, con due diverse dosi di ianalumab rispetto al placebo;
- tale ricerca si propone di valutare la capacità di ianalumab (VAY736) in confronto al placebo, di indurre una risposta emoglobinica duratura nei pazienti con anemia emolitica autoimmune (Waiha) che hanno fallito almeno una linea di trattamento precedente;
- lo studio prevede l'arruolamento di circa n.90 pazienti, di cui n. 2 pazienti presso l'A.ULSS 7, e una durata prevista, in Italia, dall'1/04/2023 al 9/01/2029;
- trattandosi di studio interventistico è prevista una copertura assicurativa per RCT derivante da sperimentazioni cliniche, a carico della società Novartis Farma Spa, come da Determinazione dell'AIFA del 20 marzo 2008, in particolare è stata stipulata con la Compagnia HDI la polizza n. 390-01579150 -14037;

- l'introito totale massimo per paziente arruolato, valutabile, che abbia completato l'intero ciclo di visite sia di trattamento che quelle opzionali per la fase di crossover varia a seconda che il paziente sia sottoposto poi al follow up TFR oppure al follow up – non in durable response, nel primo caso il totale complessivo ammonta ad € 27.650,00 + IVA, nel secondo ad € 17.450,00 + IVA, come meglio illustrato dall'articolato budget, riportante le varie opzioni, previsto dal Contratto e allegato alla presente proposta, di cui è parte integrante e sostanziale;
- il Contratto per la gestione degli aspetti economici inerenti la sperimentazione clinica, (la cui versione definitiva è pervenuta al prot. 26006 del 24/03/2023), allegato alla presente proposta di deliberazione, di cui è parte integrante e sostanziale, è redatto secondo la normativa vigente in materia;
- l'attività inerente lo studio in argomento sarà svolta, ai sensi dell'art.15 del Regolamento Aziendale per lo svolgimento delle sperimentazioni (deliberazione del Direttore Generale n. 1477/2022), in orario aggiuntivo oltre a quello istituzionalmente dovuto. La stessa verrà remunerata con i proventi derivanti dalla sperimentazione secondo le indicazioni contenute nella deliberazione sopra citata che regolamenta anche la gestione dei fondi per l'attribuzione dei compensi.

Per quanto sopra, il Direttore dell'U.O.C. Affari Generali, propone di autorizzare l'effettuazione dello studio clinico for-profit "Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di Ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (Waiha) che hanno fallito almeno una linea di trattamento (VAYHIA) – CVAY736O12301", presso l'U.O.C. Oncoematologia – Ospedale di Bassano il cui sperimentatore principale è il dr. Eros Di Bona e di approvare il Contratto con la Società Novartis Farma S.p.a., che agisce in forza di delega per conto di Novartis Pharma AG, Promotore dello studio in questione.

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;
- il D.M. 30/11/2021

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di prendere atto che il Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza (CESC) nelle sedute del 14/02/2023 (al ns prot. 19860 del 6/03/2023) e del 14/03/2023 (al ns prot. 24665 del 21/03/2023), come in premessa illustrato, ha espresso parere favorevole in ordine alla conduzione dello studio clinico "Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di Ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (Waiha) che hanno fallito almeno una linea di trattamento (VAYHIA) – CVAY736O12301";

2. di autorizzare, per quanto in premessa illustrato, lo svolgimento dello Studio suindicato presso l'A.ULSS 7, sotto la diretta Responsabilità dello Sperimentatore Principale dr Eros Di Bona, Direttore dell'U.O.C. Oncoematologia e che prevede l'inclusione nella sperimentazione di n. 2 pazienti;

3. di dare atto che sia il dr. Eros di Bona, che i co – sperimentatori, ossia la dr ssa Mariangela Brogna, la dr.ssa Stefania Fortuna e la dr.ssa Anna Artuso , tutti Dirigenti Medici in servizio presso l'U.O.C. Oncoematologia – Ospedale di Bassano, sono autorizzati a svolgere l'attività di ricerca in orario aggiuntivo oltre a quello istituzionalmente dovuto, così come previsto dall'art.15 del Regolamento aziendale sulla gestione delle sperimentazioni cliniche (deliberazione n. 1477/2022);

4. di stabilire che lo Studio clinico dovrà essere eseguito secondo quanto previsto dal Protocollo di studio, allegato alla presente deliberazione di cui è parte integrante e sostanziale e secondo quanto previsto dalla normativa vigente in ambito di sperimentazioni e dalle norme di buona pratica clinica (GCP);

5. di approvare il Contratto tra l'Azienda ULSS 7 Pedemontana e la società la Società Novartis Farma S.p.a., che agisce in forza di delega, in nome e per conto di Novartis Pharma AG, Promotore dello studio in questione, allegato alla presente deliberazione di cui è parte integrante e sostanziale;

6. di dare atto che l'introito totale massimo per paziente arruolato, valutabile, che abbia completato l'intero ciclo di visite sia di trattamento che quelle opzionali per la fase di crossover, varia a seconda che il paziente sia sottoposto poi al follow up TFR oppure al follow up – non in durable response, nel primo caso il totale complessivo ammonta ad € 27.650,00 + IVA, nel secondo ad € 17.450,00 + IVA, come meglio illustrato dall'articolato budget, riportante le varie opzioni, previsto dal Contratto e allegato alla presente deliberazione di cui è parte integrante e sostanziale;

7. di dare atto che ai sensi dell'art.8 del Regolamento aziendale sulla gestione delle sperimentazioni cliniche (deliberazione n. 1477/2022):
   a) il Responsabile della Sperimentazione durante il corso dello studio è tenuto a comunicare al CESC, per il tramite del NRC, le informazioni necessarie a consentire il periodico aggiornamento sull'andamento della ricerca, ogni evento o reazione avversa, l'interruzione anticipata di uno studio, con l'indicazione dettagliata dei motivi e degli eventuali risultati parziali ottenuti;
   b) lo Sperimentatore si impegna a fornire annualmente al CESC un rapporto scritto sullo stato di avanzamento dello studio (monitoraggio periodico) e una relazione analitica alla conclusione dello studio e pubblicazione se previsto;
8. di dare atto che dall'esecuzione del predetto studio non deriverà nessun onere aggiuntivo di spesa in capo all'Azienda ULSS 7 Pedemontana;
9. di incaricare l'U.O. proponente di pubblicare la presente deliberazione nella sezione Amministrazione Trasparente del sito istituzionale, ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;

10. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 1386 del 22.07.2022.

NOVARTIS

Novartis Research and Development

Clinical Trial Protocol Title:

A phase 3, randomized, double-blind, study to assess efficacy and safety of ianalumab (VAY736) versus placebo in warm autoimmune hemolytic anemia (wAIHA) patients who failed at least one line of treatment (VAYHIA)

Clinical Trial Protocol Number:	CVAY736O12301
Version Number:	V02 (Amended Protocol version) (Clean)
Compound:	VAY736
Brief Title:	A study of efficacy and safety of ianalumab in previously treated patients with warm autoimmune hemolytic anemia
Study Phase:	III
Sponsor Name:	Novartis
Regulatory Agency Identifier Number(s):	2022-001773-31
Approval Date:	29-Sep-2022 (content final)

Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022

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Amendment 2 (29-Sep-2022)

Amendment rationale

At the time of the amendment, no patients have been enrolled into the study.

The main purpose of this amendment is to comply with Health Authority recommendations as follows:

1. To remove adolescent participants from the study given lack of ianalumab data on safety and efficacy in wAIHA patients at this stage. With that, the role of the DMC in guiding the decision to enroll adolescent patients no longer applies. In addition, participants with Evans' Syndrome or other cytopenias are excluded.
2. To clarify that only patients with confirmed primary or secondary wAIHA as documented by positive direct antiglobulin test (DAT) are eligible; in addition, all the patients enrolled into the study must have symptoms of anemia to be eligible.
3. To demonstrate a robust and durable response, the primary endpoint definition has been modified; to meet the criteria of durable response, hemoglobin levels ≥10 g/dL and ≥2 g/dL increase from baseline must be maintained for at least 8 consecutive weeks instead of 2 weeks and will be assessed between Week 9 Day 1 and Week 25 Day 1 instead of Week 9 Day 1 and Week 17 Day 1.
4. To avoid potential confounding of efficacy due to effects of transfusions and IVIG (i.v. immunoglobulins), a wash out of 4 weeks has been implemented; only hemoglobin values taken after this wash out period will be used for assessments of efficacy endpoints (durable response, response, complete response).
5. To modify the key secondary endpoint from "time to treatment-free-remission (TFR) failure" to "duration of response". This endpoint more accurately addresses the clinical question of interest of maintaining a durable hemoglobin response during and after treatment. Duration of the response is also one of the key criteria for assessing response to treatments recommended by the First International Consensus Meeting for AIHA (Jäger et al, 2020).
6. To change the randomization stratification factor from wAIHA subtype (primary vs secondary) to previous exposure to rituximab prior to randomization (Yes vs No). With the additional changes to the patient population described above, up to 90% of patients are expected to have primary wAIHA, thus, stratification by this factor is not appropriate anymore.

In addition, the following changes were introduced:

- Clarification of requirements regarding visit flow, dose modifications and assessments were made throughout the protocol,
- Collection of medical resource utilization during the follow-up period and corresponding exploratory endpoint was added to assess the impact of the treatment on the health system burden,
- Collection of patient-reported outcome data during long-term follow-up was added also for participants not in durable response, to obtain similar data for the entire population,
- Participants not in durable response will not discontinue from study after administration of B-cell depleting or immunosuppressive treatments but will continue in safety follow-up

until 2 years after last dose. In long-term follow-up, AE reporting after administration of B-cell depleting or immunosuppressive drugs will be limited to SAEs suspected to be related to ianalumab,

- Infusion duration window of +/- 15 minutes was introduced to be in line with the pharmacy manual,
- The requirement to perform a serum pregnancy test at LTFU1 (first Long Term Follow Up visit, W37) at site for participants not in durable response was changed to a urine pregnancy test that can be done at home. Serum testing will only be needed if the urine test is positive. As no other assessments are done at LTFU1, a site visit solely for pregnancy testing would be an inappropriate burden for the participant,
- A change in study drug formulation to Final Market Image (FMI) was added to allow use of the FMI formulation in later stages of the study.

Further typological, grammatical, and formatting errors have been addressed as part of this document.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Throughout the document, key secondary endpoint “time to treatment-free-remission (TFR) failure” was replaced by “duration of response”
- Throughout the document, wording on adolescents was removed
- Updated throughout the protocol the visit nomenclature from “Week x” to “Wx” to align with Schedule of Assessments (i.e., W1, W3, W5, etc)
- Section 1.1: Summary was updated to reflect the changes in Full Protocol
- Section 1.2 Figure 1-1 was updated to reflect the new name of the key secondary endpoint
- Section 1.3: Primary endpoint and efficacy secondary endpoints were updated; a new exploratory objective/endpoint was added related to medical resource utilization
- Section 1.3: Clarification was added for collection of unscheduled assessments in case of treatment delays outside of the allowed visit window
- Section 1.3 Table 1-1 and Table 1-2: update of footnotes to add further clarification in regards of need to repeat assessments at W1 done less than 7 days before during screening, meaning of CO EOT (cross over end of treatment) column and update of relapse to confirmed loss of durable response. Additional line added for TGFβ1 assay to reflect the change of matrix.
- Section 1.3 Table 1-3: header updated to reflect “participants not in durable response” instead of “Participant NOT in TFR”. Removal of collection of adolescent’s body height as no longer applicable. Removal of serum pregnancy test at LTFU1 and added a urine pregnancy test at LTFU1 and added footnote that result can be reported via phone call. Added procedures next to concomitant medications. Added Medical resources utilization to be collected continuously during short- and long-term safety follow up. Clarification added that in case the participant starts a new B-cell depleting treatment, collection of SAEs during safety follow up will be limited to those suspected to be related to ianalumab. PROs (patient

reported outcomes) to be collected also during the Long Safety Follow Up period from LTFU3 until ESFU (End of Safety Follow Up, LTFU21). Additional line added for TGFβ1 assay to reflect the change of matrix. Removal of footnote that refers to adolescents. Removal of footnote that long term follow up will end when patient received B cell depleting or immunosuppressive therapy.

- Section 1.3 Table 1-4: header was updated to reflect "participants in durable response" instead of "Participant in TFR". Removal of collection of adolescent's body height as no longer applicable. Added procedures next to concomitant medications. Added Medical resources utilization to be collected continuously during short- and long-term safety/efficacy follow up and during long term efficacy follow-up. Removal of Study Disposition collection during STFU2 (Short Term Follow Up, 20W post last dose). Updates throughout the table and footnotes from "relapse" to "confirmed loss of durable response". Clarification added that in case the participant starts a new B-cell depleting or immunosuppressing treatment, collection of SAEs during safety follow up will continue and be limited to those suspected to be related to ianalumab. PROs to be collected also during the Long Safety Follow Up period from LTFU3 until ESFU (LTFU21) and during long term efficacy follow up until confirmed loss of durable response or end of study. Additional line added for TGFβ1 assay to reflect the change of matrix. Added Medical resources utilization to be collected continuously during short- and long-term safety follow up. Removal of footnote that refers to adolescents. Removal of footnote that long term follow up will end when patient received B cell depleting or immunosuppressive therapy.
- Section 2: Removal of sentence in reference to children as no longer applicable
- Section 2.2.2: Number of patients treated with ianalumab updated per most current IB ed. 14
- Section 3 table 3-1: Adolescent PROs were removed from the exploratory objectives. An exploratory objective related to medical resource utilizations was added to align with the ITP study protocols in the VAY736 program. The wording of the endpoints was updated to reflect the changes in the endpoints.
- Section 3.1: The wording of primary estimand was reworded to reflect the new definition of durable response and the associated intercurrent events.
- Section 3.2: The wording of the key secondary estimand was updated to reflect the changes in endpoint definition and intercurrent events
- Section 4 Figure 4-1: Study design updated to reflect the update of TFR failure to confirmed loss of durable response.
- Section 4.1: Removal of inclusion of adolescents. Changed the stratification from primary vs secondary wAIHA to prior exposure to rituximab. Added wording of infusion time flexibility to 2h +/- 15 minutes to align with the pharmacy manual. Added that in case the participant starts a new B-cell depleting or immunosuppressing treatment, the AE collection during long-term safety follow-up will continue and be limited to the SAE suspected to be related to ianalumab. Added that throughout the entire safety and efficacy follow-up period, information regarding PROs, medical resources utilization, concomitant medications including rescue treatments, concomitant procedures and subsequent anti-wAIHA treatments will be collected. Figure 4-2 was updated to reflect the changes from term "TFR failure" to "confirmed loss of durable response" and the AE collection. Added further

clarification in regards the scenarios when a patient discontinues treatment earlier. Added further clarification on when a patient starts a new line of wAIHA therapy and what data is to be collected during short- and long-term safety follow-up. Updated the eligibility criteria for open label treatment related to hemoglobin results.

- Section 4.2 Table 4-1: removal of rationale of inclusion of adolescents, adapted rationale for stratification based on prior use of rituximab and for interval of primary endpoint assessment.
- Section 4.3: Removal of reference to adolescents. Moved paragraph about i.v. route to improve flow of reading. Added justification for open label treatment dose.
- Section 5: Patient population updated to remove adolescents
- Section 5.1: Inclusion criteria
  - Criterion #1 updated to remove requirement of parental consent and adolescent assent as adolescents are no longer enrolled.
  - Criterion #2 updated to enroll only participants aged older than 18 years old
  - Criterion #3 updated to require previous documentation of wAIHA diagnosis by a positive direct antiglobulin test
  - Criterion #4 updated to require presence of symptoms related to anemia
- Section 5.2: Exclusion criteria
  - Criterion #2 updated to exclude patients with Evans syndrome or other cytopenias
  - Criterion #5 removal of glomerular filtration rate as no longer applicable
  - Criterion #6 reworded
- Section 6.1 Added details of final market image (FMI) formulation. Wording on infusion time flexibility 2 hours +/- 15 min was added to align with the pharmacy manual.
- Section 6.1.2 Updated definition of eligibility criteria for open label treatment related to hemoglobin and updated the stratification from primary vs secondary wAIHA to prior exposure to rituximab.
- Section 6.2.3 Wording on infusion time flexibility 2 hours +/- 15 min was added to align with the pharmacy manual.
- Section 6.3.1 Changed the stratification from primary vs secondary wAIHA to prior exposure to rituximab.
- Section 6.1.4.1 Update from “Treatment after TFR failure” to “Treatment after confirmed loss of durable response” and details
- Section 6.5.2 Added further wording to clarify on dose delay scenarios, clarified CTCAE criteria for infections in Table 6-3
- Section 6.5.3.1 Removal of details linked to adolescents as no longer enrolled
- Section 6.5.5 Added definition of eligibility criterion for open label treatment related to hemoglobin results, removal of eGFR criteria for open label crossover as no longer applicable, removal of requirement to stop transfusion and IVIG administration after CO W7
- Section 6.8.1.1 Removed limitation to allow transfusion and IVIG administration until W7 only

- Section 6.8.2 Table 6-5 Update on the actions to be taken in case prohibited medications are utilized
- Section 6.8.3 Adjusted wording for transfusions and IVIGs in list of rescue medications as their use is allowed throughout study but subject to washout period for efficacy assessments
- Section 8.1.1.1 Removed requirement for HCV RNA test
- Section 8.2.2 Changed the stratification from primary vs secondary wAIHA to prior exposure to rituximab.
- Section 8.2.3 Added collection of number of RBC (red blood cell) transfusions prior study entry
- Section 8.3.2 Removal of paragraph now enclosed within subsequent section 8.3.3
- Section 8.3.3 Newly added section.
- Section 8.4.4 Table 8-2 Removal of SARS-CoV-2 testing
- Section 8.4.5 Clarification that pregnancy serum sample is collected for patients in durable response. For patients not in durable response a urine test can be done at home and result can be confirmed by phone.
- Section 8.5 Removal of adolescent PROs throughout the whole section
- Section 8.6 Modified AE collection requirements after B-cell depleting or immunosuppressive treatment
- Section 8.7.1 Table 8-3 Removal of PK and ADA volumes
- Section 8.10 Added details in regards collection of medical resource utilization
- Section 9: Timing of cutoff for primary analysis was updated.
- Section 9.2.1: Baseline definition was updated to add rule for hemolysis parameters.
- Section 9.3: Primary endpoint and corresponding analysis were updated.
- Section 9.3.7: Supplementary analysis was updated to remove subgroups analysis for age group and sub-type of disease.
- Section 9.3.2: It was clarified that the estimated odds ratio corresponding to the primary estimand will be the *marginal* odds ratio.
- Section 9.3.4 Update methods for handling of missing data was updated following change in primary endpoint
- Section 9.4.1: Secondary efficacy endpoints and corresponding analysis were updated. Table 9-1 was updated to use different symbols for Dunnett's adjusted alpha level of the intersections (H1 and H2) vs (H3 and H4)
- Section 9.4.3: The method for calculation of area under the curve was updated to use linear up log down trapezoidal rule, instead of linear trapezoidal rule. It was also specified that derivation of PK parameters using NCA approach will not be performed on open label data.
- Section 9.4.4 and 9.5.2 Wording on PRO data analysis in adolescents was removed.
- Section 9.5.4 Descriptive analysis of medical resource utilization was added according to the newly added exploratory objective.
- Section 9.9.2 Power evaluation was updated for the new key secondary endpoint duration of response, with new assumptions on recruitment duration.
- Section 10.1.2 and 10.1.4.1 Wording on enrollment of adolescents was removed.

- Section 10.2.1 List of abbreviations was updated.
- Section 10.6 Table 10-4 Renal event criteria for adolescents was removed.
- Section 11 References no longer mentioned in the protocol were removed

Further typographical, grammatical and formatting errors have been addressed as part of this document.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (15-Sep-2022)

Amendment rationale

At the time of the amendment, no patients have been enrolled into the study.

The purpose of this amendment is as follows:

1. The main purpose of this amendment is to remove the exclusion criterion #4 related to B-cell count at screening, since the patients with severe hematologic diseases, immunodeficiencies or diseases requiring immunosuppression are already excluded, and no cut-off to predict outcomes has been established. In addition, B-cell count is not used as a criterion to initiate treatment with any of the approved B-cell depleting agents. Of note, B-cell count will continue to be assessed at baseline and monitored throughout the study for up to 2 years after the last dose.
2. Benefit/risk section was updated in line with the latest edition of the investigator's brochure (ed. 14, dated 24-May-2022), e.g., addition of information on neutropenia.
3. In addition, the protocol has been updated to reflect a change done during setup of the study. The laboratory for repeating follow up assessments of DILI cases was changed from central to local lab to allow investigators quick access to the results.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.1: removed exclusion criterion #4
- Section 2.3: added information on neutropenia in the benefit/risk section
- Section 5.2: removed exclusion criterion #4
- Section 10.5: changed lab for repeat testing for liver safety monitoring from central to local lab

Additional corrections of minor errors have been made and are visible in track changes.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

A phase 3, randomized, double-blind, study to assess efficacy and safety of ianalumab (VAY736) versus placebo in warm autoimmune hemolytic anemia (wAIHA) patients who failed at least one line of treatment.

Brief Title:

A phase 3, randomized, double-blind, study of ianalumab (VAY736) versus placebo in warm autoimmune hemolytic anemia (wAIHA) patients who failed at least one line of treatment.

Purpose

The purpose of this study is to assess the efficacy and safety of ianalumab (VAY736) compared to placebo in wAIHA patients who have failed at least one line of treatment.

Study Indication /Medical Condition:

Warm autoimmune hemolytic anemia

Treatment type

Biological

Study type

Interventional

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that either dose of ianalumab induces durable hemoglobin (Hb) response compared to placebo in patients with wAIHA. The primary clinical question of interest is: What is the effect of either dose of ianalumab versus placebo (with or without supportive care), in inducing durable hemoglobin response, in wAIHA patients ≥18 years of age who failed at least one line of treatment, regardless of premature discontinuation from study treatment or temporary treatment interruption/delay, and in the absence of rescue or prohibited treatment?	Binary variable indicating if a participant achieves a durable response (increased Hb) for a period of at least 8 consecutive weeks, between W9 and W25, in the absence of rescue or prohibited treatment

Objectives	Endpoints
Secondary	
Key secondary objective: To demonstrate that either dose of ianalumab maintains durable hemoglobin response, compared to placebo	Duration of response
Other secondary objectives: To assess the time to durable response/response/complete response in each treatment group	Time from randomization to achievement of durable response, to first response, to first complete response
To assess the quality of response in each treatment group	Response rate, complete response rate and hemoglobin level
To assess the need for rescue treatments in each treatment group	Number and proportion of participants that receive rescue treatment overall and by type of rescue treatment
	Time-standardized numbers of each type of rescue treatment
	Change from baseline in time-standardized number of transfusions
To assess the safety profile of ianalumab	Frequency of adverse events (AEs) and other safety parameters
To characterize the pharmacokinetics (PK) of ianalumab	Ianalumab concentration in serum and PK parameters after the first and last dose
To assess B-cell levels and immunoglobulin levels at each treatment group	B-cell levels: ● Change from baseline in the frequency and absolute number of CD19+ B cell counts ● Time to first occurrence of B cell recovery, defined as ≥80% of baseline or ≥50 cells/µL Immunoglobulins: ● Change from baseline in immunoglobulin levels
To assess the immunogenicity against ianalumab	Incidence and titer of anti-drug antibodies (ADA) in serum over time
To assess the quality of life (QoL) in each treatment group	Dedicated Patient Reported Outcomes (PROs)

Trial Design:

Type of design: Randomized, double-blind, multicenter, 3-arm study with 2 different ianalumab (VAY736) doses (3 and 9 mg/kg) compared to the placebo. Participants originally randomized to placebo who do not achieve durable response (see above definition of the primary endpoint) until the end of the treatment period will have the option to switch to an open-label period with 9 mg/kg ianalumab. After the treatment period, all participants will enter the primary endpoint follow-up period to be monitored for efficacy until W25. During this period, participants will also be followed-up for safety at least for 20 weeks after the last actual dose (Short-Term Safety Follow-Up), up to 2 years from the last actual dose (Long-Term Safety Follow-Up), and for efficacy up to 39 months from last participant randomized (Efficacy Follow-Up).

Study population: Adult (≥18 years of age) patients with primary or secondary wAIHA who failed at least one previous line of treatment.

Method of blinding: Double-blind (ianalumab versus matching placebo) with optional open label cross-over period.

Study Treatment Assignment Method: Participants will be randomized in a 1:1:1 ratio to one of the three treatment groups. Central randomization will be stratified by prior use of rituximab (yes versus no).

Committees: An independent Data Monitoring Committee (DMC) will be utilized for safety review throughout the study. A Steering Committee will ensure transparent management of the study according to the protocol.

Brief Summary:

The purpose of this study is to assess the ability of ianalumab (VAY736) (compared to the placebo) in inducing a durable hemoglobin response in wAIHA patients who failed at least one line of treatment.

- The investigation study treatment ianalumab (VAY736) and placebo will be supplied in a double-blinded manner. For the open label cross-over period, ianalumab will be provided in an open label manner.
- The study duration will be up to 39 months post randomization of the last participant.
- The treatment duration will be 16 weeks and includes a total of 4 doses. For participants randomized to the placebo arm and switching to the open label cross-over period, there will be an additional 16 weeks and will receive 4 doses of open label ianalumab at 9 mg/kg.
- The visit frequency will be every other week (q2w) during the treatment period and the primary endpoint follow-up period; for safety monthly during the first 20 weeks from the last dose, then quarterly up to 2 years from the last dose; for efficacy monthly during the first 2 years after the last dose, and then quarterly afterwards until confirmed loss of durable response or end of study.

Treatment of interest

The randomized treatment (ianalumab 3 or 9 mg/kg or the placebo), with or without the allowed supportive care. The dose of supportive care should be stable for at least 4 weeks prior to the randomization into the study and should not be increased during the study. Transfusions of red blood cells (RBC) and intravenous immunoglobulins (IVIG) will be allowed during the study.

Number of Participants:

90 participants will be randomly assigned to study intervention (in a 1:1:1 ratio).

The study population will include male and female adult participants (≥18 years of age).

Key Inclusion criteria

- Written informed consent form (ICF) must be obtained prior to any screening assessments
- Male or female participants aged 18 years and older on the day of signing the ICF
- Participants with primary or secondary wAIHA (previously documented by positive direct antiglobulin test (DAT) specific for anti-IgG or anti-IgA), who had an insufficient response to, or relapsed after at least one line of treatment, including patients with steroid resistance, dependence or intolerance
- Hemoglobin concentration at screening below 10 g/dL, associated with presence of symptoms related to anemia.
- The dose of supportive care must be stable for at least 4 weeks prior randomization

Key Exclusion criteria

- Patients with wAIHA secondary to hematologic disease involving bone marrow or other immunologic disease requiring immunosuppressant or presence of other forms of AIHA (cold or intermediate), Evan's Syndrome or other cytopenias
- Prior use of B-cell depleting therapy within 12 weeks prior randomization
- Active viral, bacterial or other infections (including tuberculosis or SARS-CoV-2)
- Known history of primary or secondary immunodeficiency, or a positive human immune deficiency virus (HIV) or positivity for hepatitis C virus (HCV) or hepatitis B virus (HBV)
- Live or live-attenuated vaccination within 4 weeks before randomization

Treatment Groups:

At the end of the screening period (28 days), participants will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1 (randomized double-blinded treatment period):

- Arm A (investigational): ianalumab at 3 mg/kg dose, intravenously, every 4 weeks (4 doses in total)
- Arm B (investigational): ianalumab at 9 mg/kg dose, intravenously, every 4 weeks (4 doses in total)
- Arm C (control): placebo, intravenously, every 4 weeks (4 doses in total).

Participants in the placebo arm who do not achieve a durable response until the end of the randomized double-blinded period will have the option to switch to the below period:

- Open label: ianalumab at 9 mg/kg dose, intravenously, every 4 weeks (4 doses in total).

Data Monitoring/Other Committee:

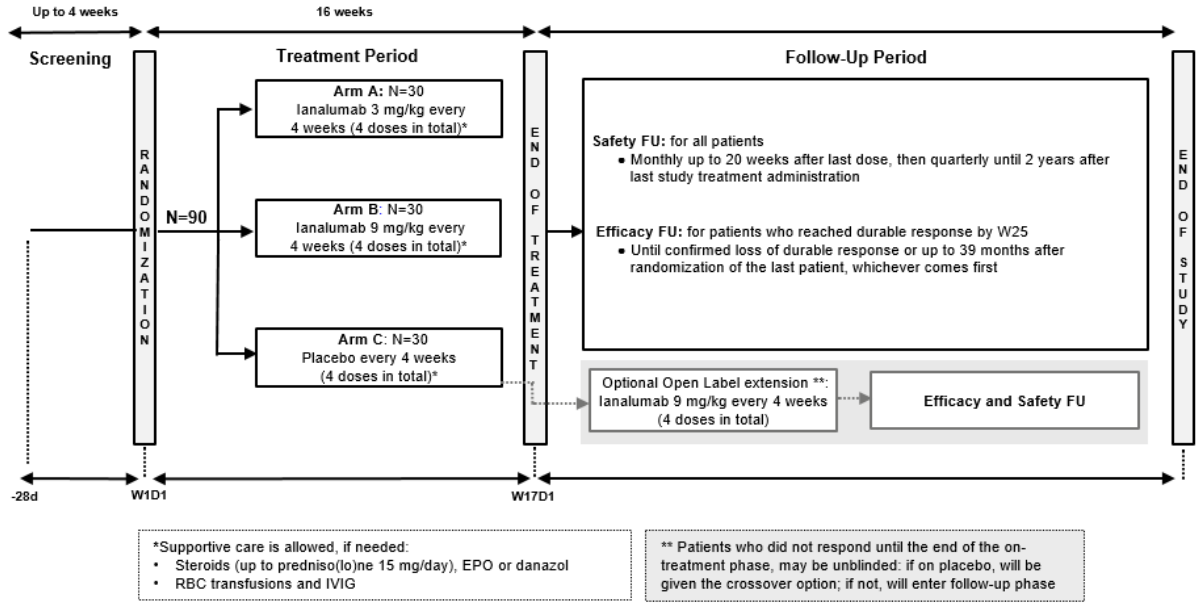
Yes (see Section 10.1.4 Committees Structure)

Key words

Warm autoimmune hemolytic anemia (wAIHA), ianalumab, VAY736, B-cell depletion, B-cell Activating Factor Receptor (BAFF-R) blockade.

1.2 Schema

Figure 1-1 CVAY736O12301 Study Design



1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the schedule of assessments or as close to the designated day/time as possible. All visits are to be scheduled at Day 1 of the week given in:

- Table 1-1: for the randomized double-blinded treatment period
- Table 1-2: for the open label/cross-over treatment period (for eligible participants only, see Section 6.5.5)
- Table 1-3: for the primary endpoint follow-up until W25 and safety follow-up period applicable for participants not in durable response after W25/CO W25
- Table 1-4: for the primary endpoint follow-up until W25 and safety/efficacy follow-up period, applicable for participants in durable response after W25/CO W25. After confirmed loss of durable response, participants need to follow Table 1-3

The criteria for confirmed loss of durable response are defined in Section 3.2 .

The following visit windows are allowed:

- +/- 3 days visit window allowed for dosing visits (W1, W5, W9 and W13 during double-blind treatment period) and (CO W1, CO W5, CO W9 and CO W13 during open label/cross-over period) and for every other week visits (q2w)
- +/- 7 days visit window allowed for monthly visits (q4w, meaning every 4 weeks)
- +/- 14 days visit window allowed for quarterly visits (q12w, meaning every 12 weeks)

Missed or rescheduled visits should not lead to automatic discontinuation.

In case of delays in treatment administration, clinically relevant assessments might need to be repeated. Any unscheduled assessment will be recorded as unscheduled visit. Participants who prematurely discontinue from study treatment need to complete all visits up to W25 visit, and then enter the efficacy/safety follow-up period (scheduled according to the actual last dose date). The follow-up period is described in Section 4.1.

Participants who prematurely discontinue from study should perform all the assessments listed for the final visit (STFU2 or ESFU, see footnotes in Table 1-3 and Table 1-4) during their last study visit.

All assessments (except post dose samples) must be completed before the study treatment infusion, and PROs should be completed before other assessments. Recommended order: to start with PROs, ECG, vital signs, blood collection, physical examination, infusion.

Participants on placebo arm who join the open label cross-over part of the study will follow the assessments during the treatment period as outlined in Table 1-2. Afterwards, they will follow the same rules for efficacy and safety follow-up as defined following the blinded treatment period.

Off-site visits are allowed in this protocol. Selected visits during long-term follow up can be done outside of the study site as listed in Table 1-4 and described in Section 8.11.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-1 Assessment Schedule, Randomized Double-Blinded Treatment Period

Period	**Screening**	**Blinded Treatment Period**									**End of Treatment (EOT)[2]**
Visit Name	**Screening**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17[1]**	**EOT**
Months	**-1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**-**
Weeks	**-4 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**-**
Days	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**within 113 days**
Informed consent	X										
Demography	X										
Inclusion / Exclusion criteria	X										
Medical history/ current medical conditions/ prior transfusions	X										
Smoking history	X										
Physical Examination	S	S		S		S		S		S	
Abbreviated Physical Examination			S		S		S		S		
Body Weight	X	X		X		X		X		X	
Body Height	X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medications	Continuous										
Concomitant Medication (only related to wAIHA)	Continuous										
Procedures	Continuous										
Adverse Events/Serious Adverse Events	Continuous										
Pregnancy Test (serum)	S										S[2]
Pregnancy Test (urine)		S[3]		S[3]		S[3]		S[3]			
HBV, HCV, HIV, , TB Testing	X										
Full Hematology[4]	X	X[8]	X	X	X	X	X	X	X	X	
Full Chemistry	X	X[8]	X	X	X	X	X	X	X	X	
Coagulation	X	X[8]		X		X		X		X	
Urinalysis	X	X[8]		X		X		X		X	

Period	**Screening**	**Blinded Treatment Period**									**End of Treatment (EOT)[2]**
Visit Name	**Screening**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17[1]**	**EOT**
Months	**-1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**-**
Weeks	**-4 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**-**
Days	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**within 113 days**
Immunoglobulin (IgG, IgA, IgM)	X	X[8]		X		X		X		X	
Electrocardiogram (ECG)	X										X[2]
Patient reported outcomes	X[5]	X[5]		X		X		X		X	
Trial Feedback Questionnaire	X										X[2]
Study drug administration		X		X		X		X			
Study Disposition	X										X[2]
PK blood collection		X[6]	X	X[6]	X	X[6]	X	X[6]	X	X	
Immunogenicity (ADA)		X[7]		X[7]		X[7]		X[7]			
B, T and NK cell count and subsets		X[7]		X[7]		X[7]		X[7]		X	
Serum soluble biomarkers including sBAFF		X[7]	X	X[7]		X[7]		X[7]		X	
Plasma soluble biomarkers (TGFβ1)		X[7]		X[7]		X[7]		X[7]		X	
Autoantibodies (anti-RBC)		X[7]		X[7]		X[7]		X[7]		X	
Complement (C5b-9)		X[7]		X[7]		X[7]		X[7]		X	
Transcriptomic		X[7]									X[2]
Proteomics		X[7]									X[2]

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 For participants that receive the 4 doses, this will also correspond to the first monthly Safety Follow-Up Visit
2 EOT is not a separate visit but lists the assessments to be done after completion of treatment, i.e., at W17 visit for patients receiving all four doses. For patients discontinuing treatment early, all EOT assessments have to be done at the next visit after discontinuation, and participants will continue with all visits as per schedule of assessments, including the follow up periods
3 If result is positive, local lab serum test will be required
4 After a visit where a patient reports a hemoglobin value below 10g/dL, an unscheduled assessment should be performed one week later to confirm the loss of durable response
5 All questionnaires should be completed at this visit except PGIC

Period	**Screening**	**Blinded Treatment Period**									**End of Treatment (EOT)[2]**
Visit Name	**Screening**	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W15**	**W17[1]**	**EOT**
Months	**-1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**-**
Weeks	**-4 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**-**
Days	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**within 113 days**

6 Two samples to be collected: first sample pre-dose (before start of infusion), second sample 2 hours after start of infusion (at end of infusion)
7 Samples to be taken pre-dose (before start of infusion)
8 Samples do not need to be repeated if screening samples were collected less than 7 days before W1

Table 1-2 Assessment Schedule, Open Label/Cross-Over Treatment Period

Period	**Open Label/Cross-Over (CO) Treatment Period**									**Cross-over (CO) End of Treatment (EOT)**
Visit Name	**CO W1**	**CO W3**	**CO W5**	**CO W7**	**CO W9**	**CO W11**	**CO W13**	**CO W15**	**CO W17[1]**	**CO EOT[2]**
Months	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**-**
Weeks	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**-**
Days	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**within 113 days**
Review & Confirm Eligibility	X									
Physical Examination	S		S		S		S		S	
Abbreviated Physical Examination		S		S		S		S		
Body Weight	X		X		X		X		X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Prior/concomitant medications	Continuous									
Concomitant Medication (only related to wAIHA)	Continuous									
Procedures	Continuous									
Adverse Events/Serious Adverse Events	Continuous									
Pregnancy Test (serum)										S[2]
Pregnancy Test (urine)	S[3]		S[3]		S[3]		S[3]			
Full Hematology[4]	X	X	X	X	X	X	X	X	X	
Full Chemistry	X	X	X	X	X	X	X	X	X	
Coagulation	X		X		X		X		X	
Urinalysis	X		X		X		X		X	
Immunoglobulin (IgG, IgA, IgM)	X		X		X		X		X	
Electrocardiogram (ECG)										X[2]
Patient reported outcomes	X[5]		X		X		X		X	
Study drug administration	X		X		X		X			
Study Disposition										X[2]
PK blood collection	X[6]		X[7]		X[7]		X[6]		X	

Period	**Open Label/Cross-Over (CO) Treatment Period**									**Cross-over (CO) End of Treatment (EOT)**
Visit Name	**CO W1**	**CO W3**	**CO W5**	**CO W7**	**CO W9**	**CO W11**	**CO W13**	**CO W15**	**CO W17[1]**	**CO EOT[2]**
Months	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	**5**	**-**
Weeks	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**-**
Days	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**within 113 days**
Immunogenicity (ADA)	X[7]		X[7]		X[7]		X[7]			
B, T and NK cell count and subsets	X[7]		X[7]		X[7]		X[7]		X	
Serum soluble biomarkers including sBAFF	X[7]	X	X[7]		X[7]		X[7]		X	
Plasma soluble biomarkers (TGFβ1)	X[7]		X[7]		X[7]		X[7]		X	
Autoantibodies (anti-RBC)	X[7]		X[7]		X[7]		X[7]		X	
Complement (C5b-9)	X[7]		X[7]		X[7]		X[7]		X	
Transcriptomic	X[7]									X[2]
Proteomics	X[7]									X[2]

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
1 For participants that receive the 4 doses, this will also correspond to the first Safety Follow-Up Visit
2 CO EOT is not a separate visit but lists the assessments to be done after completion of treatment, i.e., at CO W17 visit for patients receiving all four doses. For patients discontinuing treatment early, all EOT assessments have to be done at the next visit after discontinuation, and participants will continue with all visits as per schedule of assessments, including the follow up periods
3 If result is positive, local lab serum test will be required
4 After a visit where a patient reports a hemoglobin value below 10g/dL, an unscheduled assessment should be performed a week later to confirm the loss of durable response
5 All questionnaires should be completed at this visit except PGIC
6 Two samples to be collected: first sample pre-dose (before start of infusion), second sample 2 hours after start of infusion (at end of infusion)
7 Samples to be taken pre-dose (before start of infusion)

Table 1-3 Assessment Schedule, Follow-Up Period after W17/CO W17, for participants NOT in durable response

Period	**Primary Endpoint Follow Up**				**Short Term Safety Follow Up[1,2]**		**Long Term Safety Follow Up[3]**							
Visit Name	**W19**	**W21**	**W23**	**W25**	**STFU1**	**STFU2 [5,6]**	**LTFU1[7]**	**LTFU3**	**LTFU6**	**LTFU9**	**LTFU12**	**LTFU15**	**LTFU18**	**ESFU (LTFU21)[8,9]**
Months	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**12**	**15**	**18**	**21**	**24**	**27**	**30**
Weeks	**19**	**21**	**23**	**25**	**29**	**33**	**37**	**45**	**57**	**69**	**81**	**93**	**105**	**117**
Days	**127**	**141**	**155**	**169**	**197**	**225**	**253**	**309**	**393**	**477**	**561**	**645**	**729**	**813**
Abbreviated Physical Examination		S		S	S	S								
Vital Signs		X		X	X	X								
Body Weight		X		X	X	X								
Pregnancy Test (urine)		S[10]		S[10]	S[10]	S[10]	S[7, 10]							
Full Hematology	X	X	X	X	X	X								
Full Chemistry	X	X	X	X	X	X								
Coagulation		X		X	X	X								
Urinalysis		X		X	X	X								
Immunoglobulin (IgG, IgA, IgM)		X		X	X	X		X	X	X	X	X	X	X
PK blood collection		X		X		X								
Immunogenicity (ADA)						X								
Electrocardiogram (ECG)														
Adverse Events/Serious Adverse Events	Continuous													
Concomitant medications and procedures	Continuous						Collect only data for therapies used for management of adverse events suspected to be related ianalumab							
AEs/SAEs potentially related to B-cell depletion & SAEs suspected to be related to ianalumab	Continuous. In case the participant starts a new B-cell depleting or immunosuppressive treatment, the AE collection during long-term safety FU will be limited to the SAEs suspected to be related to ianalumab.													
Concomitant Medication and procedures (only related to wAIHA)	Continuous													

Period	**Primary Endpoint Follow Up**				**Short Term Safety Follow Up[1,2]**		**Long Term Safety Follow Up[3]**							
Visit Name	**W19**	**W21**	**W23**	**W25**	**STFU1**	**STFU2 [5,6]**	**LTFU1[7]**	**LTFU3**	**LTFU6**	**LTFU9**	**LTFU12**	**LTFU15**	**LTFU18**	**ESFU (LTFU21)[8,9]**
Months	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**12**	**15**	**18**	**21**	**24**	**27**	**30**
Weeks	**19**	**21**	**23**	**25**	**29**	**33**	**37**	**45**	**57**	**69**	**81**	**93**	**105**	**117**
Days	**127**	**141**	**155**	**169**	**197**	**225**	**253**	**309**	**393**	**477**	**561**	**645**	**729**	**813**
Medical resource utilization[4]	Continuous													
Patient reported outcomes		X		X	X			X	X	X	X	X	X	X
Trial Feedback Questionnaire	At last study visit													
Study Disposition														X
B, T and NK cell count and subsets		X		X	X	X		X	X	X	X	X	X	X
Serum soluble biomarkers including sBAFF		X		X	Not applicable									
Plasma soluble biomarkers (TGFβ1)[12]		X		X	Not applicable									
Autoantibodies (anti-RBC)		X		X	Not applicable									
Complement (C5b-9)		X		X	Not applicable									
Transcriptomic					Not applicable									
Proteomics					Not applicable									

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 Safety Follow-Up for at least 20 weeks after last dose
2 For participants who prematurely discontinue treatment, safety period will be scheduled according to the last actual dose date
3 Every 12 weeks (quarterly), up to 2 years after last dose
4 Hospitalizations, outpatients visits, or emergency room visits due to underlying disease or its management
5 STFU2= End of Short-Term Safety
6 If a participant discontinues study before date of STFU2, all assessments from STFU2 should be done at the last visit.
7 This visit is applicable only to female participants and results can be discussed by phone. Please refer to Section 8.4.5
8 If a participant discontinues study between STFU2 and before LTFU21 (ESFU) visit, all assessments from LTFU21 (ESFU) should be done at the last visit.
9 ESFU = End of Long Term Safety Follow-Up
10 If urine pregnancy test result is positive, local lab serum test will be required

Table 1-4 Assessment Schedule, Follow-Up Period after W17/CO W17, for participants in durable response

Period	**Primary Endpoint Follow Up**				**Short Term Safety FU[1,2,3]**		**Long Term Safety and Efficacy Follow Up[1,4,5]**												
Visit Name	**W19**	**W21**	**W23**	**W25**	**STFU1**	**STFU2[6,7]**	**LTFU 1**	**LTFU 2**	**LTFU 3**	**LTFU 4**	**LTFU 5**	**LTFU 6**	**LTFU 7**	**LTFU 8**	**LTFU 9**	**LTFU 10**	**LTFU 11**	**LTFU 12**	**LTFU 13**
Months	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Weeks	**19**	**21**	**23**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**
Days	**127**	**141**	**155**	**197**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**
Off-site visit allowed[8]								X		X	X		X	X		X	X		X
Abbreviated Physical Examination		S		S	S	S													
Vital Signs		X		X	X	X													
Body Weight		X		X	X	X													
Pregnancy Test (serum)							S												
Pregnancy Test (urine)		S[10]		S[10]	S[10]	S[10]													
Full Hematology[11]	X	X	X	X	X	X													
Reduced Hematology[11]							X	X	X	X	X	X	X	X	X	X	X	X	X
Full Chemistry	X	X	X	X	X	X													
Reduced Chemistry							X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation		X		X	X	X													
Urinalysis		X		X	X	X													
Immunoglobulin (IgG, IgA, IgM)		X		X	X	X			X			X			X			X	
PK blood collection		X		X		X													
Immunogenicity (ADA)						X													
Electrocardiogram (ECG)						X													
Adverse Events/Serious Adverse Events	Continuous																		

Period	**Primary Endpoint Follow Up**				**Short Term Safety FU[1,2,3]**		**Long Term Safety and Efficacy Follow Up[1,4,5]**												
Visit Name	**W19**	**W21**	**W23**	**W25**	**STFU1**	**STFU2[6,7]**	**LTFU 1**	**LTFU 2**	**LTFU 3**	**LTFU 4**	**LTFU 5**	**LTFU 6**	**LTFU 7**	**LTFU 8**	**LTFU 9**	**LTFU 10**	**LTFU 11**	**LTFU 12**	**LTFU 13**
Months	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Weeks	**19**	**21**	**23**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**
Days	**127**	**141**	**155**	**197**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**
Concomitant medications and procedures	Continuous																		
AEs/SAEs potentially related to B-cell depletion & SAEs suspected to be related to ianalumab	Continuous																		
Concomitant Medication and procedures (only related to wAIHA)	Continuous																		
Medical resource utilization[4]	Continuous																		
Patient reported outcomes		X		X	X				X			X			X			X	
Trial Feedback Questionnaire	At last study visit																		
Study Disposition																			
B, T and NK cell count and subsets[12]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum soluble biomarkers including sBAFF[12]		X		X	X	X			X			X			X			X	
Plasma soluble biomarkers (TGFβ1)[12]		X		X	X	X			X			X			X			X	

Period	**Primary Endpoint Follow Up**				**Short Term Safety FU[1,2,3]**		**Long Term Safety and Efficacy Follow Up[1,4,5]**												
Visit Name	**W19**	**W21**	**W23**	**W25**	**STFU1**	**STFU2[6,7]**	**LTFU 1**	**LTFU 2**	**LTFU 3**	**LTFU 4**	**LTFU 5**	**LTFU 6**	**LTFU 7**	**LTFU 8**	**LTFU 9**	**LTFU 10**	**LTFU 11**	**LTFU 12**	**LTFU 13**
Months	**5**	**6**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Weeks	**19**	**21**	**23**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**
Days	**127**	**141**	**155**	**197**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**
Autoantibodies (anti-RBC)[12]		X		X	X	X			X			X			X			X	
Complement (C5b-9)	At confirmed loss of durable response or end of study[12]																		
Transcriptomic	At confirmed loss of durable response or end of study[12]																		
Proteomics	At confirmed loss of durable response or end of study[12]																		

Period	**Long Term Safety and Efficacy Follow Up[1,4,5]**								**Long Term Efficacy Follow Up[13]**
Visit Name	**LTFU14**	**LTFU15**	**LTFU16**	**LTFU17**	**LTFU18**	**LTFU19**	**LTFU20**	**ESFU (LTFU21)[14,15]**	**LTFU22, 23, 24 ..., XX/EOE[16]**
Months	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**0**
Weeks	**89**	**93**	**97**	**101**	**105**	**109**	**113**	**117**	**0**
Days	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**813**	**Every q12w until EOE**
Off-site visit allowed[8]	X		X	X		X	X		X
Abbreviated Physical Examination									
Vital Signs									
Pregnancy Test (serum)									
Pregnancy Test (urine)									
Full Hematology[11]									
Reduced Hematology[11]	X	X	X	X	X	X	X	X	X
Full Chemistry									
Reduced Chemistry	X	X	X	X	X	X	X	X	X
Coagulation									

Period	**Long Term Safety and Efficacy Follow Up[1,4,5]**								**Long Term Efficacy Follow Up[13]**
Visit Name	**LTFU14**	**LTFU15**	**LTFU16**	**LTFU17**	**LTFU18**	**LTFU19**	**LTFU20**	**ESFU (LTFU21)[14,15]**	**LTFU22, 23, 24 ..., XX/EOE[16]**
Months	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**0**
Weeks	**89**	**93**	**97**	**101**	**105**	**109**	**113**	**117**	**0**
Days	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**813**	**Every q12w until EOE**
Urinalysis									
Immunoglobulin (IgG, IgA, IgM)		X			X			X	
PK blood collection									
Immunogenicity (ADA)									
Electrocardiogram (ECG)									
Adverse Events/Serious Adverse Events									
Concomitant medications and procedures									
AEs/SAEs potentially related to B-cell depletion & SAEs suspected to be related to ianalumab	Continuous								
Concomitant Medication and procedures (only related to wAIHA)	Continuous								
Medical resource utilization[4]	Continuous								
Patient reported outcomes		X			X			X	At confirmed loss of durable response or at last study visit
Trial Feedback Questionnaire	At last study visit								
Study Disposition								X	X[9]
B, T and NK cell count and subsets[12]	X	X	X	X	X	X	X	X	X
Serum soluble biomarkers including sBAFF[12]		X			X			X	
Plasma soluble biomarkers (TGFβ1)[12]		X			X			X	

Period	**Long Term Safety and Efficacy Follow Up[1,4,5]**								**Long Term Efficacy Follow Up[13]**
Visit Name	**LTFU14**	**LTFU15**	**LTFU16**	**LTFU17**	**LTFU18**	**LTFU19**	**LTFU20**	**ESFU (LTFU21)[14,15]**	**LTFU22, 23, 24 ..., XX/EOE[16]**
Months	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**0**
Weeks	**89**	**93**	**97**	**101**	**105**	**109**	**113**	**117**	**0**
Days	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**813**	**Every q12w until EOE**
Autoantibodies (anti-RBC)[12]		X			X			X	
Complement (C5b-9)	At confirmed loss of durable response or end of study[12]								
Transcriptomic	At confirmed loss of durable response or end of study[12]								
Proteomics	At confirmed loss of durable response or end of study[12]								

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
1 At confirmed loss of durable response, switch to Table 1-3 Safety Follow Up for safety monitoring
2 Safety Follow-Up for at least 20 weeks after last dose
3 For participants who prematurely discontinue treatment, safety period will be scheduled according to the last actual dose date (see Section 4.1)
4 Hospitalizations, outpatient visits or emergency room visits due to underlying disease or its management
5 Every 4 weeks for efficacy assessments, and every 12 weeks for safety assessments, up to 2 years after last dose
6 STFU2 = End of Short Term Safety
7 If a participant discontinues study before date of STFU2, all assessments from STFU2 should be done at the last visit
8 Except visits to confirm the loss of durable response and end of study visit
9 Only at the last long term efficacy follow up visit (EOE)
10 If result is positive, local lab serum test will be required
11 After a visit where a patient reports a hemoglobin value below 10g/dL, an unscheduled assessment should be performed a week later to confirm the loss of durable response
12 Collect samples during unscheduled visit confirming the loss of durable response
13 Until confirmed loss of durable response or up to 39 months after randomization of last participant
14 ESFU= End of Long Term Safety Follow Up
15 If a participant discontinues study between STFU2 and before LTFU21 (ESFU) visit, all assessments from LTFU21 (ESFU) should be done at the last visit.
16 EOE = End of Efficacy (and end of study)

2 Introduction

2.1 Study rationale

Based on the growing evidence and understanding of the pathophysiology of autoimmune diseases such as warm auto-immune hemolytic anemia (wAIHA) (with the critical role of autoreactive B-cells) and potential mechanisms involved in treatment resistance (increased levels of B-cell-activating factor (BAFF) and the presence of CD20-negative B-cells), a promising treatment with dual action approach targeting 1) the BAFF-receptor pathway as well as 2) B-cell depletion can address the unmet medical needs in wAIHA.

B-cells play an important role in the pathogenesis of autoimmune diseases and therefore, B-cell depletion with the anti-CD20 monoclonal antibody rituximab is an established approach to treat autoimmune diseases, including wAIHA. However, the use of rituximab is associated with some limitations, including insufficient B-cell depletion, especially in tissues, and persistence of rituximab-resistant B-cells that play a critical role in autoimmune disease refractoriness and chronicity (Mahévas et al 2015, Crickx et al 2021). It also has been shown that enhanced antibody-dependent cellular cytotoxicity (ADCC), as a result of using afucosylated antibodies, can improve clinical outcomes in autoimmune diseases such as lupus nephritis (LN) (Furie et al 2021).

Recent studies have demonstrated that the BAFF-R signaling pathway is critically involved in the activation of B-cell effector functions such as antibody production, isotype class switching, B-cell proliferation, maturation, and survival (Mackay and Schneider 2009). BAFF overexpression results in disruption of B-cell immune tolerance and consequently autoimmune disorders (Mackay and Browning 2002). Increased concentrations of soluble BAFF were found in various autoimmune diseases, including Sjögren syndrome (SS), pemphigus vulgaris (PV), and also hematologic autoimmune diseases such as wAIHA and immune thrombocytopenia (ITP) (Emmerich et al 2007, Quartuccio et al 2008, Zhou et al 2009,Molica et al 2009, Krumbholz et al 2012, Stohl 2014, Hébert et al 2021). Increased serum BAFF levels were also detected in wAIHA patients with low hemoglobin (<8 g/dL) and high lactate dehydrogenase (LDH) activity (Xu et al 2015). Targeting the BAFF pathway in autoimmune diseases such as SLE and LN to improve clinical outcomes has been successfully demonstrated with the monoclonal antibody belimumab (Furie et al 2020).

Recent evidence from a phase 2 clinical study (Mahévas et al 2021) further confirms the importance of targeting the BAFF-R signaling pathway to achieve long-term response in ITP. In this study, the anti-BAFF antibody belimumab (5 doses for up to 12 weeks) was added to rituximab (2 doses for up to 2 weeks) to combine inhibition of the above-mentioned BAFF-mediated mechanisms responsible for ITP resistance with peripheral B-cell depletion. Out of the 15 patients with persistent or refractory ITP, 80% responded to this combination and maintained the response for 12 months (67% even with complete response). This very high rate of prolonged response compares favorably with the one reported with rituximab alone (roughly 40% after 12 months) (Lucchini et al 2019).

Ianalumab is a glycoengineered (afucosylated), fully human IgG1 monoclonal antibody directed against BAFF-R, which is expressed on the surface of B-cells, thereby targeting B-cells and their function with two modes of action:

1. Direct lysis and depletion of BAFF-R-expressing B-cells by enhanced ADCC due to its fucose-deficient Fc (fragment crystallizable) region
2. BAFF receptor blockade that interrupts BAFF-mediated signaling for B-cell activation, maturation, proliferation, and survival (Bowman et al 2021).

In preclinical studies, ianalumab significantly enhanced ADCC against B-cells and cytokine production by NK cells, and was more potent in depleting B-cells when compared to approved anti-CD20 antibodies, including rituximab, obinutuzumab and ofatumumab (McWilliams et al 2013).

Through its dual mechanism of action, ianalumab is expected to address the above-described limitations of currently available B-cell depleting therapy such as rituximab, by potent B-cell depletion and BAFF-R blockade, thereby preventing the BAFF-driven pathogenic rebound and resistance mechanisms (Genovese et al 2010, Furie et al 2011, Mariette 2012).

Ianalumab entered the clinic in patients in Nov-2010 with four Phase I studies: two in patients with rheumatoid arthritis (RA) and two in patients with chronic lymphocytic leukemia. As of 24-Mar-2021 (the cut-off date for the [ianalumab Investigator's Brochure (IB)] ed. 14), out of 495 subjects enrolled and treated (with any study drug) across eleven clinical trials, data from a total of 455 patients (enrolled in phase 1 and phase 2a and 2b trials) have been analyzed. These clinical trials include the studies in rheumatoid arthritis and chronic lymphocytic leukemia (CLL), primary Sjögren's syndrome (pSS), multiple sclerosis, pemphigus vulgaris, idiopathic pulmonary fibrosis and systemic lupus erythematosus (SLE) and autoimmune hepatitis.

The development of ianalumab in hematological autoimmune diseases, including wAIHA, is supported by the following:

- B-cell depletion is a well-established therapeutic measure in the treatment of wAIHA;
- BAFF-R pathway inhibition has been demonstrated to be effective and safe in non-hematologic autoimmune diseases (Furie et al 2020);
- BAFF-R blockade combined with B-cell depletion has been demonstrated to be effective and safe in ITP, a condition belonging to the same family of hematological autoimmune diseases as wAIHA (Mahévas et al 2021);
- Clinical studies with ianalumab have demonstrated its efficacy in other autoimmune diseases (e.g., RA, pSS) ([ianalumab IB] ed. 14);
- Ianalumab demonstrated a favorable benefit-risk profile based on data from 480 patients exposed to ianalumab in several autoimmune diseases ([ianalumab IB] ed. 14).

Based on the strong biologic rationale and the reassuring efficacy and safety profile of ianalumab, Novartis plans to conduct a pivotal phase 3 study to assess the efficacy and safety of ianalumab in patients with wAIHA who failed previous treatment(s).

2.2 Background

2.2.1 Pathophysiology of Warm Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemias (AIHAs) are rare and heterogeneous disorders characterized by the destruction of red blood cells (RBC) through autoantibodies directed against erythrocytes, with or without complement activation (Barcellini 2015). The disease may be primary or secondary (drug-induced, or associated with lymphoproliferative, autoimmune, or infectious diseases, immunodeficiencies, solid tumors, or transplants). Although rare, AIHA is one of the most common forms of acquired hemolytic disorders with an incidence rate of 1.8 per 100,000 person/year, and a prevalence of 9.5 per 100,000 (Tranekær et al 2021, Hansen et al 2020).

AIHA can occur at any age, but is most common among older adults, with the majority of AIHA patients being above 40 years at diagnosis (Sokol et al 1981, Hansen et al 2020). Females are reported to have a higher risk of developing AIHA, often explained by an increased prevalence of other autoimmune diseases commonly associated with AIHA, such as systemic lupus erythematosus (SLE) (Hansen et al 2020 Beeson 1994).

The ability of the bone marrow to compensate for the increased destruction of RBC and resulting anemia determines clinical severity. Clinical course can be variable and severe with a reported mortality rate of around 10% (Barcellini et al 2014). The main clinical presentations are associated with hemolysis and anemia, including fatigue, dyspnea, palpitations, as well as pallor, or icterus. About 15–20% of AIHAs display thrombotic events, including potentially severe events such as pulmonary embolism, stroke, or cardiac infarction, which are generally proportional to active hemolysis. Acute and severe disease course may present a challenge in the clinic, and rapidly worsening organ failures lead to a burden of overlapping therapies (Barcellini and Fattizzo 2021).

Serologically, cases are usually classified as either warm antibody- (wAIHA) or cold antibody-mediated AIHA (cAIHA). wAIHA accounts for 48–70% of patients with AIHA. wAIHA is characterized by binding of polyclonal immunoglobulin (mainly IgG) to RBC antigens (Rh proteins or glycophorins A–D). This binding is referred to as “warm” in that it occurs at most temperatures but is maximal at 37°C. The density of these RBC antigens is usually not high enough to fix complement, but in some instances complement also becomes attached to the RBC. The opsonized RBCs are then modified (becoming spherocytes) and eventually cleared by FcγRIII or C3b receptors on macrophages/activated lymphocytes in lymphoid organs and the spleen (extravascular hemolysis) (Jäger et al 2020).

Primary wAIHA is reported to be slightly less frequent compared to secondary wAIHA, with an assumed distribution of 35–50% of all wAIHA being primary (Lechner and Jäger 2010, Puthenparambil et al 2010). Primary wAIHA is the most frequent type in children (Voulgaridou and Kalfa 2021).

Apart from the primary, wAIHA can also be secondary to underlying diseases, or be caused by various medicinal products as well as organ transplantation (Kalfa 2016). In adults, the most frequent underlying disorders associated with wAIHA are lymphoproliferative malignancies, such as CLL, and connective tissue disorders, especially SLE (Gehrs and Friedberg 2002, Packman 2008, Lechner and Jäger 2010, Puthenparambil et al 2010, Tai et al 2010, Zent and Kay 2010, Hodgson et al 2011, Alonso et al 2017, Sudulagunta et al 2017).

To date, there are no approved therapies for the treatment of wAIHA. With a paucity of randomized and prospective clinical trials, the management of wAIHA has been empirically derived or is based on retrospective studies. Nonetheless, a group of international experts representing study groups, registries, and academic centers with large basic scientific and clinical experience, attempted to provide an international consensus for the diagnosis and clinical management of all major forms of AIHA (Jäger et al 2020).

For primary wAIHA, the principal indication for medical therapy is symptomatic anemia. In patients with milder and partially compensated hemolytic anemia (e.g., with hemoglobin (Hb) level >10 g/dL), patients are generally monitored without treatment, i.e., "watch and wait" approach, after weighing its potential burdens and benefits, taking into consideration individual patient factors such as symptoms, frailty, and co-morbidities. Spontaneous remission is very uncommon, and the majority of patients require treatment as disease is usually acute and severe, however, many of the treated patients do not achieve or sustain a complete remission (Birgens et al 2013, Michel et al (2017), Jäger et al 2020).

Management of secondary wAIHA depends on the underlying cause. While secondary wAIHA associated with autoimmune diseases like SLE or ES, is managed using a similar approach, i.e., use of steroids and immunosuppressive agents, secondary wAIHA associated with lymphoproliferative disorders, immunodeficiencies and other conditions should be treated with targeted therapy as per current guidelines according to age and the underlying disease (Jäger et al 2020).

In absence of approved therapies for wAIHA, existing treatment options are limited. Available therapies are mostly symptomatic with limited efficacy, where responses are typically not durable/sustained after treatment discontinuation and can be associated with significant side effects as well as negative impact on quality of life. This highlights the need for new therapies in wAIHA that can induce confirmed responses, which are maintained after the end of the treatment period , preventing the need for chronic interventions and associated consequences for the patient.

2.2.2 Ianalumab

Clinical experience with ianalumab

To date, ianalumab has been investigated in a number of autoimmune disorders such as primary Sjögren`s Syndrome (pSS), and in hematologic malignancies such as chronic lymphocytic leukemia (CLL).

The placebo-controlled, proof-of-concept (PoC) study CVAY736X2201 conducted in 27 pSS patients receiving a single, intravenous (i.v.) dose of ianalumab (either 3 mg/kg or 10 mg/kg), showed rapid and profound depletion of circulating B-cells and clear signs of efficacy reflected by consistent reductions in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), a validated disease outcome measure for pSS, and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) scores. The improvement was especially clear in patients receiving the higher dose of 10 mg/kg, in whom the reduced ESSDAI and ESSPRI scores were still seen at the end of the study at the time of B-cell recovery. In contrast to studies with rituximab where high baseline BAFF levels were correlated with reduced efficacy (Carter et al 2013,

Cornec et al 2016), no correlation was found between baseline BAFF serum levels and ianalumab efficacy. This supports the concept of BAFF-R blockade as a measure to both improve and prolong outcomes in autoimmune diseases given BAFF protects B-cells and drives disease relapse after treatment with B-cell depleting agents (Carter et al 2013).

In the randomized study CVAY736A2201, 190 patients with pSS were treated with subcutaneous ianalumab (5, 50, 150 or 300 mg q4w for 24 weeks) or placebo (Bowman et al 2021). The study showed a significant dose-response effect of ianalumab on the ESSDAI, and an increase in stimulated salivary flow, with the greatest effect observed at the highest dose.

In the ongoing clinical study CVAY736Y2102, 32 patients with CLL unsuccessfully treated with ibrutinib (lack of CR or resistance mutation to ibrutinib) were given ianalumab intravenously at doses ranging from 0.3 to 9 mg/kg every two weeks (6-8 cycles) in addition to ibrutinib. The overall response rate was 57% and the complete response rate was 43%. Eight patients achieved undetectable minimal residual disease (MRD) in both blood and bone marrow at the end of treatment. Eight patients were able to discontinue ibrutinib therapy for up to 26 months (Rogers et al 2021).

Safety overview of ianalumab

The safety profile of ianalumab has been extensively described in several non-clinical and clinical studies ([ianalumab IB ed.14]).

As of 24-Mar-2022, 492 patients with autoimmune diseases (mainly pSS, RA, autoimmune hepatitis, or SLE) and CLL have been exposed to ianalumab at different dose levels (from 0.0003 mg/kg up to 10 mg/kg i.v. as single dose, up to 300 mg subcutaneous (s.c.) every 4 weeks for 52 weeks and up to 9 mg/kg i.v. every 2 weeks for up 16 weeks) ([ianalumab IB ed.14]).

Overall, the clinical safety profile of ianalumab is favorable. Ianalumab treatment is generally well tolerated, with most adverse events (AEs) being mild to moderate in severity. The overall frequency of AEs across the investigated doses has been similar, except for local injection-related reactions with subcutaneous administration. The systemic reactions that have occurred in ianalumab single-dose and multiple-dose studies, were in most of the cases mild-to-moderate, including symptoms such as headache, fever/pyrexia, shivering/chills, mild nausea, dizziness, rash, flushing, myalgia, fatigue, tachycardia and hypotension, typically within a range of 30 minutes up to 24 hours after initial administration of ianalumab. Symptoms were mostly observed after the first ianalumab dose but new-onset symptoms and recurrence after repeated dosing have also been reported. Symptoms either did not require any treatment or were manageable by administering either paracetamol, corticosteroids or antihistamines. There was only one case of systemic injection-related reaction (moderate in severity) in CVAY736A2201 study which led to hospitalization. There were no life-threatening or severe cases of systemic injection reactions (please refer to the [ianalumab IB ed.14]).

Infections have been the most frequently reported system organ class (SOC) category. The majority were mild-to-moderate and non-serious events that did not lead to study drug discontinuation, were self-limited or responded promptly to treatment. There were three infection AEs that led to study treatment discontinuation (non-serious bronchitis, herpes zoster

and a serious event of wound infection). The proportion of patients with serious infections showed no dose-response relationship.

In the CLL study CVAY736Y2102, using doses of ianalumab from 0.3 mg/kg up to 9 mg/kg i.v. every 2 weeks in combination with ibrutinib at the standard approved dose for CLL, the observed safety profile was consistent with what has been observed in autoimmune disease studies. Premedication with oral acetaminophen, antihistamine, and intravenous corticosteroid effectively prevented infusion-related reactions. "Decreased neutrophil count" was the only Grade 4 AE reported, which could be explained by concomitant administration of ibrutinib. The event resolved upon discontinuation of ibrutinib and ianalumab and treatment with filgrastim and did not reoccur upon restarting the drugs. No severe case of hypogammaglobulinemia and no dose-limiting toxicities were reported with the different i.v. doses of ianalumab tested in this study ([ianalumab IB ed.14]).

2.3 Benefit/Risk assessment

For the latest information on risks and benefits of ianalumab, please refer to the most recent version of the [ianalumab IB].

Ianalumab is a glycoengineered (afucosylated), fully human IgG1 monoclonal antibody directed against BAFF-R. It targets B cells via two mechanisms, by enhanced ADCC that depletes the circulating BAFF-R expressing B-cells and another by blocking BAFF-mediated activation of BAFF-R thereby blocking the B-cell activation, differentiation, and survival.

So far, ianalumab has been investigated across multiple indications in autoimmune disorders and hematologic malignancies. Data from the ongoing and completed studies shows that treatment with ianalumab was generally safe and well tolerated. The most frequently reported AEs were infusion/injection-related reactions and infections, mainly upper respiratory tract infections. In the vast majority, severity of these events was reported as mild-to moderate and non-serious that did not lead to study drug discontinuation, were self-limited or responded promptly to treatment. The proportion of patients with serious infections showed no dose-response relationship. None of these studies found ianalumab to be associated with severe cases of disseminated opportunistic infections, clinically significant neutropenia or hypogammaglobulinemia, or other adverse signals of immune suppression.

Expected pharmacological effect of ianalumab treatment is sustained B-cell depletion, which may be related to some safety risks. The identified safety risks of ianalumab are infusion-related reactions. Potential risks include infections, malignancies, reproductive toxicity, allergic reactions, immunogenicity, lower response to vaccinations and neutropenia. Since B-cell depletion can last several months or even years after last treatment with B-cell depleting agents, monitoring requirements are put forth to be adhered to during the post-treatment safety follow-up period, and are detailed below.

Across the different disease indications, time to B-cell count recovery occurred between 6 days and 1759 days after ianalumab treatment. Substantial variability was observed between individual patients within the different trials according to the of B-cell count recovery time. There was no evidence for a relationship between time to B-cell count recovery and disease type, ianalumab dose or baseline B-cell levels.

Please refer to the latest [ianalumab IB] for further information.

Important identified risk

Infusion or Injection-related reactions: These reactions are anticipated based on the mode of action of ianalumab, whereby B-cell killing leads to release of intracellular cytokines by ADCC. Clinically, this may induce a range of symptoms, from mild systemic reactions to cytokine storm in very rare cases.

Mild-to-moderate, systemic injection-related reactions including symptoms such as headache, fever/pyrexia, shivering/chills, mild nausea, dizziness, rash, flushing, myalgia, fatigue and tachycardia have occurred in ianalumab single dose and multiple dose studies. Reactions typically occur within 30 minutes and up to 24 hours after the first administration of ianalumab. Symptoms were most often observed after the first ianalumab dose but new-onset and recurrent reactions after repeated dosing have occasionally been reported. Symptoms either did not require any treatment or were manageable with paracetamol, antihistamines and corticosteroids.

Patients must be observed/clinically monitored during first 2 hours after injection for symptoms of possible injection-related reactions. Patients must be instructed to promptly report symptoms occurring within 24 hours after study drug administration

The incidence of infusion or injection related reactions can be reduced or prevented by pre-medicating the patients with corticosteroids ± paracetamol (acetaminophen) and antihistamines before the first two administrations of study treatment (and as medically indicated thereafter).

Important potential risks

Infections: The potential of ianalumab to increase the risk of infections has been identified (see Section 7 of [ianalumab IB]). The most commonly reported infections occurring ≥5% by preferred terms were nasopharyngitis, upper respiratory tract infection, urinary tract infection, sinusitis, bronchitis, oral herpes and conjunctivitis, with no relation to dose. The majority of the events were mild to moderate and did not lead to study drug discontinuation. They were self-limited or responded promptly to treatment. In the phase 2b Sjögren's syndrome study, the incidence of infections during the double-blind placebo-controlled period was comparable between all exposed ianalumab groups and placebo.

The risk of infection may increase if ianalumab is combined with steroids or strong immunosuppressive drugs. Strong immunosuppressive drugs, such as cyclophosphamide, mycophenolate, cyclosporine are prohibited. The Investigator should remind the patient of the risk of infections and ask them to promptly report any symptoms of infections to the Investigator. Participants in this study will be monitored regularly and carefully for signs and symptoms for at least 20 weeks and up to 2 years after last dose of study treatment.

COVID-19 has similar impact on risk-benefit as other infections. Any immunosuppressive/ immunomodulatory agent may be associated with an increased risk of infections including vaccinations that may also cause serious adverse events. Therefore, the risk of becoming infected or potentially developing a severe respiratory illness may be further increased in patients who are treated with ianalumab (VAY736) and receiving other immunosuppressant medications as standard of care for their chronic illness.

Allergic reactions: Although no allergic reactions following i.v. or s.c. administration were observed so far, the potential to develop an allergic reaction in a predisposed subject cannot

entirely be ruled out. Routine monitoring as for other biological treatments is warranted, as described in the [ianalumab IB].

Immunogenicity: Although no signs and symptoms of immunogenicity have been observed so far, administration of monoclonal antibody (mAb), independent of the antibody specificity for antigen, carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of anti-drug antibodies. Other clinical manifestations can include local skin reactions at the injection site, pyrexia, and an influenza-like syndrome.

Vaccinations: In immune suppressed patients, live vaccinations may cause serious adverse events and vaccination success may be attenuated. No data exists on the effect of ianalumab on response to vaccinations in general. It is recommended that patients receive appropriate vaccinations in accordance with current immunization guidelines at least 2 weeks prior to the first administration of the study treatment, noting that randomization must not occur less than 4 weeks after a live vaccine is given.

Neutropenia: In toxicity studies in monkeys, transient neutropenia was observed, which correlated with subsequent infections; however, the mechanism observed in monkeys was not translatable to humans. In clinical studies, AEs of neutropenia were reported, these have been primarily mild to moderate in severity and were not associated with any severe infections. Neutrophil counts will be measured regularly to mitigate the risk.

Malignancies: There is a potential risk of malignancies in immunocompromised patients in general, including patients receiving immunosuppressive therapies and/or patients who were immunocompromised from prior therapies. Patients with autoimmune disorders are also prone to develop specific types of cancer, depending on type of autoimmune disease. Based on the description of individual cases of malignancies reported from clinical trials with ianalumab, and the confounding factors present (e.g. underlying disease, prior/concomitant treatment with immunosuppressants), a causal association with ianalumab cannot be established at this time. In ongoing non-oncology studies, there exists long-term treatment-free safety follow-up of patients until B-cell count recovery thresholds are met (up to 2 years post-treatment).

Reproductive toxicity: Based on a reproductive toxicity study (enhanced pre-and postnatal development [ePPND]) in cynomolgus monkeys, there was no teratogenicity observed over 6 months monitoring after birth. However, there was reported an increased number of abortions, as well as one stillbirth and two postnatal deaths of infant monkeys. The stillbirth and one perinatal death was likely attributed to immunosuppression in mother animals and associated infections. Some outcomes were considered secondary to effects specific to the animal species being tested, while there may have been a contributory effect from ianalumab in some other outcomes relevant to humans resulting from the pharmacologically intended immunosuppression (B-cell depletion).

In humans, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to anti-CD20 antibodies during pregnancy. The potential duration of B-cell depletion in infants following maternal exposure to ianalumab in utero and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy occurs during the study, and of the importance of

contraceptive measures. Before enrollment, they must agree that in order to participate in the study, they must adhere to highly effective contraception requirements for the duration of the study treatment and 6 months after its discontinuation, as outlined in the protocol's exclusion criteria (Section 5.2). If there is any question that the participant will not reliably comply, she should not be entered or continue in the study.

Monitoring of safety risks: The risk for patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring (see Section 10), compliance with criteria for treatment interruption outlined in the protocol and periodic review of data by an independent Data Monitoring Committee (DMC). Drug-drug interactions are unlikely with biologics; however, sites and patients must strictly observe and adhere to the list of prohibited medications listed in the protocol (Section 6.8.2). In this study, low dose steroid (predniso(lo)ne or equivalent, will be allowed in combination with ianalumab. Strong immunosuppressive drugs, such as cyclophosphamide, mycophenolate, cyclosporine are prohibited.

Based on overall data analysis to date, the benefit-risk profile of ianalumab remains favorable. Please refer to the [ianalumab IB] for further guidance.

3 Objectives, endpoints, and estimands

Table 3-1 below list the primary, secondary and exploratory objectives and endpoints analyzed in this study.

Exploratory data requiring testing of biological samples may not be collected for participants from all countries, depending on the local regulations for collection and shipping of samples.

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate that either dose of ianalumab induces durable hemoglobin (Hb) response compared to placebo, in patients with wAIHA who failed at least one previous line of treatment	● Binary variable indicating whether a patient achieves a durable response (Hb ≥10 g/dL and ≥2 g/dL increase from baseline), for a period of at least 8 consecutive weeks, between W9 and W25, in the absence of rescue or prohibited treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● Key secondary objective: to demonstrate that either dose of ianalumab maintains durable hemoglobin response, that is sustained beyond the end of the treatment period, compared to placebo	● Duration of response
● To assess the time to durable response/response/complete response in each treatment group	● Time from randomization to achievement of durable response, to first response, to first complete response
● To assess quality of response in each treatment group	● Response rate, complete response rate and hemoglobin level
● To assess the need for rescue treatments in each treatment group	● Number and proportion of participants who received rescue treatment overall and by type of rescue treatment Time-standardized numbers of each type of rescue treatment

Objective(s)	Endpoint(s)
	Change from baseline in time-standardized number of transfusions
● To assess the safety profile of ianalumab	● Frequency of adverse events and other safety parameters
● To characterize the pharmacokinetics (PK) of ianalumab	● Ianalumab concentration in serum and PK parameters after the first and last dose
● To assess B-cell levels and immunoglobulin levels in each treatment group	● B-cell levels: ● Change from baseline in the frequency (%within the CD45) and absolute number of CD19+ B cell counts ● Time to first occurrence of B cell recovery, defined as ≥80% of baseline or ≥50 cells/μL Immunoglobulins: ● Change from baseline in immunoglobulin levels
● To assess the immunogenicity of ianalumab	● Incidence and titer of anti-ianalumab antibodies in serum (ADA assay) over time
● To assess quality of life in each treatment group	● Change from baseline on the 8 domains (Physical Functioning, Role Functioning-Physical, Role Functioning-Emotional, Bodily Pain, General Health, Vitality, Social Functioning and Mental Health), and summary scores (PCS-36 and MCS-36) of the SF-36 ● Change from baseline on the PROMIS Fatigue-13a total score
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
● To identify biomarkers predictive of response, to assess the immunomodulatory effects in each treatment group and correlate biomarker measurements with key outcomes of efficacy (Hb level)	● Change from baseline in Peripheral immune cell subset (e.g., overall B cells, T helper cells 1 (Th1), T helper cell 2 (Th2), T regulatory cells (T-reg) and B regulatory cells (B-reg) populations), memory B cells, plasma cells and monocyte/macrophage profiling) ● Baseline and changes from baseline in levels of sBAFF, TGFβ1 and IL-21 ● Baseline and change from baseline in gene expression and proteomic signatures ● Change from baseline in the levels of sC5b-9 ● Change from baseline in titers of anti-RBC autoantibodies
● To explore patient reported outcomes in each treatment group	● Change from baseline on FACT-GP5 item ● PGIS score at each visit ● PGIC score at each visit ● Time to achieve a clinically meaningful improvement in PROMIS Fatigue-13a total score (5 points) ● Time to achieve a clinically meaningful improvement in Vitality from the SF-36 (8 points)
● To explore exposure-response relations	● Pharmacokinetic, pharmacodynamic, safety and efficacy endpoints
● To explore medical resource utilization	● Frequency of hospitalizations, outpatient visits or emergency room visits
● To assess efficacy, safety, PK/PD/immunogenicity of ianalumab in the open label extension part	● Same efficacy, safety and PK/PD/immunogenicity endpoints as described above

3.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: Can ianalumab (with or without supportive care) induce a durable hemoglobin response, without the need for rescue or prohibited treatment, in adult participants with wAIHA who failed prior therapy? **The primary estimand is described by the following attributes:**

- **Population:** adult patients (18 years of age and greater) with primary or secondary wAIHA, who failed at least one previous line of treatment including being intolerant to it.
- **Endpoint:** binary variable indicating whether a patient achieves a durable response (Hb ≥10 g/dL and ≥2 g/dL increase from baseline) for a period of at least 8 consecutive weeks, between W9 and W25, in the absence of rescue or prohibited treatment prior to that durable response achievement.
- **Treatment of interest:** ianalumab or placebo, intravenously every 4 weeks (4 doses for 4 cycles), with or without the allowed supportive care.

The justification for targeting an effect after W9 is to allow sufficient time for the study treatment to establish its effect. Response will be measured over a period of 8 consecutive weeks in order to establish a robust and durable response as well as to account for fluctuations in hemoglobin level. Intake of rescue therapies may have an impact on response assessment in some specific situations and their management is described below in the intercurrent event section.

Intercurrent events and handling principles:

- **Intake of rescue or prohibited treatment (except RBC transfusions/IVIG):** if a patient receives rescue medication (>20% increase in dosage of steroids vs pre-enrolment dose) or prohibited treatments (e.g., other B-cell depleting therapies) at any time which is post randomization but before a durable response is achieved, the corresponding patient will be conservatively considered as non-responder (composite strategy).
- **Red blood cell (RBC) transfusion or intravenous immunoglobulins (IVIG) administration:** hemoglobin values measured within 4 weeks after RBC transfusion or IVIG administration will be excluded from the assessment of durable response, in order to avoid any confounding effect when evaluating the primary endpoint ("while on treatment strategy" according to ICH E9 Addendum 1)
- **Premature treatment discontinuations due to any reasons:** The completion or early discontinuation status of a patient will not be taken into account when evaluating the primary endpoint (treatment policy strategy). The clinical interest is the treatment effect measured between W9 and W25, regardless of whether patient was treated for that full duration or not; even patients who receive less than 4 infusions may benefit from ianalumab. In line with this estimand strategy, efficacy data will continue to be collected beyond early discontinuation of study treatment.

- **Temporary treatment interruptions (within or between infusions) or infusions delay for any reasons during the 16-week on-treatment period:** those events will be ignored, and hemoglobin levels will be considered for response assessment (treatment policy strategy), as the purpose is to measure a treatment effect closer to real life situation.
- **Death (whatever the cause):** those events will conservatively be considered as treatment failure if they happen before a durable response is achieved. The corresponding patient will thus be counted as non-responder (composite strategy).

The summary measure of the treatment effect will be the odds ratio, with the associated confidence intervals, between each of the two active arms versus the control arm, obtained from a logistic regression stratified by the randomization stratification factor (prior use of rituximab, yes vs. no).

3.2 Secondary estimands

The key secondary clinical question of interest is: Can ianalumab (with or without supportive care), maintain a durable hemoglobin response (including beyond the end of the treatment period), without the need for rescue or prohibited treatment, in adult participants with wAIHA who failed prior therapy?

The key secondary estimand is described by the following attributes:

- **Population:** adult participants (18 years of age and greater) with primary or secondary wAIHA, who failed at least one previous line of treatment including being intolerant to it.
- **Endpoint:** Duration of response, defined as
  - For participants who previously reached durable response: the time from the first hemoglobin assessment showing durable response (as defined in primary endpoint) to confirmed loss of durable response, defined as the first of the following events:
    - hemoglobin level below 10 g/dL in at least two consecutive weekly assessments* (date of the first of the 2 relapsed assessments will be considered as relapse date),
    - start of any rescue or prohibited treatment,
    - death (whatever the cause);
  - For participants who did not achieve durable response according to the primary endpoint definition: the duration of response will be zero day.

*(*Of note: after a visit where a patient reports a relapsed hemoglobin assessment, an unscheduled assessment should be performed a week later to confirm the loss of response).*

- **Treatment of interest:** ianalumab or placebo, intravenously every 4 weeks (4 doses for 4 cycles), with or without the allowed supportive care.

Targeting this treatment effect as key secondary endpoint is based on the following justification: this endpoint covers the ability of the treatment strategy to sustain a durable hemoglobin response including after the last infusion, while preventing the need for rescue therapy/transfusions or subsequent (chronic) therapies. Duration of the response is one of the key criteria for assessing response to treatments, defined by the First International Consensus Meeting for AIHA (Jäger et al 2020).

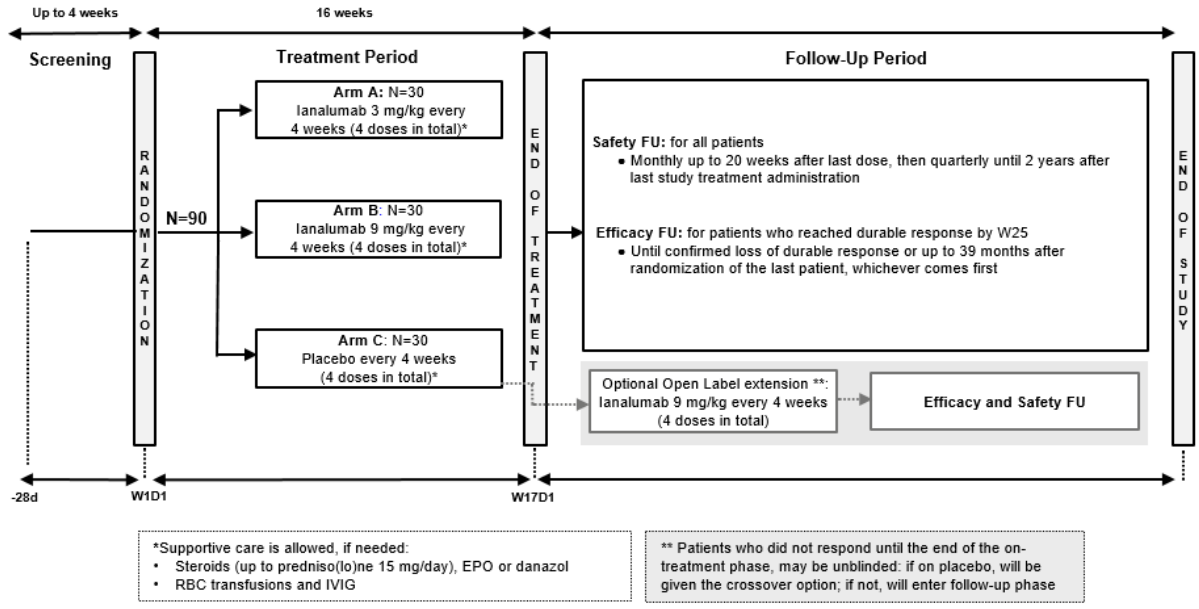
Intercurrent events and handling principles:

- **Intake of rescue, prohibited treatment or RBC/IVIG administration** after reaching durable response as defined in the primary endpoint are considered as an unfavorable outcome (composite strategy): these events will be treated as confirmed loss of response.
- **Premature treatment discontinuations due to any reasons:** a participant who prematurely discontinues treatment will continue to be assessed for loss of response, regardless of treatment discontinuation (treatment policy strategy) (efficacy data will continue being collected beyond completion or early discontinuation of study treatment).
- **Temporary treatment interruptions (within or between infusions) or infusions delay for any reasons during the 16-week on-treatment period:** this event will be ignored, and hemoglobin levels will be considered for loss of response assessment (treatment policy strategy).
- **Death (whatever the cause):** those events will be considered as loss of response (composite strategy).

The summary measure is the hazard ratio for confirmed loss of durable response, with the associated confidence interval, between each of the two active treatment groups versus the control group, estimated using Cox proportional hazard model stratified by the randomization stratification factor, the prior use of rituximab (yes vs. no).

4 Study design

Figure 4-1 CVAY736O12301 Study Design



4.1 Overall design

This is a multicenter, randomized, double-blinded, parallel-group Phase 3 study to assess the efficacy and safety of two different doses level of ianalumab (3 and 9 mg/kg) compared to

placebo, in adult patients with wAIHA who failed previous treatment. Since there is no approved medication for the treatment of wAIHA, participants randomized to the comparator arm will receive placebo.

90 participants will be randomized in a 1:1:1 ratio to either 3 mg/kg or 9 mg/kg of ianalumab or placebo. Central randomization will be stratified by the prior exposure to rituximab (yes/no). In order to avoid major over-representation of one type of participants, a capping of 54 participants (i.e., 60% of the targeted sample size) per category (with vs without rituximab history) will be implemented.

The study consists of the following periods (Figure 4-1):

Screening period (up to 4 weeks):

Participants with primary or secondary wAIHA who failed at least one prior line of treatment will be screened within 4 weeks (Day -28 to Day 0) prior to randomization. During this time the inclusion and exclusion criteria will be assessed, and all screening laboratory and procedures will be evaluated. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to enrolment of that patient into the study to ensure that all inclusion and exclusion criteria have been satisfied.

All study participants must be thoroughly informed about all aspects of the study, including the study visits and assessments schedule and all regulatory requirements for informed consent. The written inform consent must be obtained prior to the performance of any screening/baseline evaluations.

Randomized double-blinded treatment period (16 weeks):

At W1, patients will be randomly assigned in a 1:1:1 ratio to one of the following three arms: Arm A (ianalumab 3 mg/kg intravenously every 4 weeks), Arm B (ianalumab 9 mg/kg intravenously every 4 weeks) or Arm C (placebo intravenously every 4 weeks).

During this 16-week randomized treatment period, participants will receive a total of 4 doses of the study treatment, one dose every 4 weeks at the following visits: W1, W5, W9, and W13. The study treatment will be administered via i.v. infusion over 2 hours (+/- 15 min). In addition to the study treatment, the patient will receive premedication (see Section 6.1.1) to mitigate risk of potential systemic infusion-related reactions and supportive care will be also allowed in all treatment arms (see Section 6.8.1). All participants including those who will prematurely discontinue treatment will be monitored every other week (q2w) for efficacy and safety up to W17 which concludes the treatment period. All participants will have to perform the EOT assessments either at W17 or at time of early treatment discontinuation: ECG, collect biomarkers samples (proteomic and transcriptomics), serum pregnancy test for female participants, TFQ and the EOT disposition:

- For participants who have received the 4 doses, these assessments will have to be done at W17.
- For participants who early discontinue the study treatment, they will have to be performed during the discontinuation visit which should be the visit when decision to discontinue is made, or latest the next regular visit per schedule of assessments.

After completion of the 16-week randomized treatment period, all participants will enter the primary endpoint follow-up period to be monitored for efficacy until W25, which is the last visit for assessment of the primary endpoint. During this period also safety assessments are done.

Participants not responding to treatment at W17 may be eligible to enter the open-label extension period for placebo treated participants after W17 (see Section 6.5.5 for details).

Safety and Efficacy Follow-Up period:

After completing the treatment period, all participants (including early study treatment discontinuation) will be monitored for safety. They will enter a full safety monitoring on a monthly basis for at least 20 weeks after the last study treatment dose (short-term safety follow-up). After these 20 weeks, participants will continue to be monitored monthly/quarterly and safety follow-up will be restricted to selected AEs/SAEs potentially related to B-cell depletion (regardless of causality with ianalumab), SAEs suspected to be related to ianalumab (see Section 10.7) and selected B-cell related lab parameters (see Table 1-3 and Table 1-4), for up to 2 years after the last study treatment dose (long-term safety follow-up).

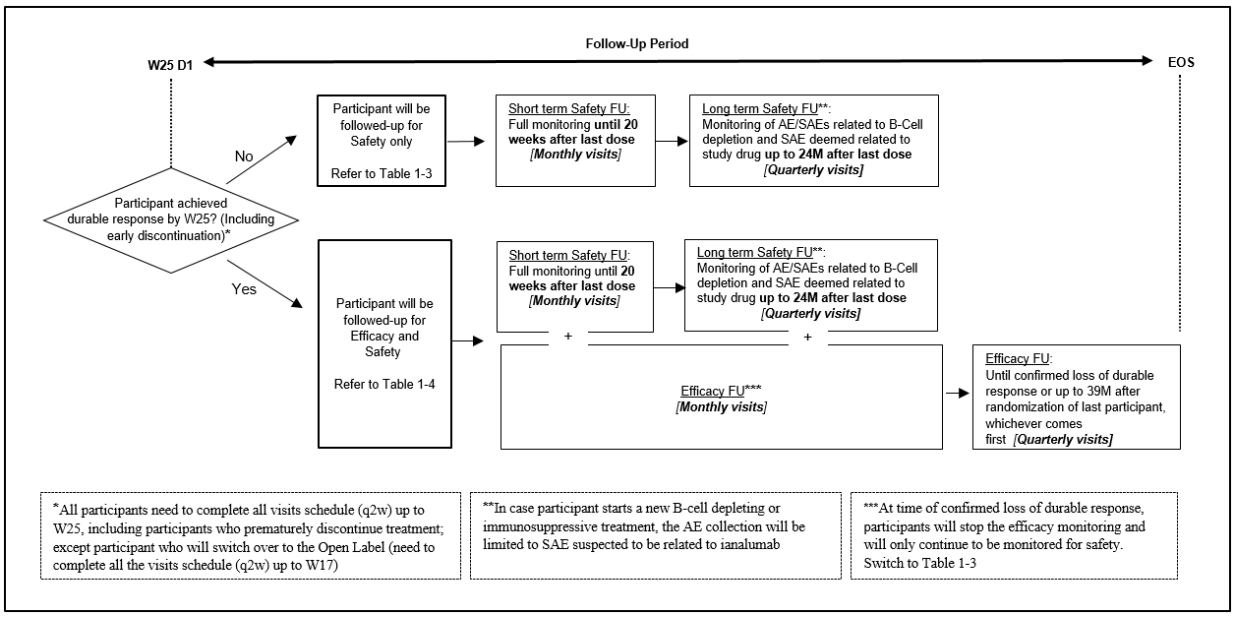
In case the participant starts a new B-cell depleting or immunosuppressing treatment, the AE collection during long-term safety follow-up will be limited to the SAEs suspected to be related to ianalumab.

In parallel to the safety monitoring (short-term and long-term safety follow-up) as described above, all participants who did not yet meet the criteria of confirmed loss of durable response (see definition in Section 3.2 on key secondary endpoint) will be followed for efficacy until confirmed loss of durable response or up to 39 months after randomization of the last participant, whichever occurs first. This includes participants who have completed the treatment period as well as participants who prematurely discontinued the treatment but remain in the study.

In addition, throughout the entire safety and efficacy follow-up period, information regarding PROs and medical resources utilization (event of hospitalization, outpatient visit or Emergency Room visit due to underlying disease or its management), concomitant medications including rescue treatments, concomitant procedures, subsequent anti-wAIHA treatments will be collected.

Details of corresponding follow-up visits (safety only or overlapping safety/efficacy follow-up, depending on whether the participant has not met the criteria for confirmed loss of durable response) are described in the below charter (Figure 4-2) and paragraphs.

Figure 4-2 Follow-Up Period Post Treatment: Safety and Efficacy Follow-Up



1) Participants not in durable response at W25 will be followed for safety only. Refer to Table 1-3 for the schedule of activities:

- For participants who complete the treatment period (4 doses), the monthly safety follow-up visits will be part of W17 (EOT) and the subsequent regular visits up to STFU2 (end of short-term safety follow-up). Refer to Table 1-1 and Table 1-3.
- For participants who discontinue study treatment before W13, they will perform the following additional EOT assessments: ECG, collect biomarkers samples (proteomic and transcriptomic), serum pregnancy test for female participants, TFQ and the EOT disposition at time of the discontinuation visit, i.e., either at the visit when the decision was made to discontinue treatment, or at the next regular visit. They will then continue all visits to W25 (the additional EOT assessments should not be repeated during W17 visit), and the follow up period visits. Safety follow-up visits will be scheduled based on the last received dose, monthly after date of last dose. The safety follow-up visits will overlap with the treatment period and primary endpoint FU visits. The following scenarios should be considered depending on the time of participant's study treatment discontinuation, as an example:
  - Participants getting W9 infusion as last dose should complete all visits until W25, then four weeks later STFU2, and then all LTFU visits, starting with LTFU1, 4 weeks after STFU2. STFU1 (intended for 16 weeks after the last dose) is not needed, as W25 covers the safety follow up 16 weeks after last dose.
  - Participants getting W5 infusion as last dose reach the end of the 20 weeks safety follow up at the W25 visit. They should complete all visits until W25, then proceed with all LTFU visits, starting with LTFU1, 4 weeks after W25.
  - Participants getting W1 infusion as last dose reach end of the 20 weeks safety follow up at the W21 visit. They need to continue to W25 for primary endpoint assessments and then proceed with LTFU3, 12 weeks after W25.

Refer to Table 1-1 and Table 1-3.

In case participant starts a new line of wAIHA therapy:

- During Short-term safety follow-up period, any subsequent wAIHA therapy will be collected and the participant will complete all the visits up to W25, STFU1 and STFU2; all AE/SAE, concomitant therapies including use of rescue/prohibited treatment, medical resource utilization and PRO questionnaires must be collected, and clinical safety laboratory assessments performed.

During Long-term safety follow up period, any subsequent wAIHA therapy will be collected and the AE reporting will be limited to collection of AE/SAE potentially related to B-cells depletion (regardless of causality with ianalumab) and SAE suspected to be related to ianalumab. In case a participant starts a new B-cell depleting treatment or immunosuppressing treatment SAE collection will be limited only to events suspected to be related to ianalumab. In addition, concomitant therapies including use of rescue/prohibited treatment and medical resource utilization and PRO questionnaires will be collected.

2) Participants in durable response after W25 will be followed after W25 for both safety and efficacy. Refer to Table 1-4 for the schedule of activities, which includes additional visits for efficacy follow-up:

- Participants who complete the treatment period (4 doses) follow the visit schedule through W25, STFU1, STFU2 and the LTFU visits.
- For participants who discontinue treatment early, same rules for safety visit scheduling as described above apply, with the exception below:
  - Participants getting W1 infusion as last dose reach the end of the 20 weeks safety follow up at the W21 visit. They need to continue to W25 for primary endpoint assessments and then proceed with LTFU2 4 weeks after W25.

At time of confirmed loss of durable response, participant will stop the efficacy monitoring and will continue only the safety monitoring. Participants will switch to Table 1-3.

Open label cross-over period:

Participants who do not show hemoglobin response at W17 (response defined as Hb ≥10 g/dL and ≥2 g/dL increase from baseline, in the absence of rescue/prohibited treatment) or no response at W15 (if W17 assessment is missing) may be unblinded: if the participant was on ianalumab, he/she will be followed for safety as described above; if the participant was on placebo, he/she will be given the opportunity to receive four doses of ianalumab at 9 mg/kg every four weeks, open-label. After these four doses, the participants will be followed-up for safety and efficacy using the same rules for visits and assessments as defined for participants coming from the randomized treatment period. Please refer to Section 6.5.5 for details on the open label treatment option.

Remote procedures

At entry in the study, participant's capacity/willingness to perform some clinical trial procedures remotely during the long-term safety and efficacy follow-up will be collected. At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical

condition, qualifying participants will be offered the option to have clinical trial procedures during long-term safety and efficacy follow-up according to Section 1.3 Schedule of Activities performed at a remote location.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight. The Investigator retains accountability for all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

The remote procedures will be utilized in certain countries and sites as determined by protocol needs and based on national and local/site regulations.

The off-site healthcare professionals will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff may perform certain procedures remotely using tele-visits.

Please refer to Section 8.11 for details on the off-site visits.

4.2 Scientific rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall (parallel group comparison)	The need for a direct comparison to demonstrate superiority of ianalumab over placebo
Randomization and stratification	Enable the evaluation of the benefit-risk of the ianalumab dose regimens in an adequate and well-controlled setting, minimize potential bias in patient allocation Because of the overlap in its mechanism of action with the trial drug, the prior use of rituximab (yes vs no) is an important factor to stratify the study population.
Blinding (double blind)	Minimize potential bias in management and reporting of safety and efficacy data and ensure integrity of data collection and credibility of study conclusions
Inclusion of patients who failed at least one prior line of treatment	The front-line therapy generally provides an acceptable level of disease control. However, most patients do not achieve confirmed response and relapse, or become resistant/intolerant to the treatment, therefore requiring re-treatment or subsequent lines of therapy. Ianalumab is considered an appropriate treatment option for this patient population with unmet medical need
Inclusion of patients with primary or secondary wAIHA	The pathogenesis and clinical manifestation of primary and several secondary wAIHA are similar and associated with disruption of B-cell immune tolerance. Therefore, these patients are expected to benefit from the study treatment, and thus will be included in the study.
Inclusion of patients with hemoglobin level below 10 g/dL	Patients with hemoglobin level below 10 g/dL have decompensated hemolytic anemia and therefore require treatment to increase the level of hemoglobin.
Supportive care and rescue medication	To avoid fast deterioration of hemoglobin level and to prevent patients from experiencing complications during the study, supportive care is allowed in all study arms In case study treatment and supportive care are not sufficient to control the patients' condition and if clinically indicated, rescue medication could be administered.
Control arm (placebo)	No active comparator is used, as there is no approved systemic treatment for patients with wAIHA. Patients can receive allowable supportive care while on study (Section 6.8.1.1)

Study Design Aspect	Rationale
Dose selection and duration of treatment period	The doses, regimen, route of administration, and treatment duration were selected with the aim to achieve: ● rapid, profound and consistent depletion of B-cells, and ● complete inhibition of the BAFF-R pathway in both blood and tissues, ● induction of quick and confirmed response that is maintained after the end of the discrete treatment duration, allowing patients to stay off treatment with adequate hemoglobin levels. Please also refer to Section 4.3
Primary endpoint	Achievement and maintenance of sufficient hemoglobin level are important for the patients' health, well-being, and quality of life. Hemoglobin response has been used and accepted as a regulatory endpoint in other hemolytic/anemia diseases The First International Consensus Meeting on AIHA defines treatment response as increase in hemoglobin by >2 g/dL or normalization of hemoglobin without biochemical resolution of hemolysis, and absence of red blood cells transfusion for the last 7 days (Jäger et al 2020). To obtain reliable results and account for fluctuations, the targeted hemoglobin levels should be maintained for at least 8 weeks.
Primary endpoint assessment (W9 - W25)	The hemoglobin assessments during first 8-week period will be excluded from the primary efficacy assessment to ensure sufficient time to develop an effect of ianalumab and assess its durability. The interval between W9 - W25 should be sufficient to assess durable hemoglobin response which should last at least eight consecutive weeks.
Duration of safety follow-up (at least 20 weeks and up to 2 years post last dose of study treatment)	During the first 20 weeks, a full safety monitoring will be conducted. After the first 20 weeks of full monitoring, as some participant may not have yet recovered the baseline B-cell level, and the information will not be available to avoid trial unblinding, the following will be applied: the safety data collection will focus only on the AEs/SAEs potentially related to B-cell depletion as well SAEs suspected to be related to ianalumab and the monitoring of B-cells, to determine the time to B-cell recovery as well as to ensure participants' safety in light of potential risks associated with prolonged B-cells depletion and potential associated side effects (e.g. infections).
Duration of efficacy follow-up (until confirmed loss of durable response or 39 months after randomization of the last participant, whichever comes first)	Monitoring of duration of response, and evaluation of the longer-term, disease modification potential of ianalumab. Based on recruitment projections and assumptions on the speed and amount of events "loss of durable response", more than 90% of the patients will meet criteria for loss of durable response during the first three years after the last dose of the last participant randomized.
Open label cross-over	To collect additional information on ianalumab, as well as to offer the option to receive treatment with four doses of ianalumab to participants who received placebo and did not reach confirmed response until the end of the treatment period.

4.3 Justification for dose

Two ianalumab doses (3 mg/kg and 9 mg/kg), administered every 4 weeks (q4w) intravenously (i.v.) as 2-hour infusion for the treatment period of 16 weeks (4 doses in total), will be evaluated.

The doses, regimen, route of administration, and treatment duration were chosen with the aim to 1) achieve rapid, profound and consistent depletion of B cells, 2) complete inhibition of the BAFF-R pathway in both blood and tissues, and 3) with a limited treatment duration, to induce quick and confirmed responses that are maintained after the end of the treatment period, allowing patients to stay off treatment with adequate hemoglobin levels.

Treatment duration

The placebo-controlled, proof-of-concept study CVAY736X2201 conducted in 27 pSS patients provided the first evidence of potential clinical benefit of ianalumab short treatment courses. In this study, an efficient depletion of circulating B cells and clear signs of efficacy, which persisted for a subset of clinical outcomes up to EoS in the higher dose group, were observed after a single i.v. dose of ianalumab (either 3 mg/kg or 10 mg/kg).

In addition, a recent clinical study (Mahévas et al 2021) tested the anti-BAFF antibody belimumab (5 doses of 10 mg/kg i.v. for up to 12 weeks) given together with rituximab (2 doses of 1000 mg i.v. for up to 2 weeks) in 15 patients with persistent or refractory ITP, an autoimmune disease pathophysiologically closely related to wAIHA. Eighty percent of patients responded to this combination and maintained the response for 12 months. Ianalumab is characterized by a dual MoA and as such, combines BAFF-pathway blockade and ADCC-mediated peripheral B-cell depletion, similarly to the MoA of the combination of rituximab and belimumab investigated by Mahévas et al 2021.

Therefore, a 16-week ianalumab treatment duration (4 infusions q4w) was selected for this study.

Selected ianalumab doses and regimen in the double-blinded treatment period

9 mg/kg i.v. dose of ianalumab is selected, as it is the highest ianalumab dose so far tested as multiple-dose in clinical trials, with a favorable safety profile. At this dose, rapid and most extensive blockade of the BAFF pathway is expected to target the most confirmed response, after the 4-dose treatment. Simulated concentration-time profiles after ianalumab 9 mg/kg i.v. doses q4w results in mean Cmax and AUC0-28day after last ianalumab dose within those previously observed in CLL patients after multiple 9 mg/kg q2w doses (n=4) and below those observed in nonclinical toxicology studies.

3 mg/kg i.v. dose of ianalumab is selected as this is the lowest i.v. dose which was previously shown to result in clinical response in indications other than wAIHA (studies CVAY736X2101 and CVAY736X2201, in RA and pSS patients, respectively).

Q4w regimen: PopPK and PK-PD simulations of i.v. ianalumab doses of 3 and 9 mg/kg administered as 2-hour infusion q4w were performed. At these doses and regimen, ianalumab Ctrough values are predicted to be above the steady-state Ctrough observed with ianalumab s.c. doses of 300 mg q4w (most effective dose in the multiple-dose study CVAY736A2201 in pSS patients) in 50% and 92% of the patients, respectively, thereby a comparable or higher level of target engagement is anticipated, respectively. Efficient B-cell depletion is predicted for both 3 mg/kg and 9 mg/kg i.v. q4w doses, and average B-cell recovery to 80% baseline or ≥50 cells/ µL after last dose is similar and predicted by 27 and 28 weeks, respectively. No clinically relevant accumulation is anticipated with the q4w regimen, in line with ianalumab half-life of approximately 10 days.

2-hour infusion and 4-hour infusion of ianalumab have been safely administered to patients across studies, and therefore the 2-hour infusion is selected, to minimize burden to patients.

The **i.v. route of administration** is preferred as highest and targeted exposure with established and favorable safety profile in clinical setting across diseases has been achieved using this route.

The i.v. route also has the advantage of lower risks to incur into local site reactions, as observed with s.c. dosing, and for which a dose-dependency was observed. The short course of ianalumab treatment in this study in wAIHA patients will require a total of 4 monthly infusions.

Ianalumab treatment has been generally well tolerated, with most AEs being mild to moderate in severity. Overall frequency of AEs across studied doses has been similar, except for local injection-related reactions which showed a dose-response (study CVAY7236A2201), and therefore, are not considered relevant for the i.v. administration route. Infections and infestations has been the most frequently reported system organ class (SOC) category. The majority of AEs in this category have been mild to moderate and non-serious events that did not lead to discontinuation of the treatment.

Selected ianalumab doses and regimen in the open-label cross-over treatment period

At the time participants will start entering the open-label cross-over period of the study, the results from the primary analysis from the double-blinded treatment period will not yet be available. Therefore, participants who are eligible and willing to enter the open-label cross-over period will be offered the higher and potentially most efficacious dose of ianalumab, i.e., i.v. 9 mg/kg q4w. At this dose faster and more extensive blockade of the BAFF pathway and depletion of pathogenic B-cells (both in blood and tissues), compared to the lower dose of 3 mg/kg, is anticipated, thereby increasing the chances of achieving durable responses. Based on the favorable safety profile of ianalumab, both ianalumab doses (3 mg/kg and 9 mg/kg) are expected to be well tolerated with comparable safety profiles.

4.3.1 Rationale for choice of supportive care

Supportive care consists of steroids (predniso(lo)ne up to 15 mg/day), erythropoietin alpha, beta, or delta 10’000 units/week, or danazol 200 mg three times/day. Based on the expert’s opinion, the dose of predniso(lo)ne up to 15 mg/day is most appropriate to stabilize wAIHA patients during the steroid tapering. Danazol in dose of 200 mg three times per day is recommended by Jaeger (Jäger et al 2020) as a further line of anti-wAIHA treatment. Administration of erythropoietin has been successfully used in patients with refractory AIHA, particularly in the presence of reticulocytopenia (Fattizzo et al 2021). Epoetin alfa in dose of 10’000 units per week was successfully used as a maintenance treatment for the anemia of chronic kidney disease (Provenzano et al 2005).

Red blood cells transfusions and intravenous immunoglobulins are allowed if the supportive care described above is not sufficient and a participant requires additional support to maintain the safe level of hemoglobin before ianalumab develops its treatment effect.

Please refer to Section 6.8.1.1 for details about supportive care.

If clinically indicated (e.g., to ensure patient safety), the treating physician may also administer rescue medication, please see Section 6.8.3.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo is used for the control arm in this study, because there are no approved treatments for wAIHA that can be used as active control. However, it is to be noted that placebo patients (like patients from the two ianalumab arms), will also receive supportive care/rescue therapy (if needed) and will thus not remain only with placebo.

Use of a placebo arm in a randomized blinded trial supports unbiased assessment of the benefit/risk in the specific disease setting and the population.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

There is no planned interim analysis before the conduct of the primary analysis (refer to Section 9).

4.7 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure or follow-up shown in Section 1.3 Schedule of Activities for the last participant in the study globally.

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator

After the primary analysis, the study will remain open. Participants still being followed on the study after the primary analysis time point will continue as per the schedule of activities in Section 1.3.

5 Study population

The enrollment target is 90 adult participants with primary or certain secondary wAIHA who failed at least one previous line of treatment (30 participants randomized in each arm).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures.
2. Male or female patients aged 18 years and older on the day of signing informed consent.

3. Participants with primary or secondary wAIHA, as previously documented by a positive direct antiglobulin test (DAT) specific for anti-IgG or anti-IgA, who had an insufficient response to, or relapsed after at least one line of treatment, including patients with steroid resistance, dependence or intolerance.
   - Steroid resistance: failure to obtain hematologic response within 3 weeks on at least 1 mg/kg predniso(lo)ne (up to 60 mg daily in participants weighing over 60 kg).
   - Steroid dependence: Need to continue predniso(lo)ne at a dose of >10 mg/day to maintain a response.
   - Steroid intolerance: side effects or anaphylactic/ anaphylactoid reactions which lead to permanent termination of steroids
4. Hemoglobin concentration at screening below 10 g/dL, associated with presence of symptoms related to anemia.
5. The dose of supportive care (see Section 6.8.1.1) must be stable for at least 4 weeks prior to the randomization into the study.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients with wAIHA secondary to hematologic disease involving bone marrow (e.g., CLL) or other immunologic disease requiring immunosuppressant treatments that are not allowed in this study (please refer to Section 6.8.2 Prohibited Medication).
2. Presence of other forms of AIHA (cold or intermediate forms), Evans Syndrome or other cytopenias.
3. Prior use of B-cell depleting therapy (e.g., rituximab) within 12 weeks prior to randomization.

   If other immunosuppressive therapies were used prior the screening, a wash-out period should be applied (see Section 10.8 for details)
4. [removed]
5. Patients with following conditions at screening:
   - Neutrophils: <1000/mm^3
   - Serum creatinine >1.5 × upper limit of normal (ULN)
6. Active viral, bacterial or other infections (including tuberculosis -TB or SARS-CoV-2) requiring systemic treatment at the time of screening or history of recurrent clinically significant infection (e.g., bacterial infections with encapsulated organisms).
7. Positivity for hepatitis C virus (concomitant positivity for HCV antibodies), hepatitis B surface antigen (HbsAg), or hepatitis B core antibody (HbcAb) at screening.
8. Known history of primary or secondary immunodeficiency, or a positive human immune deficiency virus (HIV) (ELISA and Western blot) test result at screening.
9. Live or live-attenuated vaccination within 4 weeks before randomization.
10. Nursing or pregnancy (positive serum or urine B-human chorionic gonadotrophin (B-hCG) pregnancy test) at screening or pre-dose on Day 1.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during

the study and until six months after last dose of study drug. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy, with or without hysterectomy), total hysterectomy or female bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment in study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential. If local regulations are more stringent from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

12. Previous or concurrent malignancy except for curatively treated non-melanoma skin cancer, in situ cancer (e.g., cervix, breast, bladder, prostate), and cancer in complete remission for at least 3 years and without evidence of recurrence.
13. History of splenectomy.
14. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with patient's efficacy, safety, obtaining informed consent or compliance with the study procedures as per investigator discretion.
15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to ianalumab or drugs chemically related to ianalumab or excipients that contraindicate their participation.
16. Concurrent participation in an investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longest. Note: parallel enrollment in a disease registry is permitted.

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not assigned to study treatment. A minimal

set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures.

The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). Minimal information to be recorded on the appropriate Case Report Forms includes informed consent, demography, eligibility criteria, reason for screen failure and any serious adverse event that may have happened during screening period (see SAE section, Section 8.6.3, for reporting details). No other data will be entered into the clinical database. Screen failure event must be recorded in the IRT system. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are randomized and fail to start treatment, e.g., ineligible participants randomized, will be considered an early terminator. The reason should be recorded on the appropriate Case Report Form.

For details on screening and re-screening, please see Section 8.1.

5.3.1 Replacement policy

Participants who have been randomized and discontinue study drug treatment or study early will not be replaced.

5.3.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

If the investigator chooses to rescreen a participant after screen failure, a new ICF will need to be signed and the participant will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

Novartis Global Clinical Supplies (GCS) will supply the investigational drug ianalumab (VAY736) and placebo in either clinical supply formulation (CSF) presentation or final market image (FMI) presentation either through Novartis central depots or Novartis local offices. The FMI may be supplied at later stage and will only be used in newly enrolled patients. A switch in formulation within the same patient is not allowed.

The semi-blinded pharmacist (blinded to the treatment arm but unblinded to the dose level) or designated personnel will prepare an individual dose to study participants (as assigned by the IRT system) and it will be administered via i.v. infusion over 2 hours (+/- 15 min). Refer to [CVAY736O12301 Pharmacy Manual] for further instructions on medication handling and preparation.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
VAY736 (ianalumab) 150 mg/1mL	Concentrate for solution for infusion	Intravenous use	Double-Blinded[1], liquid in vial	Sponsor (global)
Placebo 0 mg/1mL	Concentrate for solution for infusion	Intravenous use	Double-Blinded[1], liquid in vial	Sponsor (global)
VAY736 (ianalumab) 150 mg/1mL	Concentrate for solution for infusion	Intravenous use	Open-Label[2], liquid in vial	Sponsor (global)

[1]Double-Blinded material will be used in the randomized double-blinded treatment period
[2]Open-Label material will be used in the open label cross-over treatment period

6.1.1 Additional study treatments

Infusion related reactions (IRR) have been observed with ianalumab administration. To mitigate the risk of potential systemic infusion-related reactions, 30 minutes to 2 hours prior the first two administrations of the study treatment (ianalumab or placebo), participants will receive standard premedication, which include oral acetaminophen 1000 mg (1g or equivalent), oral or intravenous antihistamine, and intravenous corticosteroid (prednisolone 100 mg or equivalent) or similar prophylaxis based on institutional guidelines. If medically indicated, this premedication should be applied prior to subsequent infusions.

Premedication drugs will be provided by the investigational site.

Please refer to Section 8.6.1 for reporting and Table 6-3 for further guidance on the management of ianalumab infusion reactions.

6.1.2 Treatment arms/group

Participants, who meet all the inclusion/exclusion criteria, will be randomized on W1 visit to one of the following three treatment arms/groups in a ratio of 1:1:1:

- Arm A (investigational): ianalumab 3 mg/kg intravenously every 4 weeks (4 doses in total)
- Arm B (investigational): ianalumab: 9 mg/kg intravenously every 4 weeks (4 doses in total)
- Arm C (control): placebo intravenously every 4 weeks (4 doses in total)

Randomization of participants will be stratified according to the prior use of rituximab (yes vs. no).

Participants in the placebo arm who show no hemoglobin response at W17 (response defined as Hb ≥10 g/dL and ≥2 g/dL increase from baseline, in the absence of rescue/prohibited

treatment) or no response at W15 (if W17 assessment is missing) will have the option to switch to the following treatment extension period:

- Open-label ianalumab: 9 mg/kg intravenously every 4 weeks (4 doses in total)

6.1.3 Guidelines for continuation of treatment

Not applicable.

6.1.4 Treatment duration

The on-treatment period runs over a period of 16 weeks and includes a total of four doses of one of the treatment arms (see Section 6.1.2), administered every 4 weeks at the following visits: W1, W5, W9, and W13. The visit W17, 28 days after the last dose, concludes the treatment period. Participants may be discontinued from treatment or interrupt it temporarily or have an infusion delay, however, these patients will continue to be monitored every other week until end of this on-treatment period.

Participants who did not respond until end of the on-treatment period, may be unblinded and if found on placebo will be given the option to enter the open-label extension period in which participants will receive a total of four doses of ianalumab 9 mg/kg for a period of 16 weeks (see Section 6.5.5).

6.1.4.1 Treatment after confirmed loss of durable response

Participants who met any of criteria for confirmed loss of durable response should be treated as per local practices and guidelines for wAIHA. These participants will be followed-up for safety as described in Section 1.3 and Section 8.4.

6.1.4.2 Treatment beyond disease progression

Not applicable.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described in Table 6-1.

The [CVAY736O12301 Pharmacy Manual] will be provided to investigational sites and contains detailed information on the preparation of the study treatment (ianalumab 3mg/kg or 9mg/kg and placebo).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document for drug accountability.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated

site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified the labels and in the [ianalumab IB].

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff (semi-blinded pharmacist) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration (e.g., i.v. bags).

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

Not applicable.

6.2.3 Instruction for prescribing and taking study treatment

Study treatment (ianalumab or placebo) is provided by the sponsor in a blinded manner.

The study treatment solution (ianalumab or placebo) will be prepared by a pharmacist or designated personnel appropriately qualified and trained in the preparation procedure in accordance with the [CVAY736O12301 Pharmacy Manual]. Based on patient body weight, the study treatment will be administered after dilution by intravenous (i.v.) infusion over 2 hours (+/- 15 min) once every 4 weeks (q4w) at the study center. In case of infusion reaction, the total administration time can be adjusted. The instruction for dose preparation, administration and storage conditions are described in the [CVAY736O12301 Pharmacy Manual].

All kits of study treatment (ianalumab/placebo) assigned by the IRT will be recorded in the IRT system.

All study treatment dose prescribed to the patients and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

At each dosing visit (W1, W5, W9, W13 during double-blind treatment period and CO W1, CO W5, CO W9 and CO W13 during open label/cross-over period), all study assessments including completion of Patient Reported Outcomes (PROs) and Pre-dose PK/ADA samples collection should be completed prior to the administration of the study treatment, refer to Section 1.3 for recommended order of assessments

Instructions on dosing window and dosing delays

Any effort should be made to perform the dosing visits within the visit windows outlined in Section 1.3: +/- 3 days of the target visit date.

Refer to Section 6.5.2 and Table 6-3 for guidance on dose interruptions due to adverse events.

In case of delay for any other reason (e.g., operational hurdle, pandemic), consultation and agreement with Novartis on a case-by-case basis will be necessary.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At W1 visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify unique medication numbers for the packages of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

90 participants will be randomized in a 1:1:1 ratio, to either 9 mg/kg dose of ianalumab, 3 mg/kg dose of ianalumab, or placebo. Central randomization will be stratified by the prior use of rituximab (yes vs. no).

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office. In order to achieve the randomization ratio of 1:1:1 to the 3 treatment arms defined above, and to keep the pharmacist blinded to the treatment (see Section 6.3.2: the semi-blinded pharmacist will only be informed about the volume to be infused, without knowing if it's placebo or ianalumab), the randomization list will be generated by considering a ratio of 2:2:1:1 to the following treatment arms respectively: ianalumab 3 mg/kg, ianalumab 9 mg/kg, placebo 3 mg/kg, placebo 9 mg/kg.

6.3.2 Treatment blinding

This is a randomized, double-blind, placebo-controlled trial with an open-label cross-over period.

Participants, investigators, investigator staff, persons performing the assessments (including the Off-site Research Nurse (ORN)) and Novartis Clinical Trial Team (CTT), will remain blinded to the identity of the treatment from the time of randomization until database lock of the primary analysis or until switching the participants to open-label cross-over period, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study, except for some selected roles indicated in Table 6-2:
  - A semi-blinded pharmacist (blinded to the treatment arm but unblinded to the dose level) or delegate, who prepares the individual doses of study treatment for study participants (no unblinding information will be entered in the CRF by the pharmacist).
  - An independent analysis team who needs to prepare data reports for the DMC.
  - The randomization codes associated with participants from whom PK samples are taken will be disclosed to bioanalytical analysts who will keep PK results confidential until database lock.
  - These personnel will not be involved in any other trial activities.
- The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, route and schedule of administration. The pharmacist will only be informed about the volume to be infused (to match 3 mg/kg or 9 mg/kg dose) without knowing if it's placebo or ianalumab. The rest of the site and study staff will be fully blinded, including to the dose.
- Blood samples for PK, immunogenicity, CD19+ and soluble BAFF assessments (collected for all study participants in order to maintain blinding) will be kept confidential until database lock. At the time of PK analysis only the ianalumab PK samples will be tested for exposure.
- Data with unblinding potential (i.e., post baseline results for CD19+ B-cell counts, and soluble BAFF results) will be blinded until the database lock for primary analysis.
- Independent sponsor staff, not involved in trial activities may be appointed to handle and review biomarker data with unblinding potential while the study is ongoing.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site (IRT). As a result, the participant should be discontinued from the study treatment.

Please refer to Table 6-2 below for details on the blinding levels of the randomized double blinded part.

Before switching any eligible participant to open label part, the data of this participant will be cleaned and frozen up to W17 in the clinical database; only after completion of these steps (see description in Section 6.5.5), the individual unblinding process can be started to know whether the participant was on placebo and can be switched to the open label ianalumab 9 mg/kg. If the participant is not eligible for the open-label/cross-over period, the blinding will be maintained to the participant/site staff/sponsor CTT.

Table 6-2 Blinding and unblinding plan in the double blinded period

	Time or Event				
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety Event (single subject unblinded)**	**Safety Review**	**Single unblinding at time of open label cross-over**
Participants	B	B	UI	B	UI*
Site Staff	B	B	UI	B	UI*
Off-site research nurse	B	B	UI	B	NA
Sponsor CTT	B	B	B	B	UI*
Randomization Office	UI	UI	UI	UI	UI
Global Clinical Supplies (GCS)	UI	UI	UI	UI	UI
Semi-blinded pharmacist or semi-blinded monitor	SB	SB	NA	NA	NA
Unblinded Sponsor Staff (i.e. for study treatment, sample analyst, cross-over coordinator)	UI	UI	NA	NA	UI
Independent committees (DMC)	UI	UI	NA	UI	NA
Independent Statistician/statistical programmer/data analyst (i.e. biomarkers, PK)	UI	UI	NA	UI	NA

B = Completely blinded, SB = Semi-blinded, NA = Not applicable, UI = Unblinded to individual participant treatment codes
* only unblinded to placebo participants approved to enter open label part

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the participant safely.

Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the Investigator to select the participant's next treatment regimen, and after discussion and agreement with Novartis.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number,
- participant number.

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.4 Study treatment compliance

Infusions will be administered in the clinic. This information must be captured in the source document, the appropriate CRF/s and in the Drug Accountability Log.

Compliance to the planned administration scheduled is expected to be high since the study treatment (i.v. infusion every 4 weeks) will be administered by trained study personnel. Compliance can also be assessed by means of site and patient-specific drug accountability by Novartis study personnel during the site monitoring visits using medication pack numbers, Drug Label Form information and information collected by IRT system.

6.5 Dose modification

Adjustment of the dose or administration of a partial dose of the study treatment is not permitted.

Dose omission and treatment discontinuation might be required for safety reasons as noted in Table 6-3.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated in order to allow participants to continue the study treatment. These dose changes must be recorded on the appropriate CRF.

These dose interruptions are summarized in Table 6-3. Deviations to mandatory dose interruptions are not allowed. Permanent discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-3 or listed in Section 6.8.2.

In case a dose needs to be delayed due to adverse events, the maximum allowed delay is 14 days and the subsequent dose should be given as per original schedule. If a dose has to be delayed by more than 14 days, the dose should be omitted, and the patient should come back for the next planned dose.

In case of delay for any other reason (e.g., operational hurdle, pandemic), consultation and agreement with Novartis on a case-by-case basis will be necessary.

Table 6-3 Criteria for dose interruption and re-initiation of study treatment for adverse drug reactions

Worst toxicity[a] CTCAE Grade (value) during a cycle of therapy
Investigations (Hematologic)
Neutropenia (ANC)

Worst toxicity[a] **CTCAE Grade (value) during a cycle of therapy**	
Grade 3 (ANC < 1000 – 500/mm^3) or Grade 4 (ANC < 500/mm^3)	Recommendation: ● monitor and determine if other causes are possible ● if persistent and not explained by other causes, re-test and monitor more frequently until the next planned dose, then if not resolved, postpone the dose ● if participant presents with signs and symptoms of infection, postpone the dose If planned dose was postponed for 14 days and neutropenia is not resolved yet, then skipping one dose of study treatment must be considered jointly by the Investigator and Novartis.
Febrile neutropenia (ANC <1.0 x 10^9/L, and fever ≥38.5°C)	Mandatory: Monitor the participant according to local/standard practice and postpone study treatment dose until resolution. If NOT resolved within ≤14 days, then skip one dose. A dose can be postponed ≤14 days only once during the study. In case the event is recurrent discontinue the treatment permanently.
Investigations (Hepatic and renal)	
Hepatic function	Please refer to Section 10.5 Appendix 5 Liver Safety Monitoring
Renal function	Please refer to Section 10.6 Appendix 6 Renal Safety Monitoring
Infections	
Mild (CTCAE Grade 1) to moderate (CTCAE Grade 2)	Recommendation: Maintain study treatment.
Severe or SAE (CTCAE Grade 3 or above)	Mandatory: Postpone the study treatment dose until resolution. If NOT resolved within ≤14 days, skip one dose. A dose can be postponed ≤14 days only once during the study. In case the event is recurrent discontinue the treatment permanently.
Other events	
Severe AE or SAE (CTCAE Grade 3 or above)	Mandatory: Postpone the study treatment dose until resolution. If NOT resolved within ≤14 days, then skip one dose. A dose can be postponed ≤14 days only once during the study. In case the event is recurrent discontinue the treatment permanently.
Infusion-Related Reaction	
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Recommendation: Continue study treatment and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Consider slowing the infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, steroids, NSAIDS, IV fluids); prophylactic medications indicated for ≤24 hours	Recommendation: Interrupt infusion and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Administer appropriate medical therapy (e.g., corticosteroids, paracetamol/acetaminophen or NSAIDs and anti-histamines), as per local institutional guidelines and clinical presentation.

Worst toxicity[a] **CTCAE Grade (value) during a cycle of therapy**	
	If symptoms resolve, restart infusion per investigator discretion at a slower rate (e.g., 50% rate or slower) under continuous observation. Administer premedication before restarting within 1 hour prior to dosing if required as per local institutional guidelines, including at subsequent infusions if needed.
Grade 3 and 4 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Life-threatening consequences; urgent intervention indicated	Mandatory: Permanently discontinue study treatment and initiate appropriate medical care.
[a] Common Terminology Criteria for Adverse Events (CTCAE Version 5)	

6.5.3 Follow-up for toxicities

Participants whose study treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately monthly intervals, until resolution or stabilization of the event.

Appropriate clinical experts should be consulted as deemed necessary for safety events management.

6.5.3.1 Follow-up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN.
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN].

NOTE: Patients with wAIHA tend to have elevated transaminases, especially AST, and indirect BIL due to the hemolytic nature of this condition. Hence, ONLY ALT and Direct BIL need to be emphasized or evaluated to differentiate further between hemolysis due to the study treatment indication (wAIHA) or DILI.

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase (CK). If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion, e.g., using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule-out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation >2.0 x ULN with R value <2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤2), hepatocellular (R ≥5), or mixed (R >2 and <5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule-out possible alternative causes of observed LFT abnormalities.

Table 6-4 Possible alternative causes of observed LFT abnormalities assessment

Disease	Assessment
Hepatitis A, B, C, E	● IgM anti-HAV; HbsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	● IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	● Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	● Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	● Ultrasound or MRI
Hypoxic/ischemic hepatopathy	● Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	● Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	● Caeruloplasmin
Hemochromatosis	● Ferritin, transferrin
Alpha-1-antitrypsin deficiency	● Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e., >50% likely), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant" and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed-up with the outcome clearly documented.

6.5.4 Retreatment criteria

This study does not allow to administer additional doses of investigational drug after the fourth drug administration on W13.

For participants entering the open-label cross-over period, the fourth dose (W13 of open-label cross-over period) is the last dose.

6.5.5 Open-label cross-over

For participants who show no hemoglobin response at W17 (response defined as Hb ≥10 g/dL and ≥2 g/dL increase from baseline, in the absence of rescue/prohibited treatment) or no hemoglobin response at W15 (if W17 assessment is missing), agree to potentially participate in the cross-over part of the study and meet respective eligibility criteria, the investigator can request unblinding of the treatment arm after completion of the treatment period (after W17 visit completed). In case the participant was assigned to the placebo arm, open label administration of 4 doses of ianalumab at 9 mg/kg every 4 weeks can be done. Upon request for open label treatment for the participant by the investigator, Novartis will review the case, clean and freeze the data of this participant up to W17 in the clinical database. Only after completion of these steps, the unblinding process can be started. In case the participant was on placebo arm and all eligibility criteria are met, Novartis will provide a written statement to site that the open label treatment is approved and assignment of open label drug was enabled in IRT for this patient. Participants need to continue with all scheduled visits until the endorsement (or rejection, if not eligible or not on placebo arm) for open label treatment from Novartis has been obtained.

Eligibility criteria for open label cross-over

The participant must meet the following criteria before administration of the first dose of open label drug:

1. The participant must have completed W17 and must not have achieved the criteria for durable response (according to the primary endpoint definition) before W17, and must not show hemoglobin response on W17, or at W15 (if W17 assessment is missing). See details above.
2. Per investigator assessment, benefit of treatment with ianalumab is expected

3. Hemoglobin: (Hb) below 10 g/dL at the last visit before administration of rescue treatment (if any).
4. Absolute neutrophil count ≥1000 /mm^3 at the last visit
5. Serum creatinine <1.5x ULN at the last visit
6. No prohibited medications before first dose of open label ianalumab
7. No active viral, bacterial, or other infection requiring systemic treatment before first dose of open label ianalumab
8. No known positivity for HIV, HBV, or HCV
9. No nursing or pregnancy
10. Participants consent to receive open label treatment is documented in the source files at site
11. The participant was initially randomized to placebo arm and did not receive any dose of ianalumab (e.g., due to kit assignment error)
12. Investigator has received written confirmation from Novartis that the participant was unblinded, was assigned to placebo arm, and that sponsor agrees to start open label treatment

In case a participant does not match a lab test-related eligibility criteria, the lab test can be repeated once. If the repeated test again does not match the criteria above, then the site should discuss with the sponsor's medical monitor if the participant can enter the open label treatment.

Open label treatment should be initiated as soon as possible and not later than 30 days after unblinding the patient. In case the crossover treatment cannot be started before time of the next regular visit (i.e., W19), then the planned visits have to be performed as per Table 1-3. Once first open label dose can be administered, continue with Table 1-2 cross-over period. After completion of the open label treatment, the participant continues with all visits as described in Table 1-3 or Table 1-4, including the W19 to W25 visits.

Open-label cross-over period

The participant will receive 4 doses of 9 mg/kg ianalumab over 16 weeks, following the same treatment scheme as during blinded treatment period: doses will be given at CO W1, CO W5, CO W9, and CO W13 of the open label period. The drug administration follows the same rules as defined for the blinded treatment period (see Section 6).

If participants received rescue medications during the double blinded period, as soon as the decision to join the open label cross-over has been made, tapering of steroids should be started so by the end of CO Week 8 the dose of predniso(lo)ne be maximum 15mg (see Section 6.8.1.1).

Administration of prohibited treatment (Section 6.8.2) requires discontinuation of open-label study treatment.

Assessments during open label cross-over period

Participants in open label cross-over period need to follow the schedule of visits and assessments as shown in Table 1-2, and subsequently the follow-up assessments described in Table 1-3 and/or Table 1-4, starting with the W19 visit.

After the primary endpoint follow-up period, the participant will enter the safety follow- up phase with visits every four weeks for 20 weeks after last dose, and afterwards visits every 12 weeks until 24 months after last dose.

Participants who did not meet any of the criteria for confirmed loss of durable response will also be followed for efficacy every four weeks until 2 years after last dose and afterwards every 12 weeks until 39 months after the last patient was randomized, or until confirmed loss of durable response, whichever comes first.

6.6 Continued access to study treatment after the end of the study

6.6.1 Post-trial access

Ianalumab is administered once for four cycles over a period of 16 weeks. As the drug is investigational and efficacy and safety in wAIHA have not been confirmed yet, there is no additional treatment with study drug allowed within the scope of this study, and no post trial access is needed. Participants should be treated per local standards and guidelines after discontinuing the study.

Participants on placebo arm that do not achieve confirmed response during blinded treatment period are eligible to receive four cycles of open label ianalumab within this study, per investigator discretion (see Section 6.5.5).

6.7 Treatment of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the next dose should be delayed.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until resolution (at least 10 days).
- Document the quantity of the excess dose as well as the duration of the overdose.
- Obtain a serum sample for PK analysis as soon as possible (collect the date and time of the PK sample and of the last dose of study treatment), if requested by the medical monitor (determined on a case-by-case basis)

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.8.1.1 Allowed Supportive Care

To avoid fast deterioration of hemoglobin level and to prevent patients from experiencing complications during the study, supportive care is allowed in all study arms.

- Supportive care might be administered at discretion of the investigators when clinically needed;
- Supportive care may consist of steroids (predniso(lo)ne up to 15 mg/day), erythropoetin alpha, beta, or delta 10'000 units/week, danazol 200 mg three times/day;
- The dose of supportive care should be stable for at least 4 weeks prior to the randomization into the study and should not be increased during the study;
- Further tapering of any supportive care medications during the study is allowed;
- Re-start of allowed supportive treatments at the pre-enrollment dose or return to the pre-enrollment dose level after dose decrease are not considered as a rescue medication and are allowed.
- Participants may receive RBC transfusions/IVIG if clinically indicated to maintain sufficient level of hemoglobin to be able to participate in the study. However, RBC transfusions/IVIG administration should be discontinued in the participants when administration is not clinically indicated any longer.

Steroids in the doses required for pre-medication before infusions of the study treatment (see Section 6.1.1) and used for treatment of AEs (i.e., infusion-related reactions) are allowed.

6.8.1.2 Permitted concomitant therapy requiring caution and/or action

Monoclonal antibodies, used for prevention or treatment of viral or bacterial infections as well as the antibodies administered intraocular for retinal disease (AMD, DME, etc.) are permitted. Please contact Novartis prior administration of these therapies.

6.8.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after screening.

Table 6-5 Prohibited medication

Medication	Prohibition period	Action taken
Any wAIHA-directed therapy different from what is specified within Section 6.8.3.	All duration (until EOS)	Study treatment discontinuation required; participants should remain in the study and follow the visit schedule.
Live or live attenuated vaccines	At least 4 weeks before randomization, during study treatment period, and until B-cell recovery	Study treatment discontinuation required; participants should remain in the study and follow visit schedule. Consider risk-benefit and following local prescribing information. Increase vigilance regarding infections; remind patients to pay attention to signs and symptoms of infection and instruct them to promptly report any symptoms of infections to the Investigator.
Intravenous or oral immunosuppressive drugs, including B-cell depleting agents	All duration (until EOS)	Study treatment discontinuation required; participants should remain in the study and follow visit schedule. Consider risk-benefit and following local prescribing information. Increase vigilance regarding infections; remind patients to pay attention to signs and symptoms of infection and instruct them to promptly report any symptoms of infections to the Investigator.
Other monoclonal antibodies not mentioned in Section 6.8.1.2.	All duration (until EOS)	Study treatment discontinuation decision and starting other monoclonal antibodies should be discussed with Novartis; patients should remain in the study and follow visit schedule. Increase vigilance regarding infections; remind patients to pay attention to signs and symptoms of infection and instruct them to promptly report any symptoms of infections to the Investigator.
Splenectomy	All duration (until EOS)	Study treatment discontinuation required; participants should remain in the study and follow visit schedule. Increase vigilance regarding infections; remind patients to pay attention to signs and symptoms of infection and instruct them to promptly report any symptoms of infections to the Investigator.
Other experimental therapies	All duration (until EOS)	Study treatment discontinuation required; patients should remain in the safety follow-up.

6.8.3 Rescue treatment

The investigator should prescribe rescue treatment per local practice, with the exception of the medication listed in Section 6.8.2.

The study site will supply rescue medication that will be obtained locally.

The following treatments are considered as rescue medications:

- Any additional wAIHA-directed treatment which is not listed among prohibited medication
- For the double blinded part: an increase in the dosage of the supportive care >20% comparing to the pre-enrollment dose, which is in line with the recommendations with

opinions of the experts. Re-start of allowed supportive treatments at the pre-enrollment dose or return to the pre-enrollment dose level after dose decrease are not considered as a rescue medication.

- For the open-label part: all intakes of supportive care with a dose >20% increase comparing to the pre-enrollment dose, from CO W9, will be considered as rescue treatment.

Red blood cells transfusions/IVIG will be allowed when clinically indicated. See Section 3.1 for more details on how these medications will impact the assessment of efficacy endpoints. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.8.2.
- Any situation in which continued study participation might result in a safety risk to the participant
- Aes or laboratory abnormalities meeting criteria for treatment discontinuation as defined in Table 6-3, reactivation of hepatitis B (i.e., if either HbsAg or HBV-DNA turns positive) or hepatitis C
- Any AE or laboratory abnormality that in the judgment of the investigator, and taking into account the participant`s overall status, prevent the participant from continuing study treatment.
- Following emergency unblinding.

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment prematurely during double-blinded period will be asked to remain in the study, and continue all assessments up to W17 as per schedule of activities in Table 1-1 and then enter the Primary Endpoint, Efficacy and/or Safety follow-up periods as described in Table 1-3 and Table 1-4. During the study treatment discontinuation visit, participants will perform the following additional assessments: ECG, biomarkers

(proteomic, transcriptomic and immune cell subpopulation), serum pregnancy test for female participants, TFQ and the EOT disposition. These additional assessments should not be repeated at W17 visit.

Participant who discontinue from study treatment prematurely during open label cross-over period will be asked to remain in the study, and continue all assessments up to CO W17 as per schedule of activities in Table 1-2 and then enter the Primary Endpoint, Efficacy and/or Safety follow-up periods as described in Table 1-3 and Table 1-4. During the study treatment discontinuation visit, participants will perform the following additional assessments: ECG, biomarkers (proteomic, transcriptomic and immune cell subpopulation), serum pregnancy test for female participants and the EOT disposition. These additional assessments should not be repeated at CO W17 visit.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule to assess the criteria for confirmed loss of durable response. The site will collect any new treatment related to wAIHA condition and Hb value if available from the source document.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Hemoglobin values if available at the source

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts).

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development in wAIHA.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be contacted and/or seen as soon as possible and treated as a participant who discontinued from study treatment, including the applicable post-treatment follow-up as described in Section 7.

The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The

Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

Screening

After signing the study ICF, the screening assessments will be done within 28 days prior to randomization (W1) (see Section 1.3 for the assessments to be performed). The investigator will obtain consent according to local procedures.

Hematology, urinalysis and serum pregnancy test will be measured locally and need to be reported in the clinical database. All other laboratory tests at screening are done by the central lab. Electrocardiograms are done locally.

The investigator should review participants' immunization history and should consider updating the participant's immunization as per local treatment guidelines, in particular Hepatitis B vaccination in participants with risk factors or in areas of high Hepatitis B prevalence.

Re-screening

A participant who has laboratory test result(s) that do not satisfy the entrance criteria may have the test(s) repeated once. These test(s) may be repeated as soon as the investigator believes the retest result(s) are likely to be within the acceptable range to satisfy the entry criteria. The retesting must be completed within the screening visit window (28 days) of the original screening visit date. In this case, the participant will not be required to sign a new ICF, and the original participant number will be used.

In the event that the laboratory test(s) cannot be performed within the visit window of the original screening visit date, or the retest does not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant will be considered a screen failure.

Participants who have failed the initial screening for any reason, may be rescreened.

Re-screening is allowed twice and only after the participant has been registered in IRT as having failed initial screening. In this case, a new participant number will be assigned via IRT and the participant will be identified with this new number for the rest of his/her participation in the study. If a participant has been randomized and treated, a re-screening is not allowed.

A new ICF will need to be signed if the investigator chooses to re-screen a participant that has been screened failed. All required screening activities must be performed when the participant is re-screened for participation in the study. All the re-assessed evaluations should meet the eligibility criteria. Assessments, AEs, and medical history will be assessed relative to the new ICF date.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the [IRT manual].

If a participant is a screen failure, only a limited set of information is required to be entered in the clinical database. Please refer to Section 5.3 or the eCRF completion guidelines.

8.1.1.1 Hepatitis and HIV screening

Hepatitis B and C

All participants will be screened for hepatitis B surface antigen (HbsAg), anti-HBs and anti-HBc antibodies. The tests will be performed by the central laboratory.

- Participants positive for anti-HBs antibodies due to previous vaccination against HBV are eligible.
- Participants tested positive for HbsAg will not be eligible for randomization.
- Participants HbsAg negative, who are hepatitis B core antibody (HbcAb) positive will not be eligible for randomization.

Screening for hepatitis C will be based on HCV antibodies.

HIV

Evaluation for HIV seropositivity will be performed centrally, and, if positive, confirmed by a second technique.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Results will be available as source data and will not be recorded within the eCRF.

Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

8.1.1.2 Tuberculosis (TB) screening

Determination of the tuberculosis (TB) status using medical history, signs, symptoms, and TB testing will be required before administration of study treatment. TB testing per local clinical practice (Quantiferon® TB-Gold test or a purified protein derivative [PPD] skin test) at

Screening is required unless such testing has been done in the past 6 months with documented negative results. For sites that don't have the possibility to test tuberculosis locally, Quantiferon TB-Gold test may be requested by the Central laboratory to assess participant's eligibility.

Quantiferon TB-Gold test

If the test result is negative, the participant may be randomized.

If the test result is positive, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to screening, the participant's results of the workup may be used to assess eligibility if the workup was conducted within 6 months prior to randomization.

NOTE: In case of unclear or indeterminate test results, Investigator should consult with an infectious disease expert to establish absence of active or latent TB infection and document in source data and as a comment in the electronic case report form (eCRF).

PPD skin test

PPD skin test will be performed as an alternative to Quantiferon TB-Gold test in accordance with local guidelines and read at screening or within 6 months prior to randomization in order to evaluate an eventual infection with tuberculosis. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the participant must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the participant has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm is interpreted as positive result.

Participants requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the participant to enter the study).

Participants testing positive for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice, and completed at least 4 weeks before randomization. Participants testing positive for active TB per workup are not eligible for the study. Participants testing negative for TB (no signs of latent or active TB) per workup may be randomized to the trial.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of baseline and demographic characteristics in alignment with CRF.

8.2.1 Demography

The following participant demographics information will be collected in the eCRF:

- Full date (only if required and permitted) or year of birth and/or age, sex, and race/predominant ethnicity (if permitted per local regulations). Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities.
- Height and weight.

8.2.2 Relevant medical history/current medical conditions

For baseline characteristics any relevant medical history/current medical conditions not related to the study indication, and present prior to signing informed consent form (ICF) will be recorded in the Medical History eCRF. This also includes surgical sterilization for women, if applicable. Where possible, the diagnosis and not symptoms should be recorded.

The current and /or previous use of tobacco will be recorded, as well as the estimate number of pack-years based on the approximate consumption per year.

Information related to COVID, including vaccinations against SARS-Cov-2 prior to study entry and during the study (if applicable), COVID prophylaxis will also be collected in specific CRFs.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF if, in their judgment, the test abnormality occurred prior to the ICF signature.

The date of first diagnosis of wAIHA will be collected from the participant's medical history. Details of the wAIHA diagnosis which will be used to stratify the participants by the prior use of rituximab (yes/no). History of any other connective tissue disorders must also be recorded on the eCRF.

Note: Significant findings that are observed after the patient has signed the ICF and that meet the definition of an adverse event (AE) must be recorded in the AE eCRF.

8.2.3 Prior wAIHA medications/therapy

Any treatment for wAIHA since initial diagnosis (as determined through medical history records or through participant interview) prior to study entry will be collected and recorded in the eCRF.

These may include:

- biologics (e.g., rituximab, etanercept, ocrelizumab, epratuzumab, infliximab, belimumab, alefacept, abatacept, iscalimab). Note: please check applicable eligibility criteria in Section 5.2
- another disease modifying or immunosuppressive therapy (e.g., hydroxychloroquine, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, leflunomide)
- Number and doses of RBC transfusions received during two months prior to randomization

Note: Symptomatic and systemic background therapy for any underlying disease which is ongoing at study entry must be recorded on "Prior and Concomitant medications" eCRF.

8.2.4 Supportive care therapy

Supportive care therapy is allowed during the study conduct and will be reported in the eCRF.

The dose should be stable for at **least 4 weeks prior to the randomization** into the study and to be maintained stable during the study. Please refer to Section 6.8.1.1.

8.2.5 Prior and concomitant medications

Concomitant medications and prior medications taken over 6 months preceding study enrollment for reasons other than wAIHA will be captured at the Screening visit, and updated as necessary in the relevant eCRF.

Any new medication taken during the course of the study should be collected on the relevant eCRF.

Please refer to Section 6.8.

8.3 Efficacy assessments

Planned time points for all assessments are provided in Section 1.3.

Clinical efficacy measurements related to primary and secondary objectives are described in the subsections below.

Pharmacokinetic and biomarker samples will be collected at the time points defined in Section 1.3, Section 8.7 and Section 8.8.

Follow the instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

During a local or regional public health emergency, i.e., pandemic, epidemic or natural disaster, virtual contacts and/or visits by site staff/home nursing service to the participant´s home as per local regulations and capabilities, can replace on-site study visits to assess and collect efficacy endpoints.

8.3.1 Concentration of hemoglobin

Hemoglobin results are used for primary and secondary efficacy endpoints (see Section 3).

Level of hemoglobin will be performed at screening visit to assess the eligibility of the patient. Hematology will be assessed at W1 and every other week (q2w) up to W25.

During the first two years of efficacy follow-up, hematology will be performed monthly (every 4 weeks) and quarterly (every 12 weeks) thereafter until the end of efficacy follow-up.

During the efficacy follow-up period to assess the key secondary endpoint (duration of response), after the first visit where a patient reports a hemoglobin value below 10g/dL, an unscheduled assessment should be performed a week later to confirm the loss of durable response.

Additional assessments of hemoglobin level could be performed more frequently than the schedule if needed in accordance with the clinical judgment of the investigator.

Hemoglobin and all other hematology assessments are performed at the local lab of the clinical site to allow the investigator to review the results on the day of the visit and take any treatment decision, if needed. Local laboratory results will be entered in the eCRF by the clinical site staff.

Laboratory normal ranges and laboratory certificates must be provided for the local lab. The same laboratory should be used for all hematological assessments throughout the study.

8.3.2 Assessment of hemolysis

The secondary efficacy endpoint best response to treatment (response and complete response) is based on hematology and chemistry results. Parameters analyzed are hemoglobin, hemolytic markers (unconjugated bilirubin, LDH, haptoglobin and reticulocytes) and absence of red blood cells transfusions (see Section 9.4.1).

Hematology and chemistry assessments will be performed at screening visit to assess the eligibility of the patient, at W1 and every other week (q2w) up to W25. During the first two years of efficacy follow-up, these parameters will be performed monthly (every 4 weeks) and thereafter quarterly (every 12 weeks) until the end of efficacy follow-up.

Hematology assessments are performed at the local laboratory of the clinical site. Chemistry assessments will be done at the central laboratory.

8.3.3 Other efficacy assessments

Administration of red blood cells transfusions (prior and during study), rescue or prohibited treatments and new line of subsequent wAIHA therapy will be captured on the corresponding eCRF pages to enable analysis of efficacy endpoints.

In addition, medical resource utilization data (events of hospitalization, an outpatient visit or Emergency Room visit) will be collected during follow-up period.

8.3.4 Appropriateness of efficacy assessments

Level of hemoglobin as the treatment response, signs of biochemical resolution of hemolysis and duration of response are well established parameters to assess effectiveness of anti-wAIHA treatment and are recommended by First International Consensus Meeting (Jäger et al 2020).

8.4 Safety assessments

Safety assessments are specified below and in Section 1.3 detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

Table 8-1 Assessments and Specifications

Assessment	Specification
Physical Examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or

	symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical examination will be done at some visits. Please refer to Section 1.3 for more details The investigator should pay attention to presence to clinical signs related to previous serious illnesses. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Section 1.3.

8.4.2 Vital signs

Vital signs include blood pressure (BP), pulse measurements, and body temperature will be assessed according to the visit schedules as described in Section 1.3. After the patient has been sitting for 3 minutes with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device with an appropriately sized cuff.

8.4.3 Electrocardiograms

An ECG will be performed in this study as part of screening assessments and at end of treatment and at end of short term follow up (STFU2). Refer to Section 1.3 for details. Additional unscheduled safety ECGs may be repeated at Investigator's discretion at any time as clinically indicated.

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is PRO first, followed by ECG, vital signs, blood collection, physical examination and infusion.

QT interval corrected by Fridericia formula (QTcF) should be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single 12-lead ECGs are collected. The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

For any ECGs with participant safety concerns (e.g., severe arrhythmia, QTcF >500 ms), two additional ECGs must be performed to confirm the safety finding. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis/Sponsor prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.4 Clinical safety laboratory tests

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

A central laboratory will be used for analysis of all specimens listed below, except for hematological assessment, urine pregnancy and serum tests, urinalysis (dipstick and microscopic analysis, if applicable). Clinical site practice can be applied for point-of-care tests (urine for pregnancy test and urinalysis). Adequate documentation of these test results needs to be maintained in participants' medical notes.

Blood withdrawals and safety assessments should be done prior to study treatment administration. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out-of-range values.

The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant, or until a valid reason, other than treatment related AE, is defined. In case of doubt, Novartis personnel should be contacted.

In all cases, the investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

Table 8-2 Clinical safety laboratory tests

Test Category	Test Name
Full Hematology (locally)	Erythrocyte Cell Morphology, Erythrocyte count, Hematocrit, Hemoglobin, Leukocytes, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils (absolute value), Reticulocytes, Erythrocyte Sedimentation Rate
Reduced Hematology (locally)	Hemoglobin and reticulocytes
Full Chemistry (centrally)	Albumin, Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Glucose non-fasting, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Lactate dehydrogenase (LDH), Amylase, Lipase, Calcium, Magnesium, Phosphate, Potassium, Sodium, Urea Nitrogen or Urea, Uric Acid, Haptoglobin
Reduced Chemistry (centrally)	LDH, Indirect Bilirubin and Haptoglobin

Test Category	Test Name
Urinalysis (locally)	Macroscopic Panel (Dipstick) (pH, Glucose, Protein, Blood, Bilirubin, Urobilinogen, Ketones, Nitrite, Leucocyte esterase), Specific Gravity If the dipstick result is positive for nitrite, leukocyte esterase or blood, further testing in the local lab must be performed for culture and microscopic analysis (Erythrocytes, Leucocytes, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation (centrally)	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Immunology (centrally)	Immunoglobulins (total Ig, IgG, IgM, IgA)
B-cell count (centrally)	CD19+ B-cell count (other cell types a part of biomarkers)
Hepatitis markers & HIV & TB (centrally)	Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis B Virus Core Antibody, Hepatitis C antibodies HIV-1/HIV-2 Antibody Screen; if positive, confirmation by second technique (e.g., PCR) Quantiferon TB-Gold assay or, if per local requirement only, a purified protein derivative (PPD) At screening the assessments will be performed by central lab. Results must be known prior to randomization to determine the participant's eligibility for the trial.
Pregnancy Test (locally)	Serum pregnancy test Urine pregnancy test Confirmatory serum pregnancy analyzed by lab required in case of positive urine pregnancy test.
Inclusion/Exclusion	For inclusion or exclusion criteria testing not already included above, please refer to Section 5.1and Section 5.2.

8.4.5 Pregnancy testing

All female participants with the exception of those with documented post-menopausal status or documented hysterectomy will have a serum β-hCG test (serum pregnancy test) performed at the screening visit. A urine pregnancy test will be performed on the day of administration of the study treatment and during the 6 months after last dose, except for last visit (LTFU1) where serum sample will be collected for patients in durable response. The site staff must check that the urine pregnancy result is negative before administration of the study treatment. A positive urine test requires immediate interruption of study drug and needs to be confirmed with a serum test. If positive, the participant must be discontinued from the study treatment.

For participants not in durable response before LTFU1 visit, the LTFU1 visit (6 months after the last study treatment dose) will be a phone contact to confirm urine pregnancy test results. If the corresponding urine pregnancy test result is positive a confirmatory serum test must be performed at the site, refer to Table 1-3.

Highly effective method of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 5.2).

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result

to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of child-bearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy with or without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms).

In the absence of the above medical documentation, Follicular Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Appropriateness of safety measurements

The selected safety assessments are standard for this indication/participant population.

8.5 Additional assessments

The other assessments planned for the study are:

- Clinical outcome assessments (COAs): These include patient-reported outcomes (PRO)
- Pharmacokinetics and anti-drug antibodies (described in Section 8.7 and Section 8.9)
- Biomarkers (described in Section 8.8)

During a local or regional public health emergency, e.g., pandemic, epidemic or natural disaster, visits by site staff/home nursing service to the patient´s home as per local regulations and capabilities, can replace on-site study visits to collect pharmacokinetics, biomarker, and other samples and completion of Electronic Clinical Outcome Assessments (eCOAs), as applicable.

8.5.1 Clinical Outcome Assessments (COAs)

If data cannot be obtained due to a local or regional public health emergency, i.e., pandemic, epidemic or natural disaster, Clinical Outcome Assessments may be collected remotely/tablet device, with or without Site Staff/Home Nursing Service depending on local regulations

A PRO is a measurement based on a report that comes from the study participant about the status of a participant's health condition without interpretation of the participant's report by a Medical Lead or anyone else. A PRO can be measured by self-report or by interview, provided that a trained interviewer records only the participant's response. Symptoms or other unobservable concepts known only to the participant (e.g., fatigue or pain severity) can only be captured by PRO measures.

The COAs will be applied in all countries where validated translations are available, or from the time when the translations become available and have received all necessary approvals.

Patient reported outcomes (PRO)

For this study, the PROs listed below will be used to evaluate patient-reported measures of health-related quality-of-life (HRQoL), disease symptoms, and functioning:

- SF-36 v2.0 (acute, one-week recall)
- PROMIS Short Form v1.0 Fatigue 13a
- Functional Assessment in Cancer Therapy – item GP5 (Fact-GP5)
- Patient Global Impression of Change (PGIC) – Fatigue
- Patient Global Impression of Severity (PGIS) – Fatigue

Assessment of ePRO

All PRO data will be collected using an electronic patient reported outcome (ePRO) tablet device. The ePRO device will be programmed for collection at the study visit, refer to Section 1.3.

Sites will ensure set up of ePRO device is completed according to ePRO vendor training. In case of malfunction with ePRO device, sites should refer to backup procedure in accordance with ePRO vendor training.

The PRO measures should be provided to the participant in the language they are most familiar with.

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Study participants should be given sufficient space and time to complete all PRO questionnaires.

Participant's refusal to complete all or any part of a PRO measure should not be captured as a protocol deviation.

The participant should be made aware that completed PRO measure(s) are not reviewed by the Investigator/study personnel for Aes and that they should report any discomfort, unusual symptoms or medical problems directly to the Investigator/ study personnel, according to the ICF.

SF-36v2 (acute)

The SF-36 v2.0 (acute) is a 36-item questionnaire generic, comprehensive measure of functioning and well-being. The recall period is the past week. The measure is scored to produce

8 domain scores: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. A physical component summary (PCS) score and a mental component summary (MCS) score will also be calculated (Ware and Sherbourne 1992, Jenkinson et al 1999). Scoring will be calculated according to the instructions in the SF-36 User's Manual.

Responses to items are based on a 5-point Likert scale with transformation to a norm- based score. Scores below 50 indicate less than average health, while scores above 50 indicate better than average health.

PROMIS SF v1.0 Fatigue-13a (FACIT-F)

The Patient-Reported Outcomes Measurement Information System (PROMIS™) is a commonly used self-report measurement system of HRQoL and physical function, developed by the National Institutes of Health (NIH) for pediatric and adult patients.

The PROMIS Short Form v1.0 Fatigue-13a (PROMIS-Fatigue-13a) includes 13 items that assess fatigue. All items ask the participant to recall their experiences during the past 7 days.

All items in the PROMIS-Fatigue-13a utilize a 5-point response scale (e.g., not at all, a little bit, somewhat, quite a bit, very much).

In general, a high score represents more of the concept being measured. Therefore, higher scores on the PROMIS-Fatigue-13a represent greater fatigue. All scoring will follow the scoring procedures defined by Health Measures ([PROMIS Fatigue Scoring Manual, 2019]).

FACT-GP5

The single FACT item, GP5, is a summary measure of the overall impact of treatment toxicity that has demonstrated a significant relationship to overall quality of life as indicated by ability to enjoy life. In addition, the item is aligned with current Food and Drug Administration research interest in evaluating the patient's perspective on treatment of adverse events, and it has been shown to be significantly associated with clinician-reported adverse events. Patients are asked to rate the side effect bother (e.g., "I am bothered by side effects of treatment") on a 5-point Likert scale from "not at all" to "very much." (Pearman et al 2018).

PGIC Fatigue

The PGIC is a single-item question designed to assess the patient's overall impression of symptom severity change to help understand meaningfulness of within patient change. Patients are asked to rate the overall change in severity of their fatigue since starting study medication, on a 5-point scale: much better, a little better, no change, a little worse and much worse.

PGIS Fatigue

The PGIS is a single-item question designed to assess the patient's overall impression of disease severity and is used to help understand the meaningfulness of within patient change. Patients are asked to rate the overall severity of their fatigue over the past 7 days, on a 5-point scale: none, mild, moderate, severe and very severe.

8.5.2 Trial Feedback Questionnaire (TFQ)

By participating in the clinical trial, participants may be contacted for feedback about the trial experience, as appropriate and in adherence to local regulations and guidelines. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process.

This feedback asks questions about trial experience. It does not ask questions about the trial participant's disease, symptoms, treatment effect, or adverse events. Therefore, it is not considered as trial data and will be received electronically outside the clinical database.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.1 and Section 8.6.2, respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, or surrogate).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up of all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

As the study consists of several periods, type of reporting of AEs/SAEs will vary:

- All kind of AEs/SAEs, regardless of causality will be collected and reported during Treatment period and Short-Term Safety Follow-up (up to 20 weeks after the last dose of the study drug).
- Only AEs/SAEs potentially related to B-cell depletion (e.g., infections, malignancy, etc) regardless of causality; additionally, any SAE suspected to be related to ianalumab will be collected during the Long-Term Safety Follow-up (up to 2 years after the last dose of the study drug). In case the participant starts a new B-cell depleting or immunosuppressing treatment, the AE collection during long-term safety follow-up will be limited to the collection of SAE suspected to be related to ianalumab.

8.6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events. All adverse events must be treated appropriately.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The Common Terminology Criteria (CTC) AE grade. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes an SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken with study treatment which may include one or more of the following:
   - Dose not changed
   - Drug interrupted/permanently discontinued
6. Its outcome
   - not recovered/not resolved
   - recovered/resolved
   - recovering/resolving
   - recovered/resolved with sequelae
   - fatal
   - unknown.

If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For Grade 3 and Grade 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 20 weeks following the last dose of study treatment. After these 20 weeks, follow-up will be restricted to AEs potentially related to B-cell depletion (see Section 10.7) and SAEs suspected to be related to ianalumab, for up to 2

years after last study treatment dose. In case the participant starts a new B-cell depleting or immunosuppressing treatment, the AE collection during long-term safety follow-up will be limited to the collection of SAEs suspected to be related to ianalumab. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the [ianalumab IB].

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.

Infusion-related reactions will be reported using a dedicated CRF.

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening. Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines)
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the end of 20-week Safety follow-up after the last study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail).

During the long-term safety follow-up (up to two years after the last dose of the study treatment) only identified AEs/SAEs potentially related to B-cells depletion and SAEs suspected to be related to ianalumab will be monitored (See Section 4.1 for definitions and Table 1-3 as well as Table 1-4 for details on the safety monitoring). In case the participant starts a new B-cell depleting or immunosuppressing treatment, the safety follow-up will be limited to the collection of SAE suspected to be related to ianalumab.

Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

1. Screen Failures (e.g., a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated participants: SAEs collected between time participant signs ICF until the end of Safety follow-up. See Section 4.1.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the [ianalumab IB] or Package Insert (new occurrence) and is thought to be related to ianalumab, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with *EU Guidance 2011/C 172/01* or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 20-week period after the last study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

A female trial participant must not become pregnant during the study and six months after last dose of study drug. If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment, and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy will be reported during the study period and will be followed up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.6.6 Adverse events of special interest

Not applicable.

8.7 Pharmacokinetics

All patients will undergo ianalumab PK and ADA sampling according to the visits defined in Section 1.3 and Table 8-3 below.

Pharmacokinetic (PK) samples will be obtained in all participants but ianalumab concentrations will be evaluated only in the participants receiving ianalumab. ADA samples will be evaluated in all participants.

Any residual PK/ADA samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the Clinical Study Report.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Ianalumab PK parameters will be estimated from each evaluable individual serum concentration-time profile by non-compartmental analysis (NCA) with WinNonLin Phoenix (Version 6.4 or higher). A table of PK parameters to be evaluated (e.g., Cmax, Tmax, AUC) is included in the statistical and data analysis Section 9.4.3.

8.7.1 Pharmacokinetic blood collection and handling

At each visit indicated (Table 8-3), a blood sample will be taken prior to start of infusion (pre-dose), at end of infusion (as applicable), or at the scheduled post-dose time (time after start of infusion) by either direct venipuncture or an indwelling cannula inserted in a forearm vein. In the latter case, the line used to collect the PK and/or ADA sample must be a different one than the line used for ianalumab infusion.

In participants who prematurely discontinue the study treatment, ianalumab PK samples will be collected at end of infusion, 2 and 4 weeks after last dose and thereafter, PK samples will only be collected at time of ADA sampling (W5, W9, W13, and STFU2 [week 33]). ADA sample collection will remain according to schedule.

On days and time points where blood PD samples are to be drawn, the PK sample must be drawn first. The exact date and time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate CRF. Any sampling problem must be recorded on the appropriate CRF page.

Patients who receive transfusions within 24 hours of PK and/or ADA sample collection will be identified as such in the PK dataset.

If the patient experiences an AE which is considered drug-related and meets criteria of a SAE, or discontinues the drug due to drug-related toxicities, unscheduled PK and ADA samples will be obtained as soon as possible after the reporting of the event and information on date and time of last ianalumab dose will be collected. An unscheduled PK and ADA blood sample may be collected at any time for measurement of serum drug concentrations and ADA if clinically indicated or at the Investigator's discretion. In addition, an unscheduled PK and ADA blood sample may be collected if additional ECG measurements are conducted.

Refer to the [CVAY736O12301 Laboratory Manual] for detailed instructions for the collection, handling, numbering, processing and shipment of PK samples.

Table 8-3 Ianalumab PK and ADA sampling schedule

Scheduled/ Unscheduled	Dose	Visit per SoA	Day Nominal	Hour Nominal[1]	PK	ADA
SCHEDULED	x	W1 Pre-dose	1	0	x#	x#
SCHEDULED		W1	1	2 (+/- 10min)[2]	x#	-
SCHEDULED		W3	15	336 (+/- 36 h)	x	-
SCHEDULED	x	W5 Pre-dose	29	0 / 672 (+/- 56 h)[3]	x#	x#
SCHEDULED		W5	29	2 (+/- 10min)[2]	x	-
SCHEDULED		W7	43	336 (+/- 36 h)	x	-
SCHEDULED	x	W9 Pre-dose	57	0/ 672 (+/- 56 h)[3]	x#	x#
SCHEDULED		W9	57	2 (+/- 10min)[2]	x	-
SCHEDULED		W11	71	336 (+/- 36 h)	x	-
SCHEDULED	x	W13 Pre-dose	85	0/ 672 (+/- 56 h)[3]	x#	x#
SCHEDULED		W13	85	2 (+/- 10min)[2]	x#	-
SCHEDULED		W15	99	336 (+/- 36 h)	x	-
SCHEDULED		W17	113	672 (+/- 56 h)	x#	-
SCHEDULED		W21	141	1344 (+/- 4 days)	x	-
SCHEDULED		W25	169	2016 (+/- 6 days)	x	-
SCHEDULED		STFU2 (week 33)	225	3360 (+/- 11 days)	x#	x#
UNSCHEDULED[4]		na	na	na	x#	x#

Pre-dose samples must be collected before the start of infusion. na= not applicable. For patients who enter the open label cross-over period PK/ADA samples with the symbol # will be collected. [1]Elapsed time from start of infusion; [2]to be collected at end of infusion (+/- 10 min); [3]elapsed time from previous dose; [4]unscheduled samples in case of suspected allergic hypersensitivity or relevant safety event.

8.7.2 Analytical method

A validated ELISA will be used to determine ianalumab serum concentrations in the clinical trial participants. The anticipated lower limit of quantification (LLOQ) is 0.025 µg/mL. Concentrations of ianalumab will be expressed in µg/mL.

The data and details of the analytical methods will be provided in the Bioanalytical Data Report (BDR). Concentrations below the LLOQ will be reported as 'zero' and missing data will be labeled as such in the BDR.

8.8 Biomarkers

Biomarker assessment will be performed to support the identification of biomarkers involved in the targeted pathway, associated with response to treatment with ianalumab or that may correlate with disease regression and/or progression. Some aspects of this biomarker plan may only apply at selected study sites.

Biomarkers will be evaluated at baseline, at different time points during and after ianalumab treatment, to determine disease characteristics and their variability at baseline and the response to ianalumab during and after treatment.

Key Biomarker investigations in this trial may include but not limited to assessment of PD biomarkers (CD19+ B-cells counts, serum BAFF levels) to confirm biological activity of ianalumab. The pathogenesis of wAIHA is a complex multistep process, the last step of which being the destruction of red blood cells (RBCs) in the presence of anti-RBC autoantibodies with or without complement activation. Autoantibodies, the complement system, phagocytes, cytotoxic CD8+ T cells and NK cells performing ADCC, B and T lymphocytes including the CD4+ T regulatory (Treg) cells, and cytokines are all key players in the pathogenesis of wAIHA. Several mechanisms are described in the literature to be mediators of the breakdown of immunologic tolerance to erythrocyte-associated self-antigens that are derived from phagocytosis, processing and antigen presentation to adaptive immune cells. As such, development of wAIHA is thought to be secondary in approximately 50% of cases (Berentsen et al 2019). Processing and presentations of antigen mimicking self-antigens can lead to failure of T-cell regulation of B-cells that are permitted the development and maturation of autoreactive B-cell and production of autoantibodies (warm agglutinins) predominately of IgG subclass but can be combined with warm reactive IgA or IgM. Biomarkers such as autoantibodies associated with wAIHA, complement factors, Immunoglobulins as well other biomarkers associated with cellular mediated autoimmunity and tolerance in wAIHA will be assessed to explore potential disease modifying effects and safety of ianalumab treatment.

Additionally, the biomarker plan includes transcriptomics and protein profiling to identify potential signatures related to wAIHA and ianalumab safety and treatment effects.

Whole Blood, plasma, and serum samples will be collected from patients in all treatment arms of the study at the timepoint(s) defined in Section 1.3 Schedule of Activities.

Follow instructions for sample collection, processing, and shipment provided in the laboratory manual.

If bone marrow aspiration or tissue biopsy are performed as part of standard clinical care at diagnosis or during the study, the patients may optionally consent to its use for exploratory research purposes (e.g., IHC) by the study sponsor.

The sample collection information must be entered on the appropriate sample collection eCRF page(s) and requisition form(s).

Optional Additional Research

If the participant agrees, by signing the optional consent for Additional Research, biological samples and data may be used for additional research to help better understand how the study treatment works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.8.1 PD biomarkers

B-cell count

The effect of ianalumab treatment on circulating CD19+ B-cells will be assessed by flow cytometry on whole blood using the validated TBNK assay which allows additional analyses of CD3+ T-cell subsets, including CD4+ and CD8+, and CD16+/CD56+ NK cells.

B-cell counts are intended to be used for the exploratory assessment of the relationship of ianalumab exposure and PD. B-cell counts at baseline and visits after the end of treatment determine the minimal level of recovery of the B-cells defined as ≥80% of baseline or ≥50 cells/μL.

Level of soluble BAFF and other exploratory soluble biomarkers

Soluble B-cell activating Factor (BAFF) will be measured in serum applying a specific analytical method established and validated. BAFF level will be used to assess the relationship, respectively to confirm the inverse correlation of BAFF levels and B-cell counts and ianalumab exposure and PD.

Other exploratory biomarkers may be measured such as IL-21 and TGFβ1.

8.8.2 Exploratory biomarkers

Immune cell subpopulations

The presence and ratio of B-cell subpopulations and other immune cells and their activation state and the change by ianalumab treatment will be assessed by flow cytometry in whole blood to characterize the effect of ianalumab on immune cell subpopulations, especially long-term B-cells (B memory cells) in blood. Immune cell subtyping including but not limited to unswitched and switched memory B-cells and assessment of regulatory cells will expand the understanding of ianalumab mode of action and the correlation of the clinical outcome.

Additionally, markers involved in phagocytosis of opsonized red blood cells such as, FcγR subtypes and Signal regulatory protein α (SIRPα) expression on monocyte/macrophages may be analyzed as well.

Autoantibodies (anti-RBC) assessments

Whole blood will be collected for the analysis of circulating autoantibodies using a validated analytical method such as Coombs test or direct antiglobulin test (DAT) as potential disease and efficacy biomarkers.

Additionally, profiling to identify so far unknown wAIHA antibody profile, potentially associated with disease or response to ianalumab may be performed.

Complement (C5b-9 levels)

Destruction of RBC occurs as extravascular lysis in the spleen and liver or as intravascular lysis. While extravascular lysis in the spleen is mostly mediated via agglutinins and macrophages intravascular lysis is mostly associated with the activation of complement system and formation

of a MAC on RBC. Similarly, extravascular lysis of RBCs in the liver is associated with C3b opsonization. As surrogate for complement activation C5b-9 levels will be measured in plasma

Serum biomarker profiling (Proteomics)

Protein profiling may be performed in serum using highly multiplexed technologies (e.g., SomaScan) to identify molecular biomarkers associated with the wAIHA diseases state and severity, effect and response to the ianalumab treatment.

In addition, specific panels of biomarkers may be measured using specific methods to confirm proteomics finding or test hypotheses based on results of other studies and published data.

Gene expression or exploratory transcriptomics

The expression of genes will be examined using RNA (or other nucleic acid) analytical technologies, such as PCR, Next Generation Sequencing techniques, or others. These analyses will be used to examine the effect of ianalumab on transient RNA expression in peripheral blood and may support the identification of pathways/markers that characterize the disease or response of treatment with ianalumab.

Analysis will be performed to identify immune cells, especially B-cell populations and their activation status.

8.9 Immunogenicity assessments

Anti-ianalumab antibodies (ADA) will be evaluated in samples collected from all participants, including placebo, according to Section 1.3 and Table 8-2 in Section 8.7.1. Samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by Novartis's designee.

In case of suspected allergic hypersensitivity or any relevant safety event (e.g., the patient experiences an AE which is considered drug-related and meets criteria of a SAE, or discontinues the drug due to related toxicities, at Investigator's discretion, if an additional ECG measurement is conducted), the participant should return to the site and an unscheduled sample to assess ADA and an unscheduled PK sample will be collected. In case of positive ADA, back-up of previous PK samples could be used to better characterize the onset of ADA response.

8.9.1 Immunogenicity blood sample collection and handling

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.9.2 Immunogenicity analytical method(s)

A bridging ELISA method that is designed to detect the presence of ADA in human serum will be used. The method contains three components:

(1) Screen assay, which identifies initial positive or negative samples, (2) Confirmation assay, which assesses specificity of the positive screen samples, and (3) Titration assay which estimates the level of antibody for the confirmed positive samples.

Confirmed ADA positive samples will be further characterized for neutralizing capacity in a competitive ligand binding neutralizing antibody assay and a domain specificity assay. A cell-based functional neutralizing antibody assay could also be considered depending on feasibility assessment that is ongoing.

The detailed methods for ADA assessment will be described in the Bioanalytical Data Report (BDR).

8.10 Medical resource utilization and health economics

Health economics parameters are not evaluated in this study.

For all participants throughout the study, the Investigator and study site personnel will collect data about health care resource utilization (events of hospitalization, outpatient visit, or Emergency Room visit) associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits and
- Exclude procedures, tests, and encounters mandated by the protocol

8.11 Participant off-site research nursing visits

After completion of the 20-weeks short-term follow-up, at the investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have clinical trial assessments during the long-term safety and efficacy follow-up (Table 1-4) performed at an off-site location.

The off-site location is not a site location where the investigator will conduct the trial and where source data will be maintained but is for example the participant's home or another safe location. Suitability for the off-site location will be assessed by the off-site research nurse (ORN) and ultimately decided by the investigator.

These off-site visits will involve a qualified ORN who will visit the participant to perform study procedures according to Section 1.3 under delegation of the investigator. The investigator will retain accountability for participant oversight and all medical decisions (i.e., protocol specified medical procedures, assessment and reporting of AE/SAE potentially related to B-cell depletion and SAEs suspected to be related to ianalumab as well as wAIHA-related concomitant mediation, etc.). The rationale for the optional off-site visits is to unburden the participant by reducing the number of times they are required to travel the study site.

The off-site visits will be offered in certain countries and sites as determined by Novartis. Offsite visits may replace on-site visits if Novartis, investigator and local regulations and conditions allow, and upon agreement between investigator, participant, and Novartis.

The participants are under no obligation to participate in off-site visits, as they can decide to continue with on-site visits at the study site. Participants that the investigator identifies as suitable and who may benefit from off-site visits must have given consent for activities that may be done outside of the study site. The participant's consent to do off-site visits will be collected at the start of the study as optional part of the informed consent form. The information if a visit was conducted at an off-site location must be recorded on the corresponding eCRF.

Off-site research nursing visits will be possible during the long-term safety and efficacy follow-up period, to reduce the high site visit burden for participants that need to follow the monthly efficacy visit: LTFU visits 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, and LTFU visit 22 and all later ones, except visits to confirm the loss of durable response and end of study visit.

The following conditions must be met for the remote assessment to occur at an off-site location:

- The participant must have completed the 20-weeks short-term follow-up on-site (up to and including Week 33 visit) and needs to be followed for both safety and efficacy.
- Off-site visits can be conducted without affecting the well-being of the participant during the study and with the same level of scientific integrity as assessments conducted on-site.

The off-site visits will use a third-party vendor centrally sourced by Novartis that can provide qualified research nurses to perform study assessments. Investigator-delegated activities performed by the ORN will be under the oversight of the investigator who will be responsible to confirm that the ORN is adequately qualified and trained. The ORN will be blinded according to Section 6.3.2.

Where off-site visits are offered to participants and if allowed by local regulations, Novartis may offer an approved third party Telemedicine platform to investigators, ORNs and participants to support the management and communication of the off-site research activities. The use of the platform is recommended for off-site visits as the provided software interface allows the investigator/delegate to connect securely via video call with the ORN and the participant during the off-site visit, if agreed by the participant. In addition, both site personnel and ORN can securely upload electronic copies of helpful information to facilitate the planning and conduct of the off-site visits. As ensuring data privacy and security is essential, the selected telemedicine platform uses measures such as data encryption, access controls and audit trails to ensure integrity, reliability and security of data flow.

More details of the off-site research nursing and telemedicine processes are outlined in a separate [Off-site Study Operational Manual] that will be provided to the sites participating in the off-site research nursing visits.

9 Statistical considerations

The primary analysis will be performed when all patients have been followed for 24 weeks (W25 visit completed), or have switched to open-label treatment, or have early discontinued the study (whichever comes first), and when at least 66 events of confirmed loss of durable response have been observed in the study. All data collected up to the primary analysis cut-off date will be included in the primary analysis and reported by treatment group as defined below:

- Three randomized treatments: ianalumab 9 mg/kg, ianalumab 3 mg/kg and placebo (only inclusive of data before the switch from placebo to open-label treatment)
- Open-label ianalumab 9 mg/kg (only inclusive of data after the switch from placebo to open-label treatment, except for the determination of baseline). The open-label data will, however, be excluded from any hypothesis testing for the primary and key secondary objectives.

No interim analysis (IA) is planned. All data collected post primary analysis cut-off will be included in the final analysis, which will be performed when all patients have discontinued the study.

In addition to the primary and the study completion analyses, safety DMC analysis will also be conducted on a regular basis before the primary analysis.

The following sections will focus on the primary analysis description, however, the same analyses will be performed once more at the time of the final analysis.

9.1 Analysis sets

The Full Analysis Set (FAS) comprises all participant to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure, or assigned at the time they enter the open label extension period.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received. Before the switch to open label period, treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received. After the switch, treatment received is defined as ianalumab if the participant took at least one dose of ianalumab.

The pharmacokinetic analysis set (PAS) includes all participants who receive at least one dose of ianalumab and provide at least one evaluable ianalumab PK concentration. The definition of an evaluable PK sample and PK profile will be further defined in the SAP.

9.2 Statistical analyses

9.2.1 General considerations

Data will be summarized by treatment group: demographics and other baseline characteristics as well as efficacy data based on the FAS, PK data based on the appropriate PAS, and the safety and any other data (unless specified otherwise) based on the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Study treatment or study drug refers to ianalumab and placebo.

Baseline for efficacy and safety evaluation will be defined as below (further details will be provided in the SAP):

- In the randomized treatment groups: for hemoglobin, hemolysis parameters and all efficacy evaluations, the last available assessment on or before the randomization date is taken as baseline value; for safety (except hemoglobin and hemolysis parameters), the last available assessment before the start of the randomized treatment is taken as baseline value,
- In the ianalumab open-label treatment group: the last available assessment before the start of the open-label treatment is taken as baseline value for efficacy and safety evaluation.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

Relevant medical histories and current medical conditions at baseline (prior to randomization) will be summarized by system organ class and preferred term, by treatment group.

9.2.3 Treatments

The Safety set will be used for the analyses below.

The duration of exposure in weeks to each study drug as well as the dose intensity and the relative dose intensity will be summarized by treatment group.

Duration of exposure to each study drug will be calculated from date of first administration to last date of administration, with last date of administration defined as the earliest date between: last date of treatment + 27 days (as the study treatment are given every 4 weeks), date of death (if the participant died), last contact date (if the participant is lost to follow-up).

Dose intensity (DI) will be computed as the ratio of actual cumulative dose received and actual duration of exposure. Relative dose intensity (RDI) will be computed as the ratio of actual dose intensity and planned dose intensity. The last exposure to study drug for calculation of DI and RDI will be the intended end date of the last cycle initiated (last date of infusion + 27 days) regardless of permanent discontinuation or cutoff date occurred in that cycle.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized, by treatment group.

The number of participants with dose adjustments (reductions or interruption) and the reasons will be summarized by treatment group and all dosing data will be listed.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary objective of the study is to demonstrate that either dose of ianalumab induces durable hemoglobin (Hb) response compared to placebo, in patients with wAIHA who failed at least one previous line of treatment.

9.3.1 Definition of primary endpoint(s)

The primary endpoint is a binary variable indicating whether a patient achieves a durable response (Hb ≥10 g/dL and ≥2 g/dL increase from baseline), for a period of at least 8 consecutive weeks, between W9 and W25, in the absence of rescue or prohibited treatment (prior to achieving durable response). See more details about allowed supportive care, rescue and prohibited treatment in Section 6.8.

9.3.2 Statistical model, hypothesis, and method of analysis

The scientific objective guiding the primary analysis is to estimate the treatment effect of ianalumab compared to placebo, for the target population, on the proportion of patients with durable hemoglobin response as defined above. The justification and definition of the corresponding primary estimand are detailed in Section 3.1.

To control the overall family-wise type I error rate (FWER), an appropriate multiplicity adjustment procedure using a closed testing strategy (Bretz et al 2011) will be applied to the analyses of the primary and key secondary endpoints for the two ianalumab doses comparisons

to placebo. No formal comparisons will be made between the two active arms. This strategy to preserve the overall FWER at $\alpha = 2.5\%$ (one-sided) is described in Section 9.4.1.

To address the primary efficacy objective, the following statistical hypotheses will be tested:

$H1_0$: $\theta_1 \leq 1$ vs. $H1_A$: $\theta_1 > 1$,

$H2_0$: $\theta_2 \leq 1$ vs. $H2_A$: $\theta_2 > 1$

where θ_j (j=1, 2) is the odds ratio between either of the two randomized active treatment vs placebo, estimated from a logistic regression model stratified by the randomization stratification factor, the prior use of rituximab (yes vs. no). These hypotheses will be tested using the Wald tests on log odds ratio, at the appropriate α-level adjusted considering multiple testing (as described in Section 9.4.1).

The logistic model and the tests will be performed based on the FAS population (excluding the open label data) according to the randomized treatment group and strata assigned at randomization. The odds ratio between randomized active treatment vs placebo, for achieving durable response from the logistic model mentioned above, will be provided, along with its 95% confidence interval. The proportion of participants with durable response and exact 95% confidence intervals of proportions will be presented for each treatment group, and separately for open label treatment group (because the rescue definition is different between the blinded period and the open label period).

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

The analysis of primary endpoint will account for different intercurrent events as explained in the Section 3.1.

9.3.4 Handling of missing values not related to intercurrent event

In case of missing data not related to intercurrent events above, whether those missing data are due to early trial discontinuation or missing data due to any reasons, the below rules will be applied:

- A participant satisfying durable response criteria will be counted as responder, ignoring missing hemoglobin values that could have been observed before or after that durable response was achieved;
- Considering durable response is defined as an 8-week period of continuous response where hemoglobin will be collected every 2 weeks, the primary endpoint should translate into 5 consecutive q2w hemoglobin measures with Hb ≥10 g/dL and ≥2 g/dL increase from baseline. However, if a participant has a single missing hemoglobin value out of the 5 planned hemoglobin measures during the 8-week interval, and this missing value is in between 2 available hemoglobin values showing response (without intake of rescue medication as defined in the primary estimand), then interpolation will be applied and this single missing value will also be considered as response, allowing to count the participant as a durable responder for the primary endpoint;
- A participant who does not match the criteria for durable response due to non-response, study discontinuation, or more than one missing hemoglobin value will conservatively be counted as non-responder.

9.3.5 Multiplicity adjustment (if applicable)

A closed test procedure, preserving the overall family-wise type I error rate at 2.5% (one-sided), will be applied to the analyses of the primary and key secondary endpoints, for the comparison between each randomized active treatment versus placebo. Details on the testing strategy are specified in Section 9.4.1.

9.3.6 Sensitivity analyses

9.3.7 Supplementary analysis

Some subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed, if the primary endpoint analysis is statistically significant and if there are enough participants in each category allowing such analysis. The subgroup is :

- - sub-type of the disease : primary versus secondary wAIHAexposition to rituximab in the past: yes versus no.

No formal statistical test of hypotheses will be performed for the subgroups.

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary objectives in this study are to demonstrate that either dose of ianalumab maintains durable response that is sustained beyond the end of the treatment period compared to placebo (i.e., prolongs duration of response), and to evaluate in each treatment group the followings: time to durable response/response/complete response, response/complete response rate and hemoglobin level, the need for rescue treatments (overall and by type of recue treatment), safety, ianalumab pharmacokinetics and immunogenicity, as well as B-cell and immunoglobulin levels and PRO.

The duration of response is identified as the key secondary endpoint, which will only be formally tested if the analysis of primary endpoint is statistically significant.

Secondary efficacy and PRO endpoints will be analyzed using the FAS. For all safety analyses the safety set will be used. For PK analyses, the PAS will be used.

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

Key secondary efficacy endpoint

The key secondary efficacy endpoint/variable is: the duration of response, defined as:

- For participants who previously reached durable response, the time from the first hemoglobin assessment showing durable response (as defined in primary endpoint) to confirmed loss of durable response; confirmed loss of durable response is defined as the first of the following events:
  - hemoglobin level below 10 g/dL in at least two consecutive weekly assessments* (date of the first of the 2 relapsed assessments will be considered as relapse date),
  - start of any rescue or prohibited treatment,
  - death (whatever the cause);

- for the participants who did not achieve durable response according to the primary endpoint definition, the duration of response will be zero day.

*(*Of note: after a visit where a patient reports a relapsed hemoglobin assessment, an unscheduled assessment should be performed a week later to confirm the loss of response).*

1. The justification and definition of the corresponding key secondary estimand are detailed in Section 3.2.

Participants who met the durable response criteria and do not report a confirmed loss of durable response prior to analysis cut-off date will be censored at the date of the last available hemoglobin assessment. This rule also applies to patients who discontinue their study participation (during treatment or after treatment discontinuation) after having achieved durable response, without having reported a confirmed loss of durable response. They will contribute to the key secondary endpoint on duration of response only for the time they were followed and will be censored on the date of their last available hemoglobin count. Early study discontinuation in itself is not expected to be indicative of failure in patients who have no confirmed loss of response and do not require rescue medication nor new wAIHA therapy prior to study discontinuation. Censoring those patients corresponds to considering them at the same risk of failure as similar patients remaining on study.

Handling of missing data not related to intercurrent events is provided below:

If a confirmed loss of response is documented after two or more missing hemoglobin assessments, the time to confirmed loss of response will be censored at the last available hemoglobin assessment prior to the event.

If a participant has one relapsed hemoglobin assessment (value below 10 g/dL), but the second assessment to confirm the loss of response is missing, the situation will be handled according to the two scenarios described below:

- If the missed confirmation assessment is followed by a relapsed hemoglobin value or a record of prohibited/rescue medication at the subsequent visit: the loss of response will be confirmed and recorded at the date of the first relapsed value.
- If the missed confirmation assessment is followed by a subsequent hemoglobin value showing response or missing assessments or the cut-off, and there is no record of prohibited/rescue medication until the visit where the confirmed assessment should have been done: the time to confirmed loss of response will be censored at the last available hemoglobin assessment prior to the missed confirmation.

The rules described above are applicable for missing data due to any reasons.

Assuming proportional hazards for loss of durable response, the following statistical hypotheses will be tested to address the key secondary efficacy objective:

$H3_0$: $\theta_3 \geq 1$ vs. $H3_A$: $\theta_3 < 1$

$H4_0$: $\theta_4 \geq 1$ vs. $H4_A$: $\theta_4 < 1$

where θ_j (j=3, 4) is the hazard ratio for loss of durable response between either of the two randomized active treatment vs placebo. These hypotheses will be tested using the log-rank tests at the appropriate α-level adjusted considering multiple testing (see below), stratified by the randomization stratification factor, the prior use of rituximab (yes vs. no).

The hazard ratio for loss of durable response between each randomized active treatment vs placebo will be calculated, along with its 95% confidence interval, from the Cox model using the same stratification factor as for the log-rank test. The Cox model and log-rank test will be performed based on the FAS population (excluding the open label data) according to the randomized treatment group and strata assigned at randomization. The distribution of duration of response will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group, and separately for the open-label treatment group (as the rescue definition is different between the double blinded and the open label period).

To ensure control of FWER of $\alpha = 2.5\%$ (one-sided), the closed testing procedure will account for testing the primary (null hypotheses H1 and H2) and key secondary endpoints (null hypotheses H3 and H4) for each of the 2 doses comparisons to placebo, being a total of 4 hypotheses.

Any intersection hypothesis will be tested by either a Dunnett-test or a Bonferroni-test or a single test as described in Table 9-1 below. All intersections that include H1 and H2 will be tested by the Dunnett test of H1 and H2. All intersections which contain (H1 and H4) or (H2 and H3) will be tested by the Bonferroni-test splitting alpha between H1 and H4 or H2 and H3, respectively. The intersection of H3 and H4 will be tested by the Dunnett test. All other tests will use full level alpha test. As per the closure principle, a given hypothesis Hi (with i=1, 2, 3, 4) will be rejected if all intersections it is in, are also rejected. In other words, the adjusted p-value will be the maximum of the p-values from all intersection tests in which Hi is included. The key secondary endpoint of a given dose will be tested only if the difference in the primary endpoint for the same dose is statistically significant.

Table 9-1 Intersection hypotheses and local significance levels

Intersection hypotheses	Test	H_1	H_2	H_3	H_4
$H_1 \cap H_2 \cap H_3 \cap H_4$	Dunnett	α*	α*	0	0
$H_1 \cap H_2 \cap H_3$	Dunnett	α*	α*	0	-
$H_1 \cap H_2 \cap H_4$	Dunnett	α*	α*	-	0
$H_1 \cap H_2$	Dunnett	α*	α*	-	-
$H_1 \cap H_3 \cap H_4$	Bonferroni splitting alpha	α/2	-	0	α/2
$H_1 \cap H_3$	Full level	α	-	0	-
$H_1 \cap H_4$	Bonferroni splitting alpha	α/2	-	-	α/2
H_1	Full level	α	-	-	-
$H_2 \cap H_3 \cap H_4$	Bonferroni splitting alpha	-	α/2	α/2	0
$H_2 \cap H_3$	Bonferroni splitting alpha	-	α/2	α/2	-
$H_2 \cap H_4$	Full level	-	α	-	0
H_2	Full level	-	α	-	-
$H_3 \cap H_4$	Dunnett	-	-	α**	α**
H_3	Full level	-	-	α	-
H_4	Full level	-	-	-	α

α*, α**: adjusted alpha using Dunnett's procedure

If the key secondary endpoint analysis is statistically significant and if there is sufficient number of events in each category, subgroup analyses to assess the homogeneity of the treatment effect

across demographic and baseline disease characteristics will be performed, using the same subgroups as planned for the primary endpoint analysis (see Section 9.3.7). The number of participants censored for duration of response analysis and reasons for censoring will be summarized by treatment group using descriptive statistics and presented separately for each subgroup defined.

For all other secondary endpoints described below, no formal statistical testing will be conducted.

Response, complete response and hemoglobin level

Different response categories will be used for analysis:

- "Response" (R): hemoglobin level ≥10 g/dL and ≥2 g/dL increase from baseline, or normalization of hemoglobin (Hb level ≥11 g/dL (women) or ≥12 g/dL (men)), without biochemical resolution of hemolysis,
  - A subset of responders can reach "Complete Response" (CR): normalization of hemoglobin (Hb level ≥11 g/dL (women) or ≥12 g/dL (men)), no evidence of hemolysis (normal levels of indirect bilirubin, LDH, haptoglobin, and reticulocytes), absence of red blood cells transfusions,
- "Non Response" (NR): failure to achieve a response.

The same intercurrent events and handling strategy as for primary estimand (see Section 3.1) will also apply to the analysis of response and complete response.

The number and proportion of participants in response and in complete response will be reported by treatment group and at each timepoint. The hemoglobin level and its absolute change from baseline will also be summarized by treatment group, at each timepoint and presented graphically.

The best Response rate and best Complete Response rate (over all timepoints), with exact 95% confidence intervals, as well as the participant's best hemoglobin level (over all timepoints) will be summarized by treatment group.

Time to durable response, response and complete response

Time to durable response is the time from the date of randomization to the date of first assessment in a sequence of hemoglobin assessments matching the durable response criteria. Time to response is defined as the time from the date of randomization to the date of the first response. Time to complete response is defined as the time from date of randomization to the date of the first complete response. The same intercurrent events and handling strategy as for primary estimand (see Section 3.1) will also apply to these analyses.

Participants who do not have durable response/ response/complete response by W25 will be censored at the date of W25 visit (or 25 weeks after randomization, if they discontinued the study before W25).

The time to durable response, response and complete response will be summarized by treatment group using Kaplan-Meier method.

Use of rescue treatment

Intakes of rescue treatments (as defined in Section 6.8.3) will be listed. The number and proportion of participants requiring any rescue treatment will be presented by type of rescue treatment, by treatment group and by period: from W1 and W25 (intercurrent events impacting primary endpoint), and from W1 until loss of durable response (intercurrent events impacting key secondary endpoint).

The number of rescue treatments taken, standardized by observation duration, will also be summarized by treatment group. For RBC transfusion, change from baseline will also be summarized.

B-cell levels (PD endpoint)

Absolute B-cell count and absolute change from baseline in B-cell levels will be summarized by treatment group and by timepoint with descriptive statistics and presented graphically. The time to first occurrence of B-cell recovery (defined as ≥80% of baseline or ≥50 cells/μL) will be summarized by treatment group using Kaplan-Meier method.

9.4.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of randomized study medication to 28 days after the last dose of randomized study medication (for randomized treatment group), or from day of first dose of open-label ianalumab to 28 days after the last dose of open label ianalumab (for open-label ianalumab treatment group)
3. Post-treatment period: starting at day 29 after last dose of randomized study medication (for randomized treatment group), or at day 29 after last dose of open-label ianalumab treatment group (for open-label ianalumab treatment).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). Please refer to definition of baseline according to different treatment groups in Section 9.2.1. The randomized placebo treatment group is only inclusive of data prior to the treatment switch, and the open label ianalumab treatment group is only inclusive of data after the treatment switch. In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). In addition, some selected summaries by treatment group will also be done separately, to report safety data collected during the first 20 weeks after the last dose, and to report long-term safety data collected up to 2 years from the last dose.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity (based on CTCAE grades).
- by treatment and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

The number (and proportion) of participants with AEs/SAEs potentially related to B-cells depletion and SAEs suspected to be related to ianalumab will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

The number and percentage of participants with notable vital sign values will be presented by treatment group.

12-lead ECG

The number and percentage of participants with notable ECG values will be presented by treatment group.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

For laboratory tests where grades are defined by CTCAE version 5.0:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

If necessary, in addition to the above-mentioned tables and listings, other analyses, for example, figures plotting time course of raw or change in some laboratory tests over time or box plots might be conducted. Details will be specified in the SAP.

Immunogenicity

Summary statistics will be provided for the percent of participants with positive blood samples for immunogenicity (anti-drug antibodies), including treatment-emergent anti-drug antibodies. Shift tables will also be presented, if appropriate. All immunogenicity results will be listed by treatment group, participant, and visit/time.

9.4.3 Pharmacokinetics

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Ianalumab serum concentrations will be summarized using the PAS. Descriptive summary statistics of ianalumab serum concentration data will be provided by treatment, and visit/scheduled sampling time point, including the frequency of concentrations below the LLOQ and reported as zero. PK samples collected out of the pre-specified time window will be excluded from the plasma concentrations descriptive statistics.

In addition, graphical presentation will be provided: mean (+/-SD) and median concentration-time profiles over time, as well as individual profiles by treatment group.

All individual serum concentration data for ianalumab will be listed.

Pharmacokinetic parameters will be derived for ianalumab (except for the open-label treatment group), by non-compartmental method(s), with Phoenix WinNonlin (Version 6.4 or higher) and will include at least the PK parameters indicated in Table 9-2 for participants who are evaluable (not flagged for exclusion from the pharmacokineticist). The PK analysis will use the actual recorded sampling times, and will be conducted both after the first and the last ianalumab dose, as applicable. The linear up log down trapezoidal rule will be used for the area under the serum concentration-time curve (AUC) calculation. All individual ianalumab PK parameters will be listed.

Descriptive summary statistics of PK parameters will be presented by treatment arm and will include number of evaluable values (n), mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), 90% confidence interval of geometric mean, median, minimum, and maximum, except Tmax where n, median, minimum, and maximum will be presented.

Descriptive statistics of ianalumab serum concentrations and PK parameters will include all individual values not flagged for exclusions by the pharmacokineticist. Criteria for flagging of individual ianalumab serum concentrations or PK parameters will be defined in the SAP.

Individual flags and reason for flag will be indicated in the listing of individual ianalumab serum concentrations and PK parameters.

Table 9-2 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) (amount x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration (time)
Racc	Accumulation ratio calculated using AUC values obtained between the last and first dose [e.g. (AUC0-28d, Week 13-17)/(AUC0-28d, Week 1-5)]

Additional PK parameters to those indicated above may be derived and will be defined in the SAP.

Ianalumab PK in wAIHA patients will be further characterized via population PK analysis (Section 9.5.3).

9.4.4 Patient reported outcomes

Analyses of secondary PRO endpoints (using the FAS, according to the treatment group) are specified below. Scoring will be performed using scoring manual of the corresponding questionnaire. Missing items data in a scale will be handled based on each instrumental manual. Additional analysis might be performed for the PRO data. Further details will be provided in the SAP.

Descriptive statistics will be used to summarize the scores at scheduled assessment for the PROMIS fatigue by treatment group. The corresponding change from baseline in the scores will be summarized. A repeated measurement analysis model may be used to compare treatment groups with respect to changes in the scores (PROMIS fatigue T-score) longitudinally over time (full details will be provided in the SAP). Graphical representation of PRO scores over time will also be provided.

For SF-36, descriptive statistics will be used to summarize the scores at scheduled assessment of the 8 domains (Physical Functioning, Role Functioning-Physical, Role Functioning-Emotional, Bodily Pain, General Health, Vitality, Social Functioning and Mental Health), and the summary scores (PCS-36 and MCS-36) by treatment group. In addition, the corresponding change from baseline in the scores will be summarized. A repeated measurement analysis model may be used to compare treatment groups with respect to changes in the scores longitudinally over time. Graphical representation of PRO scores over time will also be provided.

See Section 9.5.2 for the description of exploratory analysis of other PRO.

9.5 Exploratory endpoint(s)/estimand(s) analysis

9.5.1 Biomarkers

Analyses of exploratory biomarkers will be specified in a separate biomarker SAP and report.

9.5.2 Patients Reported Outcomes

Analyses of exploratory PRO endpoints (using the FAS, according to the treatment group) are specified below. Further details will be provided in the SAP.

Time to achieve a clinically meaningful improvement on PROMIS-Fatigue score (at least 5 points) and Vitality from the SF-36 (at least 8 points) will be assessed by treatment group. The time to clinically meaningful improvement is defined as the time from the date of randomization to the date of event, which is defined as improvement of at least 5 points for PROMIS-Fatigue T-score and improvement of at least 8 points for SF-36 Vitality score, relative to baseline of the corresponding scale score. If a patient has not had an event prior to analysis cut-off or start of any rescue treatment or prohibited medications, time to clinically meaningful improvement will be censored at the date of the last adequate PRO evaluation. The distribution will be presented descriptively using Kaplan-Meier curves. Median time to clinically meaningful improvement along with two-sided 95% confidence interval will be provided.

Change from baseline in the Fact-GP5 will be summarized at scheduled assessment and by treatment group.

Analysis of the PGIC and PGIS results will be described in a separate PRO validation SAP.

9.5.3 PK/PD relationships

Relationships between PK, PD, efficacy and/or safety (e.g., ADAs) data may be explored by graphical approach and descriptive statistics will be provided. Additional statistical analysis such as regression analysis may be performed, if necessary.

Modeling of the PK and PD data may be performed as appropriate. During the modeling of the PK and PD data, the broad principles outlined in the FDA Guidance for Industry: "Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications" FDA (2003) and "Population Pharmacokinetics" FDA (2022) will be followed. As the PK and PD data from the current study may be pooled with data from previous studies, the PK/PD analysis will be described and reported separately in a modeling plan and modeling report respectively.

9.5.4 Medical resource utilization

Frequency of hospitalizations, outpatient visits, or emergency room visits due to underlying disease and its management will be summarized by treatment group.

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

Not applicable.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

Sample size calculation for primary efficacy objective assumes that the durable response rate is 70% in the active arms vs 30% in the placebo arm. The assumed response rate for active arms was defined based on literature reporting an overall response rate of 70–80% with rituximab in patients with both primary and secondary AIHA in relapsed/refractory setting (Murakhovskaya 2020). The assumed response rate for placebo arm was defined based on the trial conducted by Michel et al (2017), where the overall response rate was 31%.

It will be concluded that ianalumab is efficacious if, for the primary endpoint, at least one of the two doses of ianalumab tested is declared statistically superior to placebo. No formal comparisons will be made between the two active arms.

Under these assumptions, a total of 90 patients will need to be randomized to ensure 90% power for at least one comparison of active arm vs placebo arm to be statistically significant on the primary endpoint, using a Wald test on log odds ratio. This calculation assumes a randomization ratio of 1:1:1, normal approximation of log odds ratio, Dunnett's adjustment for multiplicity (with a correlation of 0.5 between the two test statistics) and a one-sided 2.5% significance level.

9.9.2 Secondary endpoint(s)

Key secondary endpoint (duration of response) of a given active arm will be tested only if efficacy is shown for the primary endpoint of the same arm. The hypotheses to be tested and details of the testing strategy are provided in Section 9.4.1.

The median duration of response is assumed to be 16 months in the active arms, based on literature data of rituximab in AIHA (Murakhovskaya 2020), with a hazard ratio for loss of durable response of approximately 0.3 versus placebo arm, based on above assumption of 70% and 30% of durable responders, respectively, according to the primary endpoint definition.

For participants who do not achieve a durable response as defined for the primary endpoint, the duration of response is considered as equal to zero. For participants with a durable response, exponential distributions are assumed for the time from achievement to confirmed loss of durable response in both active arms and the placebo arm, respectively, with a probability to be in durable response of 50% vs 10% by Month 16. Assuming 90 randomized patients, a 10% yearly drop-out rate, and an enrollment time of 35 months, a total of 66 events are expected to be observed at about 41 months after the first patient was randomized (when all patients have been followed for at least 24 weeks). Under these assumptions, the expected 66 events (28 events in placebo arm and 19 in each active arm) will ensure 90% marginal power for the key secondary endpoint analysis of each active arm versus placebo to be statistically significant, at the overall one-sided 2.5% level, using a log-rank test.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, IDFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:

- A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- A subsection with a separate signature for optional consent for activities that may be done outside of the study site
- A subsection with a separate signature for optional consent for open label/cross-over period
- A subsection with a separate signature for optional consent on the sharing of bone marrow/tissue collected as standard of care

- As applicable, Pregnancy Outcomes Reporting Consent for female participants.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.5, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will review the safety data of this study as well as data from studies in patients with ITP (study CVAY736I12301 in first line ITP, and study CVAY736Q12301 in second line ITP), at defined intervals prior to the primary analysis of each trial.

Specific details regarding composition, responsibilities, data monitoring, timing/frequency of safety DMC meetings and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

10.1.4.2 Steering Committee

The Steering Committee (SC) comprises Investigators participating in the trial, i.e., not being members of the DMC, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original

informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in source data agreement form.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT public website. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g., Clinicaltrials.gov, EudraCT public website etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIHA	Autoimmune hemolytic anemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAFF	B-cell activating factor
BAFF-R	B-cell activating factor receptor
BUN	Blood Urea Nitrogen
cAIHA	Cold antibody-mediated autoimmune hemolytic anemia
CK	Creatine Kinase
CLL	Chronic lymphocytic leukemia
CMO&PS	Chief Medical Office and Patient Safety
CO	Cross-over
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Clinical Supply Formulation

CSR	Clinical study report
CTC	Common Terminology Criteria
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOE	End of Efficacy Follow Up
EOT	End of Treatment
ESFU	End of Long Term Safety Follow Up
EPO	Erythropoietin
ERCP	Endoscopic retrograde cholangiopancreatography
ES	Evan's syndrome
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
FDA	Food and Drug Administration
FMI	Final Market Image
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
Hb	Hemoglobin
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDFU	Investigational directions for use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IN	Investigator Notification

INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Immune Thrombocytopenia
IVIG	Intravenous immunoglobulin
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LN	Lupus Nephritis
LTFU	Long Term Follow Up
mAb	monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
Nab	Neutralizing antibody
OHP	Off-site Healthcare Professional
ORN	Off-site research nurse
p.o.	Oral(ly)
PA	Posteroanterior
PAS	Pharmacokinetic Analysis Set
PC	Personal Computer
PD	Pharmacodynamic(s)
PerfO	Performance Outcomes
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient Reported Outcomes
PROMIS	PRO Measurement Information System
PSD	Premature Subject Discontinuation
pSS	Primary Sjögren's Syndrome
PT	prothrombin time
PV	Pemphigus vulgaris
q12w	every 12 weeks (quarterly)
q2w	every other week
q4w	Every 4 weeks
QD	Once a day
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia’s formula
R Value	ALT/ALP x ULN
RA	Rheumatoid arthritis
RAP	The Report and Analysis Plan
RBC	Red blood cells
RCT	Randomized Controlled Trial
RD	Recommended Dose
REB	Research Ethics Board

RECIST	Response Evaluation Criteria In Solid Tumors
RoW	Rest of World
RU	Resource Utilization
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SS	Sjögren's Syndrome
STFU	Short Term Follow Up
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFQ	Trial feedback questionnaire
ULN	upper limit of normal
UTI	Urinary Tract Infection
wAIHA	Warm antibody-mediated autoimmune hemolytic anemia
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.

Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.

Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Table 10-1 Clinically notable laboratory values and vital signs

Laboratory variable	Standard units	SI units
Liver function and related variables		
SGOT (AST)	≥ 3 × ULN	≥ 3 × ULN
SGPT (ALT)	≥ 3 × ULN	≥ 3 × ULN
Bilirubin	≥ 3 × ULN	≥ 3 × ULN
Alkaline phosphatase	≥ 5 × ULN	≥ 5 × ULN
GGT	≥ 5 × ULN	≥ 5 × ULN

Laboratory variable	Standard units	SI units
Renal function, metabolic and electrolyte variables		
Urea	≥ 5 × ULN	≥ 5 × ULN
Creatinine	≥ 3 mg/dL	≥ 265 µmol/L
Uric acid	M ≥ 12 mg/dL	M ≥ 714 µmol/L
	F ≥ 9 mg/dL	F ≥535 µmol/L
Glucose	< 45 mg/dL	< 2.5 mmol/L
	> 250 mg/dL	> 13.9 mmol/L
Cholesterol	≥ 350 mg/dL	≥ 9.1 mmol/L
Triglycerides	≥ 750 mg/dL	≥ 8.5 mmol/L
CK (MB)	None	None
Potassium	≤ 3.0 mEq/L	≤ 3 mmol/L
	≥ 6.0 mEq/L	≥ 6 mmol/L
Calcium	≤ 6 mg/dL	≤ 1.5 mmol/L
	≥ 13 mg/dL	≥ 3.2 mmol/L
Magnesium	< 1.0 mg/dL	< 0.4 mmol/L
	> 3.6 mg/dL	> 1.5 mmol/L
Amylase	≥ 2 x ULN	≥ 2 x ULN
Lipase	≥ 2 x ULN	≥ 2 x ULN
Hematology variables		
Hemoglobin	< 7 g/dL	< 4.39 mmol/L
Platelets (thrombocytes)	< 50 k/mm^3	< 50 × 10^9/L
	≥ 700 k/mm^3	≥ 700 × 10^9/L
Leukocytes (WBCs)	≤ 2.0 k/mm^3	≤ 2.0 × 10^9/L
	≥ 16 k/mm^3	≥ 16 × 10^9/L
Hematology variables: Differential		
Granulocytes (poly, neutrophils)	≤ 1,000/mm^3	≤ 1 x 10^9/L
Eosinophils	≥ 12%	≥ 12%
Lymphocytes	≤ 1,000/mm^3	≤ 1 × 10^9/L
Vital sign variables	**Notable criteria**	
Systolic BP (mm/Hg)	Either an increase of ≥ 30 that results in ≥ 180 or > 200 (mm/Hg) OR a decrease of ≥30 that results in ≤ 90 or < 75 (mm/Hg)	
Diastolic BP (mm/Hg)	Either an increase of ≥ 20 that results in ≥ 105 or > 115(mm/Hg) OR a decrease of ≥20 that results in ≤ 50 or < 40 (mm/Hg)	

Please refer to "Drug Safety Data: How to Analyze, Summarize and Interpret to Determine Risk" (Klepper MJ and Cobert B 2011).

Clinically notable values will be forwarded to Novartis/Sponsor at the same time that they are sent to Investigators, and give any procedures that should be followed when these values are noted.

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication
- Trial Feedback Questionnaires (TFQ) - as per time points defined within Section 1.3
- Further material might be developed once all relevant approval have been obtained.

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-2 should be followed-up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP, and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 7), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 10-3
- Imaging such as abdominal US, CT, or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

NOTE: Patients with wAIHA tend to have elevated transaminases, especially AST, and indirect BIL due to the hemolytic nature of this condition. Hence, ONLY ALT and Direct BIL need to be emphasized or evaluated to differentiate further between hemolysis due to the study treatment indication (wAIHA) or DILI.

Table 10-2 Required actions and follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	● Discontinue the study treatment immediately ● Hospitalize, if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
>8 × ULN	● Discontinue the study treatment immediately ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT until resolution[c] (frequency at investigator discretion)
>3 × ULN and INR >1.5	● Discontinue the study treatment immediately ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT until resolution[c] (frequency at investigator discretion)
>5 to ≤ 8 × ULN	● Repeat LFT within 48 hours ● If elevation persists, continue follow-up monitoring ● If elevation persists for more than 2 weeks, discontinue the study drug ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GDLH and γGT until resolution[c] (frequency at investigator discretion)
>3 × ULN accompanied by symptoms[b]	● Discontinue the study treatment immediately ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT until resolution[c] (frequency at investigator discretion)
>3 to ≤5 × ULN (patient is asymptomatic	● Measure ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT in 48-72 hours ● If elevation is confirmed, initiate close observation of the patient	Follow-up for symptoms

Criteria	Actions required	Follow-up monitoring
ALP (isolated)		
>2 × ULN (in the absence of known bone pathology)	● Repeat LFT within 48 hours ● If elevation persists, measure fractionated ALP; if > 50% is of liver origin, establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
Grade 2 (>1.5 – 3.0 ULN)	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 3 (> 3 - 10 × ULN) (in the absence of known Gilbert syndrome)	● Interrupt treatment Repeat LFT within 48-72 hours. ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
Grade 4 (> 10 x ULN)	● Discontinue the study treatment immediately Hospitalize the participant ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Jaundice	● Discontinue the study treatment immediately ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, GLDH and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory values) in the appropriate eCRF	Investigator discretion

[a]Elevated ALT/AST >3 × ULN and TBL >2 × ULN but without notable increase in ALP to >2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 10-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	● IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	● IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	● ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	● Ethanol history, GGT, MCV, CD-transferrin

Disease	Assessment
Nonalcoholic steatohepatitis	● Ultrasound or MRI
Hypoxic/ischemic hepatopathy	● Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	● Ultrasound or MRI, ERCP as appropriate.
Wilson disease	● Caeruloplasmin
Hemochromatosis	● Ferritin, transferrin
Alpha-1-antitrypsin deficiency	● Alpha-1-antitrypsin

10.6 Appendix 6: Renal safety monitoring

The available data do not suggest a safety signal for renal toxicity in ianalumab-exposed patients. Standard renal function tests will be obtained at regular intervals. Specific renal safety alert criteria, actions and follow-up for renal events are provided in Table 10-4 and Table 10-5, respectively.

Table 10-4 Specific Renal Alert Criteria and Actions

Renal Event	Action
Confirmed serum creatinine increase 25 – 49%	● Consider causes and possible interventions ● Follow-up within 2-5 days
Serum creatinine increase ≥ 50 %*	● Consider causes and possible interventions ● Repeat assessment within 24-48h if possible ● Consider drug interruption or discontinuation unless other causes are diagnosed and corrected ● Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	● Consider causes and possible interventions ● Assess serum albumin & serum total protein ● Repeat assessment to confirm ● Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document ● Repeat assessment to confirm ● Distinguish hemoglobinuria from hematuria ● Urine sediment microscopy ● Assess sCr ● Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation

Table 10-5 Follow-up for renal events

Assess, document and record in CRF
● Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells
● Blood pressure and body weight
● Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
● Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until
● Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or
● Event stabilization: sCr level with ±10% variability over last 6 months or protein- creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
● Analysis of urine markers in samples collected over the course of the Drug-Induced Nephrotoxicity (DIN) event

10.7 Appendix 7: Adverse Events potentially related to B-cell depletion

Adverse events potentially related to B-cell depletion include infections, malignancies, B-cell recovery, hypogammaglobulinemia.

10.8 Appendix 8: Wash-out period for immunosuppressive therapies

If immunosuppressive therapies were used for treatment of wAIHA prior to study enrollment, following wash-out periods should be taken into account prior to randomization:

- Azathioprine - 4 weeks
- Mycophenolate mofetil - 6 weeks
- Cyclosporine - 4 weeks
- Cyclophosphamide - 4 weeks
- Bortezomib - 4 weeks
- B-cell depleting therapy (e.g., rituximab) - 12 weeks

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CONTRATTO PER LA CONDUZIONE DELLA SPERIMENTAZIONE CLINICA SUI MEDICINALI
"Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (wAIHA) che hanno fallito almeno una linea di trattamento (VAYHIA)"

TRA

Azienda ULSS 7 Pedemontana, con sede legale in Via dei Lotti, 40, CAP 36061 Bassano del Grappa (VI), C.F. e P. IVA n. 00913430245, in persona del Legale Rappresentante, Dott. Carlo Bramezza, in qualità di Direttore Generale (d'ora innanzi denominato/a "**Ente**")

E

Novartis Farma S.p.A., con sede legale in Milano, viale Luigi Sturzo n. 43, C.F. n. 07195130153 e P.IVA n. 02385200122, in persona dei suoi Procuratori Dott.ssa Donatella Albanesi e Dott.ssa Eva Josephine Runggaldier (d'ora innanzi denominata "**Società**"), che in forza di delega è autorizzata ad agire in nome proprio e per conto del promotore Novartis Pharma AG, Lichtstrasse 35 CH-4056 Basel (Svizzera) (d'ora innanzi denominato "**Promotore**")

di seguito per brevità denominati/e singolarmente/collettivamente "la Parte/le Parti"

Premesso che:

A. la Società, affiliata del Promotore e finanziatore di studi clinici a livello internazionale nel gruppo Novartis, è stata delegata dal Promotore e ha ricevuto l'incarico di svolgere, anche in qualità di "applicant/richiedente", le attività e i servizi finalizzati alla realizzazione degli studi clinici internazionali nel territorio italiano (di seguito "**le attività**"), conformemente alla regolamentazione applicabile; tali attività vengono svolte a livello locale, anche in nome proprio e per conto del Promotore, ove previsto dallo studio specifico;
B. in virtù di quanto precede, la Società è stata incaricata di eseguire, le attività volte alla realizzazione nel territorio italiano dello studio clinico internazionale denominato "Studio di fase 3, randomizzato, in doppio cieco, per valutare l'efficacia e la sicurezza d'impiego di ianalumab (VAY736) versus placebo nei pazienti con anemia emolitica autoimmune calda (wAIHA) che hanno fallito almeno una linea di trattamento (VAYHIA)" (di seguito per brevità "**Sperimentazione**") avente ad oggetto il Protocollo CVAY736O12301 versione n. 02 del 29.09.2022 e suoi successivi emendamenti debitamente approvati (di seguito "**Protocollo**"), codice EudraCT n. 2022-001773-31, presso l'Ente, sotto la responsabilità del Dott. Eros Di Bona, in qualità di Responsabile scientifico della sperimentazione oggetto del presente Contratto (di seguito "**Sperimentatore principale**"), nell'U.O.C. Oncoematologia (di seguito "**Centro di sperimentazione**"); dette attività sono tutte quelle funzionali alla realizzazione della Sperimentazione, parte delle quali vengono sub-affidate alla CRO come specificato al paragrafo successivo;
C. la Società ha autonomamente disciplinato con la Contract Research Organization OPIS S.r.l. (di seguito "**CRO**") l'affidamento delle attività connesse alla conduzione della Sperimentazione. Dette attività, ivi inclusa l'eventuale attività quale "applicant/richiedente", sono dettagliate nel CTA Form (Clinical Trial Application Form) sottomesso all'Autorità Competente e al Comitato Etico di riferimento per l'Ente da parte della Società, che ha parimenti provveduto a nominare la CRO quale responsabile del trattamento dei dati

personali ai sensi della vigente normativa comunitaria e nazionale in materia (Regolamento Generale sulla Protezione dei Dati Reg. UE 679/2016 e Codice in materia di Protezione dei Dati Personali Decreto Legislativo 196/2003, così come modificato dal D. Lgs 101/2018, di seguito anche solo "**Normativa sulla Protezione dei Dati**");

D. la Società ha individuato quale proprio referente scientifico per la parte di propria competenza il Dott. Patrizio Stefanelli;
E. il Centro di sperimentazione possiede le competenze tecniche e scientifiche per la Sperimentazione ed è struttura adeguata alla conduzione della sperimentazione nel rispetto della normativa vigente;
F. l'Ente si obbliga a rendere edotto lo Sperimentatore principale circa i termini e le condizioni del presente Contratto;
G. lo Sperimentatore principale ed i suoi diretti collaboratori, qualificati in base al Protocollo ad intervenire con poteri discrezionali nell'esecuzione di esso (di seguito "**Co-sperimentatori**"), così come tutti gli altri soggetti che svolgano qualsiasi parte della Sperimentazione sotto la supervisione dello Sperimentatore principale, sono idonei alla conduzione della Sperimentazione in conformità alla normativa applicabile, conoscono il Protocollo e le norme di buona pratica clinica e possiedono i requisiti normativi e regolamentari necessari, compreso il rispetto della normativa vigente riguardante il conflitto di interessi; al contempo l'Ente dichiara che le Attività previste nel presente Contratto non comportano alcuna violazione di impegni assunti con soggetti terzi;
H. salvo quanto eventualmente, successivamente, diversamente concordato per iscritto dalle Parti e salvo quanto disciplinato nel successivo art. 14, l'Ente dovrà condurre la Sperimentazione esclusivamente presso le proprie strutture;
I. l'Ente si impegna per sé e per lo Sperimentatore principale a rendere disponibili tempestivamente alla Società le informazioni relative ad una eventuale radiazione dall'Albo dello Sperimentatore principale nel corso dello svolgimento della stessa, alla luce delle previsioni della sezione 306 (a) o (b) del "Federal Food, Drug and Cosmetic Act";
J. l'Ente, pur essendo dotato di apparecchiature idonee all'esecuzione della Sperimentazione, riceve in comodato d'uso gratuito dalla Società, ai sensi e per gli effetti del Codice Civile, le attrezzature e/o i beni fondamentali per il buon esito della Sperimentazione, elencate all'art. 5 del presente Contratto;
K. la Società ha presentato ad AIFA (di seguito "**Autorità Competente**"), in virtù del D. L. n. 158 del 13 settembre 2012 ("Decreto Balduzzi"), convertito con L. n. 189 del 8 novembre 2012, nei termini previsti dalla normativa, la domanda di autorizzazione allo svolgimento della Sperimentazione;
L. ai sensi dell'art. 7 del D. Lgs. n. 211 del 24 giugno 2003, in data 30.11.2022, la Società ha ottenuto il Parere Unico favorevole all'effettuazione della Sperimentazione da parte del Comitato Etico Campania Nord c/o Azienda Ospedaliera "S. Giovanni Moscati" di Avellino, cui afferisce il Centro Coordinatore della Sperimentazione per l'Italia; accettando il Parere Unico di cui sopra, il Comitato Etico competente in data 14.02.2023 ha espresso parere favorevole alla conduzione della Sperimentazione, confermato, una volta sciolte le riserve, in data 14.03.2023;
M. ai sensi dell'art. 76 del Regolamento e delle disposizioni nazionali applicabili, la Società ha stipulato la polizza assicurativa come meglio precisato all'art.8 del presente Contratto;
N. nella negoziazione del presente Contratto le Parti si sono basate sullo schema approvato dal Centro di coordinamento nazionale dei Comitati etici territoriali ai sensi dell'art. 2, comma 6, della l. 11 gennaio 2018 n. 3 e, nel rispetto dell'omogeneità degli aspetti amministrativi,

economici, assicurativi ivi richiamata, hanno ritenuto di integrare e/o modificare le relative previsioni, ai fini della disciplina delle specificità e peculiarità della Sperimentazione, sulla base di peculiarità organizzative e di specifiche esigenze operative del Promotore, della Società e dell'Ente

Tutto ciò premesso, tra le Parti si conviene e si stipula quanto segue:

Art. 1 - Interezza del Contratto

1.1 Le premesse, il Protocollo, anche se non materialmente accluso, e tutti gli allegati, incluso il budget (Allegato A) e il glossario relativo alla protezione dati personali (Allegato B), fanno parte integrante e sostanziale del presente Contratto.

Art. 2 - Oggetto

2.1 La Società affida all'Ente l'esecuzione della Sperimentazione alle condizioni indicate nel presente Contratto, in accordo col Protocollo, con gli eventuali successivi emendamenti, nonché con le modifiche al presente Contratto/budget da questi derivanti e formalizzate mediante i necessari atti di modifica tempestivamente sottoscritti.

2.2 La Sperimentazione deve essere condotta nel più scrupoloso rispetto del Protocollo, nella versione vigente, accettata dallo Sperimentatore principale e approvata dal Comitato Etico e dall'Autorità Competente, in conformità alla vigente normativa in materia di sperimentazioni cliniche di medicinali e ai principi etici e deontologici che ispirano l'attività medica dei professionisti a vario titolo coinvolti.

2.3 La Sperimentazione deve essere altresì condotta in conformità ai principi contenuti nella Convenzione sui Diritti dell'Uomo e la Biomedicina, nella Dichiarazione di Helsinki nella versione aggiornata, nelle vigenti regole della Buona Pratica Clinica, e in conformità delle leggi applicabili in tema di trasparenza e prevenzione della corruzione, nonché di protezione dei dati personali secondo la normativa vigente.

2.4 Con la sottoscrizione del presente Contratto, le Parti dichiarano di conoscere e accettare il contenuto di quanto sopra richiamato.

2.5 La Società e lo Sperimentatore principale, avendo l'obbligo di tutelare la salute dei pazienti, quando ricorrano le circostanze, possono adottare urgenti e adeguate misure a tutela della sicurezza dei pazienti, quali la sospensione temporanea dello studio (interruzione del trattamento per i pazienti già coinvolti nella Sperimentazione, ovvero interruzione dell'inclusione di nuovi soggetti), anche in assenza delle necessarie approvazioni dal parte del Comitato Etico e dell'Autorità Competente, fermo restando l'obbligo per la Società di informare immediatamente il Comitato Etico e l'Autorità Competente, oltre che i partecipanti allo studio in merito ai nuovi eventi, alle misure intraprese e al programma di provvedimenti da adottare, completando tempestivamente le procedure previste dalla vigente normativa.

2.6 Poiché la Sperimentazione prevede l'inclusione competitiva dei pazienti, è prevista da parte dell'Ente l'inclusione di circa 2 soggetti, con il limite del numero massimo di 90 pazienti candidabili alla Sperimentazione a livello globale e dei termini previsti dal Promotore.

Il periodo previsto di inclusione è suscettibile di modifiche in funzione del suo andamento anche a livello internazionale. Al raggiungimento del numero totale dei pazienti previsti per l'intera Sperimentazione, l'inclusione di ulteriori pazienti verrà automaticamente chiusa, indipendentemente dal numero di pazienti inclusi presso l'Ente, a eccezione dei pazienti che hanno già fornito il loro consenso a partecipare alla Sperimentazione, a meno che essi stessi non ritirino il consenso. La Società provvederà a inviare all'Ente adeguata e tempestiva comunicazione.

2.7 L'Ente e la Società conserveranno la documentazione inerente la Sperimentazione (fascicolo permanente "trial master file") per un periodo di 25 (venticinque) anni dal termine della Sperimentazione (o per un periodo più lungo, qualora ciò sia richiesto da altre norme applicabili). La Società ha l'obbligo di comunicare al Centro Sperimentale l'avvenuta scadenza del termine dell'obbligo di conservazione. A richiesta della Società, dopo lo spirare del termine suddetto, le Parti potranno concordare le condizioni di un ulteriore periodo di conservazione.
2.8 L'Ente e la Società, ciascuno per gli ambiti di propria competenza, si obbligano inoltre a conservare la citata documentazione adottando delle forme di digitalizzazione (o dematerializzazione) documentale, ove applicabile. Indipendentemente dal fatto che l'archiviazione della documentazione inerente la Sperimentazione riguardi o meno dati personali (di natura particolare o meno), secondo le definizioni del Regolamento (UE) n. 679/2016 (di seguito "**GDPR**"), l'Ente e la Società dovranno adottare tutte le misure fisiche e tecniche di cui all'art. 32 del GDPR ed effettuare gli eventuali controlli di sicurezza previsti dalla normativa vigente, a protezione di dati, informazioni e documenti (sia cartacei che elettronici). Il sistema di archiviazione adottato dovrà garantire non solo l'integrità dei dati, delle informazioni e dei documenti cartacei ed elettronici, ma altresì la loro futura leggibilità per tutto il periodo previsto dall'obbligo di conservazione. Per l'espletamento di tale obbligazione, sia la Società che l'Ente potranno avvalersi di soggetti esterni che gestiscano tale obbligo di archiviazione, stipulando con gli stessi separati accordi.
2.9 La Società, l'Ente e lo Sperimentatore principale devono rispettare le direttive, le indicazioni, le istruzioni e le raccomandazioni impartite dal Comitato Etico e dall'Autorità competente.

Art. 3 - Sperimentatore principale e Co-sperimentatori

3.1 Lo Sperimentatore principale sarà coadiuvato nell'esecuzione della Sperimentazione da collaboratori diretti, qualificati in base al Protocollo ad intervenire con poteri discrezionali nell'esecuzione di esso (di seguito "**Co-sperimentatori**"), nonché dal personale, sanitario e non sanitario, incaricato dall'Ente. Co-sperimentatori ed altro personale opereranno sotto la responsabilità dello Sperimentatore Principale per gli aspetti relativi alla Sperimentazione; essi dovranno essere qualificati per la conduzione della Sperimentazione ed aver ricevuto preventivamente adeguata formazione, secondo la normativa vigente, da parte della Società; ciascuno di essi dovrà aver manifestato la propria disponibilità a partecipare alla Sperimentazione.
3.2 Le Parti prendono atto che lo Sperimentatore principale è tenuto a ogni responsabilità e obbligo imposti a tale figura dalla normativa vigente in materia di sperimentazioni cliniche di medicinali.
3.3 Il presente rapporto intercorre tra la Società e l'Ente. La Società è estranea a rapporti esistenti tra l'Ente, lo Sperimentatore principale, i Co-sperimentatori, e tutto l'altro personale partecipante alla Sperimentazione, restando quindi sollevata da qualsiasi pretesa che costoro dovessero avanzare in relazione alla Sperimentazione.
3.4 In relazione alla Sperimentazione oggetto del presente Contratto, le Parti si danno atto di aver adempiuto - per quanto di propria competenza - a quanto previsto dall'art. 7 del Regolamento, nonché dall'art. 6, comma 4 del D. Lgs. 14 maggio 2019, n. 52, come modificato dall'art. 11-bis della L. 17 luglio 2020, n. 77, di conversione del D.L. 19 maggio 2020, n. 34 ("Decreto Rilancio").
3.5 Qualora il rapporto tra lo Sperimentatore principale e l'Ente dovesse per qualsiasi ragione concludersi, l'Ente deve informarne tempestivamente per iscritto la Società, indicando il nominativo di un sostituto. L'indicazione del sostituto deve essere oggetto di approvazione da parte della Società e del Comitato Etico competente. L'Ente garantisce che il nuovo

Sperimentatore principale abbia i requisiti idonei a proseguirla, accetti i termini e le condizioni del presente Contratto e assuma l'impegno di rispettare il Protocollo nell'esecuzione della Sperimentazione. Nelle more dell'approvazione dell'emendamento sostanziale di cambio dello Sperimentatore principale, lo Sperimentatore indicato dall'Ente garantisce la necessaria continuità dell'attività sperimentale.
Nel caso in cui la Società non intenda accettare il nominativo del sostituto proposto dall'Ente oppure questi non proponga un sostituto, la Società potrà recedere dal presente Contratto in accordo a quanto previsto dall'art. 7.
3.6 Lo Sperimentatore principale prima di iniziare la Sperimentazione, deve acquisire il consenso informato del paziente o del suo rappresentante legale, secondo quanto previsto dalla vigente normativa in materia di sperimentazioni cliniche e il consenso al trattamento dei dati personali ai sensi e per gli effetti della vigente normativa nazionale e comunitaria in materia di protezione dei dati personali, come successivamente declinato all'art. 11.
3.7 Lo Sperimentatore principale ha l'obbligo di registrare e documentare dettagliatamente tutti gli eventi avversi ed eventi avversi gravi e di darne comunicazione alla Società nei termini previsti dalla legislazione vigente.
Inoltre, lo Sperimentatore principale deve fornire ogni altra informazione clinica di rilievo indicata nel Protocollo (ad esempio gravidanza o scenari speciali), direttamente o indirettamente correlabile all'esecuzione della Sperimentazione, secondo quanto previsto dal Protocollo, dalle norme di Buona Pratica Clinica e dalla normativa applicabile in materia di farmacovigilanza e sperimentazione clinica di medicinali.
3.8 L'Ente garantisce il corretto svolgimento della Sperimentazione da parte dello Sperimentatore Principale e del personale posto sotto la sua responsabilità secondo i più elevati standard di diligenza. In particolare:
3.8.1 Lo Sperimentatore principale deve consegnare tutte le Schede Raccolta Dati (Case Report Forms-CRF) correttamente compilate, secondo termini e modalità previsti dal Protocollo della sperimentazione e dalla normativa applicabile, in formato cartaceo o elettronico entro 5 giorni dopo l'effettuazione di ciascuna visita ai pazienti in studio.
3.8.2 Lo Sperimentatore principale si impegna altresì a risolvere le richieste di chiarimento (*queries*) generate dal Promotore, dalla Società e/o da Società terze da questi incaricate entro 5 giorni dal ricevimento delle stesse.
3.8.3 Per verificare la corrispondenza tra i dati registrati nelle Schede Raccolta Dati e quelli contenuti nei documenti originali (per es. cartella clinica), l'Ente e lo Sperimentatore principale consentono l'accesso diretto ai dati originali durante le visite di monitoraggio e nel corso di eventuali *audit* promossi dal Promotore, dalla Società, da terze parti da questi incaricate e ispezioni da parte delle Autorità Competenti, incluse le modalità da remoto, purché non vengano violate le norme in materia di riservatezza e di protezione dei dati personali dei pazienti.
3.8.4 L'Ente e lo Sperimentatore principale, informati con congruo preavviso, devono consentire il corretto svolgimento dell'attività di monitoraggio, di auditing e di ispezioni presso il Centro sperimentale da parte del personale del Promotore, della Società, di terze parti da questi incaricate, della CRO e da parte dell'Autorità Competente, attività effettuate per garantire la regolare esecuzione della Sperimentazione.
3.9 L'Ente avviserà tempestivamente la Società qualora un'Autorità Competente comunichi all'Ente un avviso di ispezione/*audit* relativo alla Sperimentazione e, se non negato espressamente dall'Autorità Competente, l'Ente autorizzerà la Società e/o il Promotore a parteciparvi, inviando nel contempo alla Società ogni comunicazione scritta ricevuta e/o trasmessa ai fini o in risultanza dell'ispezione/*audit*.

3.10 Tali attività non devono però pregiudicare in alcun modo lo svolgimento dell'ordinaria attività istituzionale dell'Ente
3.11 L'Ente e il Promotore garantiscono che i campioni biologici (sangue, urine, saliva ecc.) dei pazienti coinvolti nella Sperimentazione di cui al presente Contratto saranno utilizzati esclusivamente per la Sperimentazione oggetto del presente Contratto, secondo le previsioni del Protocollo e della vigente normativa. L'eventuale conservazione e successivo utilizzo sono vincolati all'acquisizione di uno specifico consenso informato da parte del paziente (o del genitore/tutore legale), al parere favorevole del Comitato Etico, nei limiti e con le garanzie previste dalle norme vigenti e dalle linee di indirizzo di cui all'art. 1 del D. Lgs 14 maggio 2019 n. 52.

Art. 4 - Medicinali Sperimentali, Materiali e Servizi

4.1 La Società si impegna a fornire gratuitamente all'Ente, per tutta la durata della Sperimentazione e nelle quantità necessarie e sufficienti all'esecuzione della Sperimentazione, il/i prodotto/i farmaceutico/i oggetto della Sperimentazione e gli altri farmaci previsti dal protocollo in ottemperanza al D.M. 21 dicembre 2007, Allegato 1, punto 3 Tabella I, inclusi i medicinali da utilizzarsi in associazione o combinazione tra loro, ogniqualvolta oggetto dello studio sia appunto l'associazione o combinazione (in seguito "Medicinali Sperimentali") e a provvedere con oneri a proprio carico alla fornitura dei medicinali ausiliari e della terapia di background, cioè lo standard terapeutico per la patologia oggetto di sperimentazione, qualora inclusa, secondo il protocollo sperimentale, nel confronto fra le diverse strategie terapeutiche oggetto di sperimentazione. Le quantità dei Medicinali Sperimentali, dei medicinali ausiliari e della terapia di background a carico della Società devono essere adeguate alla numerosità della casistica trattata. La ricezione e il tracciamento dei farmaci dovranno avvenire con la registrazione dei lotti, attività a carico dell'Ente. Restano a carico dell'Ente le terapie di background non incluse nelle strategie terapeutiche di confronto.
Di seguito il dettaglio dei farmaci che la Società fornirà all'Ente: *VAY736 (ianalumab) 150 mg/1mL, concentrato per soluzione per infusione, Placebo 0 mg/1mL, concentrato per soluzione per infusione.*
Verranno inoltre forniti kit lab e test di gravidanza.
Il costo delle premedicazioni utilizzate è incluso nel compenso paziente corrisposto per lo studio.
Nel caso in cui il materiale infusionale (sacca, linea infusionale e filtro) in dotazione presso il centro per la somministrazione dell'IMP sia compatibile con i requisiti del manuale del farmacista, verrà utilizzato e il costo dello stesso è da intendersi incluso nel costo visita corrisposto dalla Società (le visite in cui è prevista l'infusione sono le seguenti: W1D1, W5D1, W9D1 e W13D1).
Nel caso in cui il materiale infusionale non fosse compatibile verrà invece fornito da Novartis.

La Società si impegna altresì a fornire con oneri a proprio carico ogni altro materiale necessario all'esecuzione della Sperimentazione (di seguito "**Materiali**"), nonché gli esami di laboratorio diagnostici o di monitoraggio, inerenti l'utilizzo dei Medicinali Sperimentali o gli obiettivi primari e secondari della Sperimentazione (di seguito "**Servizi**").
4.2 La Società non ritiene necessario specificare alcun impegno per garantire la continuità terapeutica in quanto il trattamento con il farmaco in studio prevede solo quattro trattamenti che verranno effettuati nel corso del protocollo. Non sono previsti ulteriori trattamenti per i pazienti.

4.3 I Medicinali Sperimentali devono essere inviati dalla Società alla Farmacia dell'Ente che provvederà alla loro registrazione, appropriata conservazione e consegna allo Sperimentatore principale, così come previsto dal Protocollo e dalla normativa vigente.
4.4 I Medicinali Sperimentali dovranno essere muniti di adeguato documento di trasporto destinato alla Farmacia, con la descrizione del tipo di farmaco, della sua quantità, del lotto di preparazione, dei requisiti per la conservazione, della scadenza e i riferimenti alla Sperimentazione (codice di protocollo, Sperimentatore principale e Centro di Sperimentazione interessato).
4.5 L'Ente e lo Sperimentatore principale devono utilizzare i Medicinali Sperimentali e i Materiali forniti dalla Società esclusivamente nell'ambito e per l'esecuzione della Sperimentazione. L'Ente non deve trasferire o cedere a terzi i Medicinali Sperimentali e/o i Materiali/Servizi forniti dalla Società ai sensi del presente Contratto.
4.6 I Medicinali Sperimentali scaduti o non utilizzabili, ovvero non utilizzati al termine della Sperimentazione, saranno integralmente ritirati dalla Società (o suo incaricato) e successivamente smaltiti a sue spese.

Art. 5 - Comodato d'uso

5.1 La Società concede in comodato d'uso gratuito all'Ente, che accetta ai sensi e per gli effetti degli artt. 1803 e ss c.c., lo/gli Strumento/i meglio descritti in appresso, unitamente al pertinente materiale d'uso, con relativa documentabilità della consegna e del ritiro (di seguito cumulativamente lo "Strumento"):
a) N. 2 tablet a centro (di cui n. 1 tablet come back up) per la compilazione dei questionari previsti da Protocollo messo a disposizione da Novartis Pharma AG, di cui di seguito la descrizione:
Costruttore: Samsung
Modello: X250
Fornitore: IQVIA
Valore commerciale: € 303,79 + I.V.A.

b) Qualora il Protocollo di studio preveda attività da completare attraverso una linea telefonica, ed il Centro Sperimentale non disponga di una linea telefonica adeguata, la Società provvederà all'installazione di una linea telefonica analogica. Tale linea dovrà essere utilizzata solo ed esclusivamente per adempiere alle attività Protocollo specifiche (es. trasmissione records elettronici, trasmissione/ricevimento fax) e verrà chiusa al termine dello studio. Tutti i costi relativi alla linea telefonica saranno a carico della Società.

L'Apparecchiatura recherà un'etichetta con la dicitura: "concessa in comodato d'uso da Novartis Farma S.p.A.".
La proprietà dello Strumento, come per legge, non viene trasferita all'Ente. Gli effetti del presente comodato decorreranno dalla data di consegna dello/gli Strumento/i e cesseranno al termine della Sperimentazione, quando lo/gli Strumento/i dovrà/anno essere restituito/i alla Società senza costi a carico dell'Ente.
Le Parti concordano altresì che gli eventuali ulteriori Strumenti ritenuti necessari alla conduzione dello studio nel corso della Sperimentazione, qualora ne ricorrano le caratteristiche e le condizioni, a fronte di richiesta scritta da parte dell'Ente, saranno concessi in comodato d'uso gratuito secondo la disciplina di cui al presente Contratto, previa accettazione scritta da parte della Società.

5.2 Lo/Gli Strumento/i in questione deve/sono essere munito/i di dichiarazione di conformità alle normative e direttive europee. Lo/Gli Strumento/i in questione verranno sottoposti a collaudo di accettazione, qualora lo strumento abbia un'azione diretta sul paziente o su altri macchinari presenti nell'Ente, da parte dei tecnici incaricati dell'Ente per le verifiche di corretta installazione e funzionalità e rispetto della normativa vigente. Al momento della consegna dei materiali forniti in comodato d'uso dalla Società all'Ente, viene redatta da parte dell'Ente idonea documentazione attestante la consegna.
5.3 La Società si fa carico delle spese di trasporto e di installazione dello Strumento/i e si impegna a fornire, a propria cura e spese, l'assistenza tecnica necessaria per il suo funzionamento nonché eventuale materiale di consumo per il suo utilizzo, senza costi per l'Ente.
5.4 La Società svolgerà, a sua cura e spese, in collaborazione con lo Sperimentatore, tutti gli eventuali interventi tecnici necessari per il buon funzionamento dello Strumento. In caso di disfunzione o guasto dello Strumento, tempestivamente comunicati dallo Sperimentatore, la Società provvederà direttamente o tramite personale specializzato, alla manutenzione correttiva o riparazione o sostituzione con analogo Strumento.
5.5 La Società terrà a proprio carico ogni onere e responsabilità in relazione ad eventuali danni che dovessero derivare a persone o cose in relazione all'uso dell'apparecchiatura in oggetto secondo le indicazioni del Protocollo e le istruzioni del produttore, qualora dovuti a vizio della stessa, fatto quindi salvo il caso in cui tali danni siano causati da dolo e/o colpa grave dell'Ente.
A tal fine verrà apposta sullo/gli Strumento/i apposita etichetta o altra idonea indicazione della proprietà.
5.6 Lo/gli Strumento/i sarà/anno utilizzato/i dal personale dell'Ente e/o dai pazienti e ai soli ed esclusivi fini della Sperimentazione oggetto del presente Contratto, conformemente a quanto previsto nel Protocollo. L'Ente si obbliga a custodire e conservare lo/gli Strumento/i in maniera appropriata e con la cura necessaria a non destinarlo/li a un uso diverso da quello sopra previsto, a non cedere neppure temporaneamente l'uso dello/gli Strumento/i a terzi, né a titolo gratuito né a titolo oneroso, e a restituire lo/gli Strumento/i alla società nello stato in cui gli è/sono stato/i consegnato/i, salvo il normale deterioramento per l'effetto dell'uso. Qualora lo/gli Strumento/i sia/siano consegnato/i ai pazienti, l'Ente comunicherà ad ogni paziente che quest'ultimo sarà obbligato a custodire e conservare lo/gli Strumento/i in maniera appropriata e con la cura necessaria a non destinarlo/li a un uso diverso da quello sopra previsto, a non cedere neppure temporaneamente l'uso dello/gli Strumento/i a terzi, né a titolo gratuito né a titolo oneroso, e a restituire lo/gli Strumento/i all'Ente nello stato in cui gli è/sono stato/i consegnato/i, salvo il normale deterioramento per l'effetto dell'uso.
5.7 La Società si riserva il diritto di richiedere l'immediata restituzione dello/gli Strumento/i qualora lo/gli stesso/i venga/no utilizzato/i in maniera impropria o comunque in modo difforme dalle previsioni di cui al presente Contratto.
5.8 In caso di furto o perdita o smarrimento dello/gli Strumento/i, l'Ente provvederà tempestivamente dalla conoscenza dell'evento, alla presentazione di formale denuncia alla competente pubblica autorità con comunicazione dell'accaduto alla Società nello stesso termine.
In tutti gli altri casi di danneggiamento o distruzione, l'Ente dovrà darne comunicazione alla Società tempestivamente dalla conoscenza dell'evento. L'eventuale utilizzo fraudolento o comunque non autorizzato dovrà essere segnalato immediatamente dallo Sperimentatore principale alla Società.
In caso di danneggiamento irreparabile o furto dello/gli Strumento/i, la Società provvederà alla sostituzione dello stesso/degli stessi, senza costi per l'Ente, salvo che il fatto derivi da dolo dell'Ente.

5.9 Resta inteso che per quanto attiene agli Strumenti che saranno direttamente maneggiati o gestiti dai pazienti/genitori/tutori legali (es. diari elettronici), la Società riconosce che l'Ente è sollevato da responsabilità derivanti da manomissione, danneggiamento o furto degli stessi Strumenti imputabili ai pazienti/genitori/tutori legali. In caso di guasto e/o smarrimento da parte dei soggetti che partecipano allo studio, la Società provvederà a proprie spese alla sostituzione dell'attrezzatura; l'Ente si farà carico della consegna dell'attrezzatura al destinatario, compresa la registrazione e la consegna delle istruzioni della Società, nonché del ritiro al momento dell'uscita, per qualsiasi ragione avvenuta, del soggetto dallo studio; l'Ente si farà inoltre carico di informare tempestivamente la Società per qualunque mancata restituzione dell'attrezzatura da parte dei soggetti che partecipano allo studio.
5.10 L'autorizzazione alla concessione in comodato d'uso gratuito dello/gli Strumento/i è stata rilasciata dall'Ente a seguito delle e secondo le proprie procedure interne.
5.11 Qualora lo Strumento (in toto o in parte) sia funzionale all'esecuzione di un successivo studio clinico da avviarsi al termine della Sperimentazione oggetto del presente Contratto, entro sei mesi dalla conclusione di quest'ultima, nella medesima struttura/dipartimento, essa potrà essere mantenuta nella disponibilità dell'Ente sino all'avvio del nuovo studio clinico, rimanendo inteso che le condizioni del comodato d'uso gratuito per il nuovo studio clinico saranno disciplinate da apposito contratto. Nel periodo intercorrente tra il termine della Sperimentazione e l'avvio del nuovo studio clinico l'Ente si impegna a non utilizzare lo Strumento e a custodirlo e conservarlo con ogni diligenza, rimanendo responsabile della sua integrità e funzionamento in via esclusiva.

Art. 6 - Corrispettivo

6.1 Il corrispettivo pattuito, preventivamente valutato dall'Ente, per paziente eleggibile, valutabile e che abbia completato il trattamento sperimentale secondo il Protocollo e per il quale sia stata compilata validamente la relativa CRF, comprensivo di tutte le spese sostenute dall'Ente per l'esecuzione della Sperimentazione e dei costi di tutte le attività ad essa collegate, è pari ad € 6.500,00 (seimilacinquecento/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite previste dal protocollo per la fase di trattamento (complessivi € 13.000,00 + I.V.A per n. 2 pazienti); € 5.700,00 (cinquemilasettecento/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI CROSSOVER previste dal protocollo (complessivi € 11.400,00 I.V.A. per n. 2 pazienti); € 15.450,00 (quindicimilaquattrocentocinquanta/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI FOLLOW-UP-DURABLE RESPONSE previste dal protocollo (complessivi € 30.900,00 + I.V.A. per n. 2 pazienti); € 5.250,00 (cinquemiladuecentocinquanta/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI FOLLOW-UP-NON IN DURABLE RESPONSE previste dal protocollo (complessivi € 10.500,00 + I.V.A. per n. 2 pazienti), come meglio dettagliato nel Budget qui allegato (Allegato "A").
6.2 La Società si impegna a corrispondere quanto dovuto ai sensi del presente articolo sulla base di quanto risulta da adeguato prospetto/rendiconto giustificativo, concordato tra le Parti.
Il pagamento del compenso di cui sopra verrà effettuato con la cadenza indicata nel Budget (Allegato A) sulla base del numero dei pazienti coinvolti nel relativo periodo, dei trattamenti da loro effettuati secondo Protocollo e in presenza delle relative CRF debitamente compilate e ritenute valide dalla Società in base alle attività svolte.
6.3 Gli importi previsti per gli esami di laboratorio e/o strumentali e ogni altra prestazione/attività richiesta da Protocollo svolti localmente sono inclusi nel corrispettivo pattuito per paziente eleggibile, di cui all'Allegato A, così come approvato dal Comitato Etico e dall'Autorità Competente.

6.4 L'Ente non riceverà alcun compenso per pazienti non valutabili a causa di inosservanza del Protocollo, di violazione delle norme di Buona Pratica Clinica o di mancato rispetto della normativa vigente in materia di sperimentazioni cliniche di medicinali. L'Ente non avrà diritto ad alcun compenso anche per pazienti coinvolti successivamente alla comunicazione di interruzione e/o conclusione della Sperimentazione da parte della Società od oltre il numero massimo di soggetti da includere ai sensi del presente Contratto, ove non concordati con la Società

6.5 La Società provvederà, inoltre, a rimborsare all'Ente tutti i costi aggiuntivi risultanti da attività mediche/diagnostiche, compresi eventuali ricoveri e somministrazione di farmaci, non previsti nel Protocollo o nei successivi emendamenti allo stesso, e non già coperti dai compensi sopra elencati, qualora tali attività si rendano indispensabili per una corretta gestione clinica del paziente in sperimentazione. La Società rimborserà le attività mediche/diagnostiche e gli eventuali ricoveri sulla base del tariffario dell'Ente e i farmaci sulla base del prezzo di acquisto degli stessi da parte dell'Ente. Il rimborso sarà effettuato, previa emissione della fattura da parte dell'Ente con applicazione dell'IVA, solo a condizione che tali attività e i relativi costi vengano tempestivamente comunicati, giustificati e documentati per iscritto alla Società e approvati per iscritto dalla stessa, ferma restando la comunicazione in forma codificata dei dati personali del paziente.

6.6 Se nel corso dello svolgimento della Sperimentazione si rendesse necessario aumentare il supporto economico a favore dell'Ente, la Società potrà integrare, con un addendum/emendamento, il presente Contratto, prevedendo l'adeguato aumento del Budget qui allegato.

6.7 In ottemperanza alla normativa sull'obbligo della fatturazione elettronica per le cessioni di beni e per la prestazione di servizi anche tra privati, l'Ente emetterà fatture in formato XML (Extensible Markup Language) e trasmesse tramite il Sistema di Interscambio (SDI).

La Società comunica i dati necessari per l'emissione della fattura elettronica:

Novartis Farma S.p.A.
Viale Luigi Sturzo n. 43
20154 Milano
Codice Fiscale 07195130153
Partita IVA 02385200122

Le fatture dovranno riportare il numero d'ordine preventivamente comunicato dalla Società

Codice SDI da utilizzare per l'invio delle fatture alla Società è IRKA1JB.

6.8 I pagamenti effettuati per i servizi svolti dall'Ente (i) rappresentano il corretto valore di mercato di detti servizi, poiché adeguati rispetto al tariffario applicabile presso l'Ente, (ii) sono stati negoziati a condizioni commerciali normali e (iii) non sono stati definiti sulla base del volume o valore di prescrizioni o comunque in riferimento a tali prescrizioni o altre attività economiche che si generino fra le Parti. A fronte delle attività svolte o delle spese sostenute includendo i Pazienti in Sperimentazione, al cui pagamento la Società sia tenuta, né l'Ente né lo Sperimentatore principale chiederanno altri rimborsi o corrispettivi ad altri soggetti.

La Società mette inoltre a disposizione dei pazienti che partecipano alla Sperimentazione la possibilità di ottenere la copertura delle spese "vive" sostenute in relazione a ciascuna prestazione sanitaria effettuata presso l'Ente, nel rispetto di quanto previsto dal D.M. 21 dicembre 2007, mediante le procedure, i massimali e le spese ammissibili preventivamente approvate dal Comitato Etico. La copertura delle spese deve essere effettuata solo ed esclusivamente attraverso l'amministrazione dell'Ente che attuerà le proprie procedure in materia. Ciascun paziente presenterà l'elenco delle spese all'Ente; ai fini della copertura da parte della Società, tale elenco sarà debitamente codificato a cura dell'Ente. L'Ente, in considerazione

della durata dello studio, concorderà i termini per la presentazione alla Società dell'elenco delle spese relative ai pazienti e presentate all'Ente in occasione delle prestazioni sanitarie eseguite nel periodo di riferimento. La Società potrà controllare le somme richieste confrontandole con le visite eseguite dai pazienti ed effettuerà i relativi pagamenti in favore dell'Ente, previa emissione di fattura con applicazione dell'IVA da parte di quest'ultimo. Sarà quindi responsabilità dell'Ente provvedere alla copertura delle spese per ciascun paziente coinvolto, secondo le modalità indicate nell'Allegato A.
Qualora ricorrano le condizioni di legge, è possibile un rimborso per le spese vive direttamente connesse con la partecipazione alla Sperimentazione anche per l'accompagnatore di pazienti che siano impossibilitati a viaggiare da soli quali, ad esempio, i pazienti minorenni, i soggetti incapaci, i pazienti fragili. Ciascun paziente presenterà l'elenco delle spese all'Ente o al soggetto da questo delegato, ai fini della copertura da parte della Società.
Tutti i costi relativi a voci non specificate nell'Allegato A non verranno rimborsati.
Le Parti concordano che le eventuali spese e commissioni bancarie dovute per i bonifici esteri dovranno essere addebitate interamente all'ordinante e in nessun caso potranno essere dedotte dall'importo che viene accreditato al beneficiario.

Art. 7 - Durata, Recesso e Risoluzione

7.1 Il presente Contratto produrrà effetti a partire dalla data di ultima sottoscrizione ("Data di decorrenza") e rimarrà in vigore sino all'effettiva conclusione della Sperimentazione presso l'Ente, ovvero sino alla chiusura formale del centro.
Fermo restando quanto sopra, il presente Contratto produrrà i suoi effetti a seguito del rilascio di formale autorizzazione da parte dell'Autorità Competente.
7.2 L'Ente si riserva il diritto di recedere dal presente Contratto mediante comunicazione scritta e con preavviso di 30 giorni da inoltrare alla Società con raccomandata A.R. o PEC. nei casi di:
- insolvenza della Società, proposizione di concordati anche stragiudiziali con i creditori della Società o avvio di procedure esecutive nei confronti della Società. Qualora la situazione sopra indicata riguardi la CRO, la Società sarà tenuto a subentrarle e proseguire l'attività, qualora non procuri l'intervento di un'altra CRO, approvata dall'Ente, in sostituzione di quella divenuta insolvente;
- cessione di tutti o di parte dei beni della Società ai creditori o definizione con gli stessi di un accordo per la moratoria dei debiti.

Il preavviso avrà effetto dal momento del ricevimento da parte della Società della comunicazione di cui sopra.
7.3 La Società, ai sensi dell'art. 1373, comma 2, Codice Civile, si riserva il diritto di recedere dal presente Contratto in qualunque momento per giustificati motivi mediante comunicazione scritta inviata a mezzo raccomandata A.R. o PEC, con preavviso di 30 giorni. Tale preavviso avrà effetto dal momento del ricevimento da parte dell'Ente di detta comunicazione.
In caso di recesso della Società sono comunque fatti salvi gli obblighi assunti e le spese effettuate dall'Ente alla data della comunicazione di recesso. In particolare, la Società corrisponderà all'Ente tutte le spese documentate e non revocabili che questo abbia sostenuto al fine di garantire la corretta ed efficace esecuzione della Sperimentazione, incluse le spese sostenute dall'Ente nei confronti dei pazienti-partecipanti, nonché i compensi sino a quel momento maturati.
In caso di recesso anticipato, il Promotore ha diritto di ricevere, quale proprietario a titolo originario, tutti i dati e risultati, anche parziali, ottenuti dall'Ente nel corso della Sperimentazione e anche successivamente, se derivanti da o correlati a essa.

7.4 In caso di interruzione della Sperimentazione, ai sensi della normativa applicabile, la Società corrisponderà all'Ente i rimborsi delle spese e i compensi effettivamente maturati e documentati fino a quel momento.
7.5 Resta peraltro inteso che il recesso unilaterale anticipato del Contratto non comporterà alcun diritto di una Parte di avanzare nei confronti dell'altra pretese risarcitorie o richieste di pagamento ulteriori rispetto a quanto convenuto.
7.6 Gli effetti del presente Contratto cesseranno automaticamente ai sensi dell'art. 1454 del Codice Civile nel caso in cui una delle Parti non abbia adempiuto a uno degli obblighi previsti dal presente Contratto entro 30 giorni dalla richiesta scritta di adempimento presentata dall'altra parte.
Resta in ogni caso salva l'applicabilità degli art. 1218 e seguenti del Codice Civile.
7.7 In caso di risoluzione del presente Contratto, non derivante da inadempimento dell'Ente, quest'ultimo avrà diritto al rimborso delle spese effettivamente sostenute per la Sperimentazione prima del ricevimento della notifica di risoluzione e a un compenso per i servizi proporzionale all'attività svolta sino al momento della risoluzione. L'Ente si impegna a restituire alla Società eventuali importi già liquidati e relativi ad attività non svolte.
7.8 In tutti i casi di interruzione o di risoluzione del presente Contratto, sarà attuata ogni precauzione per garantire la massima tutela dei pazienti già coinvolti, in accordo con quanto previsto dal Protocollo approvato dal Comitato Etico.

Art. 8 - Copertura assicurativa

8.1 La Società è tenuta a garantire, secondo la legislazione vigente, il risarcimento dei danni subiti dai pazienti e riconducibili alla partecipazione alla sperimentazione clinica, secondo il Protocollo, commisurato alla natura e alla portata dei rischi conseguenti.
8.2 Fatte salve le previsioni dell'art 76 del Regolamento e della L. 8 marzo 2017, n. 24 e dei rispettivi provvedimenti attuativi, la copertura assicurativa fornita dalla Società garantisce rispetto alle ipotesi di responsabilità civile del Promotore, dell'istituzione sanitaria sede della Sperimentazione, dello Sperimentatore principale, e degli altri Sperimentatori coinvolti presso il Centro dell'Ente.
8.3 La Società dichiara, con la firma del presente contratto, di aver stipulato adeguata polizza assicurativa (n. 390-01579150-14037, con la Compagnia HDI-GLOBAL SE Rappresentanza Generale per l'Italia) per la responsabilità civile verso terzi, a copertura del rischio di eventuali danni derivanti ai pazienti dalla partecipazione alla Sperimentazione, secondo quanto previsto dal D.M. 14 luglio 2009. La polizza assicurativa è stata ritenuta dal Comitato Etico rispettosa dei termini di legge e adeguatamente tutelante i soggetti coinvolti nella sperimentazione clinica.
8.4 La Società, con la firma del presente contratto, dichiara, nei limiti di cui al precedente art. 8.1, di farsi carico delle conseguenze connesse a eventuali inadeguatezze, anche sopravvenute, della copertura assicurativa in argomento, integrandole ove necessario in coerenza con quanto previsto all'art. 8.1.
8.5 La Società in particolare, nel caso in cui intenda recedere dal Contratto, garantisce che la società assicuratrice assicuri in ogni caso la copertura dei soggetti già inclusi nello studio clinico anche per il prosieguo della Sperimentazione ai sensi dell'art. 2 comma 3 del D.M. 14/07/09.
8.6 All'atto del sinistro, l'Ente è tenuto a comunicare l'esistenza di coperture assicurative per la responsabilità RCT Medical Malpractice (a copertura sia dell'Ente, sia del personale medico che ha somministrato il farmaco), ai sensi dell'articolo 1910 Codice civile.

Art. 9 - Relazione finale, titolarità e utilizzazione dei risultati

9.1 Il Promotore si impegna a divulgare tutti i risultati dello studio anche qualora negativi.

9.2 Il Promotore assume la responsabilità della preparazione del rapporto clinico finale che sarà inviato dalla Società o da società terza da questi incaricata entro i termini previsti dalla vigente normativa allo Sperimentatore principale e al Comitato Etico del riassunto dei risultati della Sperimentazione stessa. Indipendentemente dall'esito di una sperimentazione clinica, entro un anno (e sei mesi nel caso di studi pediatrici) dalla sua conclusione, il Promotore trasmette una sintesi dei risultati della sperimentazione alla banca dati EU secondo le modalità previste dall'Art 37.4 del Regolamento (UE) n. 536/2014.
9.3 Tutti i dati, i risultati, le informazioni, i materiali, le scoperte e le invenzioni derivanti dall'esecuzione della Sperimentazione nel perseguimento degli obiettivi della stessa sono di proprietà esclusiva del Promotore salvo il diritto degli Sperimentatori, ricorrendone i presupposti, di esserne riconosciuti autori.
A fronte di una procedura attivata dal Promotore e/o dalla Società per il deposito di una domanda di brevetto avente a oggetto invenzioni ricavate nel corso della Sperimentazione, l'Ente e lo Sperimentatore principale si impegnano a fornire al Promotore e/o Società tutto il supporto, anche documentale, utile a tal fine.
9.4 L'Ente può utilizzare i dati e risultati della Sperimentazione, del cui trattamento è autonomo titolare ai sensi di legge, unicamente per i propri scopi istituzionali scientifici e di ricerca. Tale utilizzo non deve in alcun caso pregiudicare la segretezza degli stessi e la tutela brevettuale dei relativi diritti di proprietà intellettuale spettanti al Promotore.
Il Promotore e l'Ente riconoscono reciprocamente che resteranno titolari dei diritti di proprietà industriale e intellettuale relativi alle proprie pregresse conoscenze (*background knowledge*) e alle proprie conoscenze sviluppate o ottenute nel corso della Sperimentazione - ma estranee alla stessa - a prescindere e indipendentemente dalla sua conduzione e dai suoi obiettivi (*sideground knowledge*).
9.5 Le disposizioni del presente articolo resteranno valide ed efficaci anche dopo la risoluzione o la cessazione degli effetti del presente Contratto.

Art. 10 - Segretezza di informazioni tecnico-commerciali e diffusione dei risultati

10.1 Con la sottoscrizione del presente Contratto, ciascuna delle Parti si impegna a mantenere riservate per un periodo di 5 (cinque) anni successivamente alla conclusione della Sperimentazione tutte le informazioni di natura tecnica e/o commerciale messe a sua disposizione dall'altra Parte e/o sviluppate nel corso della Sperimentazione e nel perseguimento degli obiettivi della stessa, che siano classificabili come "Segreti Commerciali" ai sensi degli art. 98 e 99 del Codice della Proprietà Industriale (D. Lgs. n. 30/2005, come modificato dal D. Lgs. n. 63/2018 in recepimento della Direttiva UE 2016/943), adottando ogni misura di carattere contrattuale, tecnologico o fisico idonea per la loro protezione, anche nei confronti di propri dipendenti, collaboratori, sub-appaltatori, danti o aventi causa.
Ciascuna delle Parti inoltre dichiara e garantisce quanto segue:
(i) i propri Segreti Commerciali sono stati acquisiti, utilizzati e rivelati lecitamente e non vi sono – per quanto ad essa noto – azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.
(ii) essa, pertanto, terrà indenne e manleverà l'altra Parte da azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.
10.2 Le Parti sono obbligate all'adeguata e corretta diffusione e pubblicazione dei risultati della Sperimentazione, nonché alla loro adeguata comunicazione ai pazienti partecipanti e ai rappresentanti dei pazienti. Il Promotore, ai sensi della vigente normativa, è tenuto a rendere

pubblici tempestivamente, i risultati, anche se negativi, ottenuti a conclusione della Sperimentazione, non appena disponibili da parte di tutti i Centri partecipanti e comunque non oltre i termini a tal fine stabiliti dalle disposizioni applicabili dell'Unione Europea.
10.3 Ai sensi dell'art. 5, comma secondo, lett. c) del D.M. 8 febbraio 2013, lo Sperimentatore principale ha diritto di diffondere e pubblicare, senza limitazione alcuna, i risultati della Sperimentazione ottenuti presso l'Ente, nel rispetto delle disposizioni vigenti in materia di riservatezza dei dati sensibili, di protezione dei dati personali e di tutela della proprietà intellettuale, nonché nel rispetto dei termini e delle condizioni di cui al presente Contratto.
Per garantire la correttezza della raccolta e la veridicità dell'elaborazione dei dati e dei risultati della Sperimentazione ottenuti presso l'Ente, in vista della loro presentazione o pubblicazione, almeno 60 giorni prima di esse lo Sperimentatore principale dovrà trasmettere alla Società il testo del documento destinato ad essere presentato o pubblicato. Ove dovessero sorgere questioni relative all'integrità scientifica del documento e/o questioni afferenti agli aspetti regolatori, brevettuali o di tutela della proprietà intellettuale, le Parti e lo Sperimentatore Principale procederanno nei 60 giorni successivi al riesame del documento. Lo Sperimentatore principale accetterà di tenere conto dei suggerimenti della Società nella presentazione o pubblicazione, solo se necessari ai fini della tutela della riservatezza delle informazioni, dei dati personali e della tutela della proprietà intellettuale, purché non in contrasto con l'attendibilità dei dati, con i diritti, la sicurezza e il benessere dei pazienti.
10.4 La Società riconosce di non aver diritto di chiedere l'eliminazione delle informazioni contenute nel documento, salvo quando tali richieste e modifiche siano necessarie ai fini della tutela della riservatezza dei dati, della protezione dei dati personali e della tutela della proprietà intellettuale.
10.5 La Società, allo scopo di presentare una richiesta di brevetto e qualora risulti necessario, potrà chiedere allo Sperimentatore principale di differire di ulteriori 90 giorni la pubblicazione o presentazione del documento.
In caso di sperimentazione multicentrica lo Sperimentatore principale non potrà pubblicare i dati o risultati del proprio Centro sino a che tutti i dati e risultati della Sperimentazione siano stati integralmente pubblicati ovvero per almeno 12 mesi dalla conclusione della Sperimentazione, dalla sua interruzione o chiusura anticipata.
Laddove la pubblicazione recante i risultati di una sperimentazione multicentrica ad opera del Promotore, o del terzo da questi designato, non venga effettuata entro 12 mesi dalla fine della Sperimentazione multicentrica, lo Sperimentatore potrà pubblicare i risultati ottenuti presso l'Ente, nel rispetto di quanto contenuto nel presente articolo.

Art. 11 - Protezione dei dati personali

11.1 Le Parti nell'esecuzione delle attività previste dal presente Contratto si impegnano a trattare i dati personali, di cui vengano per qualsiasi motivo a conoscenza durante la sperimentazione clinica, nel rispetto degli obiettivi di cui ai precedenti articoli e in conformità a quanto disposto dal Regolamento (UE) 2016/679 del Parlamento Europeo e del Consiglio del 27 aprile 2016 ("**GDPR**"), nonché dalle correlate disposizioni legislative e amministrative nazionali vigenti, con le loro eventuali successive modifiche e/o integrazioni (di seguito, collettivamente, "**Leggi in materia di Protezione dei dati**"),
11.2 I termini utilizzati nel presente articolo, nel Contratto, nella documentazione di informativa e consenso e in ogni altro documento utilizzato per le finalità della sperimentazione clinica devono essere intesi e utilizzati secondo il significato a essi attribuito nell'Allegato B.
11.3 L'Ente e la Società si qualificano come autonomi titolari del trattamento ai sensi dell'art. 4 paragrafo 17) del GDPR. Ciascuna delle Parti provvederà a propria cura e spese, nell'ambito del

proprio assetto organizzativo, alle eventuali nomine di Responsabili del trattamento e attribuzione di funzioni e compiti a soggetti designati, che operino sotto la loro autorità, ai sensi del GDPR e della normativa vigente.
11.4 Per le finalità della Sperimentazione saranno trattati dati personali riferiti alle seguenti categorie di interessati: soggetti partecipanti alla sperimentazione; persone che operano per le Parti. Tali interessati sono informati sul trattamento che li riguarda a mezzo di idonea informativa. Per le finalità della Sperimentazione saranno trattati le seguenti tipologie di dati personali: dati di cui all'art. 4 n.1 del GDPR; dati rientranti nelle categorie "particolari" di dati personali - e in particolare dati relativi alla salute e alla vita sessuale, dati genetici - di cui all'art. 9 del GDPR. Tali dati saranno trattati nel rispetto dei principi di liceità, correttezza, trasparenza, adeguatezza, pertinenza e necessità di cui all'art.5, paragrafo 1 del GDPR.
11.5 Il Promotore e la Società potranno trasmettere i dati ad affiliate del gruppo del Promotore e a terzi operanti per proprio conto, anche all'estero, in paesi al di fuori dell'Unione Europea, soltanto nel rispetto delle condizioni di cui agli artt. 44 e ss. del GDPR. In questo caso il Promotore e la Società garantiranno un adeguato livello di protezione dei dati personali anche mediante l'utilizzo delle Standard Contractual Clauses approvate dalla Commissione Europea. Ove il Promotore abbia sede in uno Stato che non rientra nell'ambito di applicazione del diritto dell'Unione Europea e che la Commissione Europea abbia deciso che tale Paese non garantisce un livello di protezione adeguato ex artt. 44 e 45 del GDPR UE 2016/679, il Promotore e l'Ente dovranno compilare e sottoscrivere il documento Standard Contractual Clauses (quest'ultimo non viene allegato al presente Contratto).
11.6 Le Parti garantiscono che le persone da esse autorizzate a trattare dati personali per le finalità della Sperimentazione rispettino i principi posti a tutela del diritto alla protezione dei dati personali e del diritto alla riservatezza, e che le persone che hanno accesso ai dati personali siano obbligati a trattarli in conformità alle istruzioni dettate, in coerenza con il presente articolo, dal titolare di riferimento.
11.7 Lo Sperimentatore principale è individuato dall'Ente quale persona autorizzata al trattamento ai sensi dell'art. 29 del GDPR e quale soggetto designato ai sensi dell'art. 2 quaterdecies del Codice.
11.8 Lo Sperimentatore principale deve informare in modo chiaro e completo, prima che abbia inizio la Sperimentazione (incluse le relative fasi prodromiche e di screening) ogni paziente circa natura, finalità, risultati, conseguenze, rischi e modalità del trattamento dei dati personali; in particolare il paziente deve inoltre essere informato che Autorità nazionali e straniere, nonché il Comitato Etico, potranno accedere, nell'ambito di attività di monitoraggio, verifica e controllo sulla ricerca, alla documentazione relativa alla sperimentazione così come anche alla documentazione sanitaria originale del paziente, e che ad esse potranno anche eccedere in visione, nell'ambito delle rispettive competenze, Monitor e Auditor.
11.9 Lo Sperimentatore principale deve acquisire dal paziente debitamente informato il documento di consenso, oltre che alla partecipazione alla Sperimentazione, anche al trattamento dei dati. L'Ente è responsabile della conservazione di tale documento.
11.10 Qualora una parte accerti una violazione dei dati personali, si impegna a comunicarlo all'altra entro 48 ore dall'accertamento della violazione, ferma restando l'autonomia della stessa nella valutazione della sussistenza delle condizioni e nell'adempimento degli obblighi previsti dagli artt. 33 e 34 del GDPR.

Art. 12 - Modifiche

12.1 Il presente Contratto e i relativi allegati/addendum, unitamente al Protocollo quale parte integrante, costituiscono l'intero accordo tra le Parti.

12.2 Il Contratto può essere modificato/integrato solo con il consenso scritto di entrambe le Parti. Le eventuali modifiche saranno oggetto di addendum al presente Contratto e decorreranno dalla data della loro sottoscrizione, salvo diverso accordo tra le Parti.

Art. 13 - Disciplina anti-corruzione e per la prevenzione di reati

13.1 L'Ente e la Società si impegnano a rispettare la normativa anticorruzione applicabile in Italia.

13.2 La Società dichiara di aver adottato misure di vigilanza e controllo ai fini del rispetto e dell'attuazione delle previsioni del D. Lgs. 8 giugno 2001 n. 231, nonché, in quanto applicabili e non in contrasto con la normativa vigente in Italia, dei principi del *Foreign Corrupt Practices Act* degli Stati Uniti, e loro successive modifiche e integrazioni. L'Ente e le sue strutture cliniche e amministrative, si impegnano a collaborare in buona fede, nei limiti di quanto previsto dalla normativa italiana di cui sopra, con il personale e il management della Società al fine di facilitare la piena e corretta attuazione degli obblighi che ne derivano e l'attuazione delle procedure operative a tal fine messe a punto dalla Società.

13.3 Ai sensi e per gli effetti della L. n. 190 del 6 novembre 2012 ("Legge Anticorruzione") e sue successive modificazioni, l'Ente dichiara di avere adottato il Piano Triennale per la prevenzione della corruzione con deliberazione n. 778 del 29.04.2022, nonché di aver adottato il Codice di Comportamento con deliberazione n. 2358 del 16.12.2022. La Società dichiara di aver adottato il proprio Codice etico, di cui è possibile prendere visione alla pagina web https://www.novartis.com/our-company/corporate-responsibility/reporting-disclosure/codes-policies-guidelines

13.4 L'Ente e la Società s'impegnano reciprocamente a informare immediatamente l'altra parte circa ogni eventuale violazione del presente articolo di cui venga a conoscenza e a rendere disponibili tutti i dati informativi e la documentazione per ogni opportuna verifica.

13.5 La Società può divulgare per qualsiasi scopo legittimo, nei limiti della normativa sul trattamento dei dati, i termini del presente Contratto o di qualsiasi suo emendamento.

13.6 La violazione di quanto previsto da questo articolo costituisce grave inadempimento del presente Contratto ai sensi e per gli effetti di cui all'art. 1456 Codice Civile, risultando pregiudicato il rapporto di fiducia tra le Parti.

Art. 14 - Trasferimento diritti, cessione del Contratto

14.1 Il presente Contratto ha carattere fiduciario e, pertanto, le Parti non possono cedere o trasferire lo stesso a terzi, senza il preventivo consenso scritto dell'altra Parte.

Ogni Parte acconsente a che l'altra Parte possa cedere e/o trasferire in tutto o in parte i diritti e gli obblighi a lui pervenuti direttamente o indirettamente dalla firma del presente Contratto a un suo successore o ad una società o entità ad essa collegata, previa accettazione da parte del cessionario di tutte le condizioni e i termini del presente Contratto. Qualsiasi trasferimento di diritti in assenza delle suddette condizioni sarà considerato nullo e mai avvenuto.

L'Ente potrà affidare a soggetti terzi attività non esclusivamente correlate o derivanti dalla Sperimentazione (ad esempio esami di routine a cui il paziente sarebbe in ogni caso sottoposto) sulla base di specifici accordi anche preesistenti con detti soggetti terzi. Al di fuori di tale ipotesi, l'Ente non potrà sub-appaltare le attività o parte delle attività specificamente correlate alla Sperimentazione ad un ente terzo, senza la preventiva autorizzazione scritta da parte della Società. In caso di sub-appalto, che sia quindi stato autorizzato dalla Società, in ogni caso l'Ente rimarrà integralmente responsabile nei confronti della Società.

14.2 In caso di cambio di denominazione dell'Ente non si renderà necessario l'emendamento alla presente convenzione. L'Ente sarà comunque tenuto a notificare tempestivamente alla Società tale cambio di denominazione.

Art. 15 - Oneri fiscali

15.1 Il presente Contratto viene sottoscritto con firma digitale dal Rappresentante Legale dell'Ente e dai Procuratori della Società ai sensi della normativa vigente.

L'imposta di bollo sull'originale informatico di cui all'art. 2 della Tabella Allegato A – tariffa parte I del DPR n. 642/1972 è a carico della Società ed è assolta da quest'ultima in modo virtuale ai sensi dell'art. 15 del D.P.R. n. 642/1972 e successive modificazioni, come da autorizzazione Agenzia delle Entrate n.69 del 14.12.2007, rilasciata alla Società dall'Agenzia delle Entrate Ufficio di Saronno; l'eventuale registrazione ai fini dell'imposta di registro in caso d'uso sarà a carico della parte interessata.

Art. 16 - Legge regolatrice e Foro competente

16.1 La normativa applicabile al presente Contratto è quella dello Stato italiano.

16.2 Per tutte le eventuali controversie che dovessero sorgere in relazione all'interpretazione, applicazione ed esecuzione del presente Contratto, fermo restando l'impegno delle Parti ad esperire un preventivo tentativo di conciliazione in sede stragiudiziale, sarà competente, in via esclusiva, il Foro di Vicenza In caso di contraddizioni tra le disposizioni del presente Contratto (e/o di altri documenti) e quanto previsto dal Protocollo e dai suoi eventuali Emendamenti, prevarrà quest'ultimo. Le Parti si danno reciprocamente atto che il presente Contratto è stato accettato in ogni sua parte e che non trovano pertanto applicazione le disposizioni di cui agli artt. 1341 e 1342 Codice Civile.

Milano, li __/__/_____

Per la Società

I Procuratori

Dott.ssa Donatella Albanesi

Firma _____

Dott.ssa Eva Josephine Runggaldier

Firma _____

Bassano del Grappa, li __/__/_____

Per l'Ente

Il Direttore Generale

Dott. Carlo Bramezza

Firma _____

ALLEGATO A – BUDGET

ONERI E COMPENSI

Oneri fissi:

La Società corrisponderà i seguenti importi all'Ente:

- € 1.500,00 + I.V.A. quale quota per il per il monitoraggio delle sperimentazioni (DGR 1066/2013 all B – Regione Veneto). Detto importo, sarà fatturato dall'Ente alla sottoscrizione del presente Contratto.

- quota per la valutazione della ricerca € 1.200,00 destinata al Nucleo Ricerca Clinica Aziendale (già versata in data 19.10.2022)

- € 500,00 + I.V.A: quale costo di avvio amministrativo. Detto importo, sarà fatturato dall'Ente alla sottoscrizione del presente Contratto.

- € 1.000,00 + I.V.A. quale costo archiviazione una tantum. Detto importo sarà fatturato dall'Ente al termine della sperimentazione.

- € 500,00 + I.V.A. quale costo di gestione Farmacia. Detto importo, sarà fatturato dall'Ente al momento del primo paziente trattato.

Parte 1 – Compenso per paziente coinvolto nello studio e prestazioni aggiuntive/opzionali

Compenso a paziente incluso nello studio:

€ 6.500,00 (seimilacinquecento/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite previste dal protocollo per la fase di trattamento.
Il compenso per singolo paziente che non abbia completato l'intero ciclo di visite di trattamento sarà determinato in base al numero di visite effettuate, ovvero:
- Visita Screening: € 800,00 + I.V.A.
- Visita W1: € 1.000,00 + I.V.A.
- Visita W3: € 300,00 + I.V.A.
- Visita W5: € 1.000,00 + I.V.A.
- Visita W7: € 300,00 + I.V.A.
- Visita W9: € 1.000,00 + I.V.A.
- Visita W11: € 300,00 + I.V.A.
- Visita W13: € 1.000,00 + I.V.A.
- Visita W15: € 300,00 + I.V.A.
- Visita W17: € 400,00 + I.V.A.
- Visita EOT: € 100,00 + I.V.A.

Inoltre, la Società provvederà a corrispondere i seguenti importi aggiuntivi:
- Visita Unscheduled (non programmata) (USV): € 400,00 + I.V.A. per ciascuna visita

- Visita tramite contatto telefonico (TMED): € 200,00 + I.V.A. per ciascuna visita, da considerarsi solo nel caso in cui una visita venga svolta tramite contatto telefonico

La Società si impegna a riconoscere alla Vostra Struttura l'importo di € 5.700,00 (cinquemilasettecento/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI CROSSOVER previste dal protocollo.
Il compenso per singolo paziente che non abbia completato l'intero ciclo di visite di trattamento sarà determinato in base al numero di visite effettuate, ovvero:
- Visita COW1: € 1.000,00 + I.V.A.
- Visita COW3: € 300,00 + I.V.A.
- Visita COW5: € 1.000,00 + I.V.A.
- Visita COW7: € 300,00 + I.V.A.
- Visita COW9: € 1.000,00 + I.V.A.
- Visita COW11: € 300,00 + I.V.A.
- Visita COW13: € 1.000,00 + I.V.A.
- Visita COW15: € 300,00 + I.V.A.
- Visita COW17: € 400,00 + I.V.A.
- Visita EOT: € 100,00 + I.V.A.

Inoltre, la Società provvederà a corrispondere i seguenti importi aggiuntivi:
- Visita di follow up unscheduled (non programmata) (USVFU): € 400,00 + I.V.A. per ciascuna visita
- Visita tramite contatto telefonico (TMED): € 200,00 + I.V.A. per ciascuna visita, da considerarsi solo nel caso in cui una visita venga svolta tramite contatto telefonico

La Società si impegna a riconoscere alla Vostra Struttura l'importo di € 15.450,00 (quindicimilaquattrocentocinquanta/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI FOLLOW-UP-DURABLE RESPONSE previste dal protocollo.
Il compenso per singolo paziente che non abbia completato l'intero ciclo di visite di trattamento sarà determinato in base al numero di visite effettuate, ovvero:
- Visita W19: € 300,00 + I.V.A.
- Visita W21: € 450,00 + I.V.A.
- Visita W23: € 300,00 + I.V.A.
- Visita W25: € 450,00 + I.V.A.
- Visita STFU1: € 450,00 + I.V.A.
- Visita STFU2: € 450,00 + I.V.A.
- Visita LTFU1: € 350,00 + I.V.A.
- Visita LTFU2: € 350,00 + I.V.A.
- Visita LTFU3: € 400,00 + I.V.A.
- Visita LTFU4: € 350,00 + I.V.A.
- Visita LTFU5: € 350,00 + I.V.A.
- Visita LTFU6: € 400,00 + I.V.A.
- Visita LTFU7: € 350,00 + I.V.A.
- Visita LTFU8: € 350,00 + I.V.A.
- Visita LTFU9: € 400,00 + I.V.A.
- Visita LTFU10: € 350,00 + I.V.A.
- Visita LTFU11: € 350,00 + I.V.A.

- Visita LTFU12: € 400,00 + I.V.A.
- Visita LTFU13: € 350,00 + I.V.A.
- Visita LTFU14: € 350,00 + I.V.A.
- Visita LTFU15: € 400,00 + I.V.A.
- Visita LTFU16: € 350,00 + I.V.A.
- Visita LTFU17: € 350,00 + I.V.A.
- Visita LTFU18: € 400,00 + I.V.A.
- Visita LTFU19: € 350,00 + I.V.A.
- Visita LTFU20: € 350,00 + I.V.A.
- Visita LTFU21/ESFU: € 500,00 + I.V.A.
- Visita LTFU22: € 350,00 + I.V.A.
- Visita LTFU23: € 350,00 + I.V.A.
- Visita LTFU24: € 350,00 + I.V.A.
- Visita LTFU25: € 350,00 + I.V.A.
- Visita LTFU26: € 350,00 + I.V.A.
- Visita LTFU27: € 350,00 + I.V.A.
- Visita LTFU28: € 350,00 + I.V.A.
- Visita LTFU29: € 350,00 + I.V.A.
- Visita LTFU30: € 350,00 + I.V.A.
- Visita LTFU31: € 350,00 + I.V.A.
- Visita LTFU32: € 350,00 + I.V.A.
- Visita LTFU33: € 350,00 + I.V.A.
- Visita LTFU34: € 350,00 + I.V.A.
- Visita LTFU35: € 350,00 + I.V.A.
- Visita LTFU36: € 350,00 + I.V.A.

Inoltre, la Società provvederà a corrispondere i seguenti importi aggiuntivi:
- Visita di follow up unscheduled (non programmata) (USVFU): € 400,00 + I.V.A. per ciascuna visita
- Visita tramite contatto telefonico (TMED): € 200,00 + I.V.A. per ciascuna visita, da considerarsi solo nel caso in cui una visita venga svolta tramite contatto telefonico

La Società si impegna a riconoscere alla Vostra Struttura l'importo di € 5.250,00 (cinquemiladuecentocinquanta/00) + I.V.A. per ogni paziente che abbia completato l'intero ciclo di visite PER LA FASE DI FOLLOW-UP-NON IN DURABLE RESPONSE previste dal protocollo.
Il compenso per singolo paziente che non abbia completato l'intero ciclo di visite di trattamento sarà determinato in base al numero di visite effettuate, ovvero:
- Visita W19: € 300,00 + I.V.A.
- Visita W21: € 450,00 + I.V.A.
- Visita W23: € 300,00 + I.V.A.
- Visita W25: € 450,00 + I.V.A.
- Visita STFU1: € 450,00 + I.V.A.
- Visita STFU2: € 450,00 + I.V.A.
- Visita LTFU1/LTFU1NRTC: € 300,00 + I.V.A.
- Visita LTFU3: € 350,00 + I.V.A.
- Visita LTFU6: € 350,00 + I.V.A.
- Visita LTFU9: € 350,00 + I.V.A.

- Visita LTFU12: € 350,00 + I.V.A.
- Visita LTFU15: € 350,00 + I.V.A.
- Visita LTFU18: € 350,00 + I.V.A.
- Visita ESFUNR: € 450,00 + I.V.A.

Inoltre, la Società provvederà a corrispondere i seguenti importi aggiuntivi:
- Visita di follow up unscheduled (non programmata) (USVFU): € 400,00 + I.V.A. per ciascuna visita
- Visita tramite contatto telefonico (TMED): € 200,00 + I.V.A. per ciascuna visita, da considerarsi solo nel caso in cui una visita venga svolta tramite contatto telefonico

Gli importi di cui sopra comprendono lo svolgimento di tutte le attività necessarie alla conduzione della Sperimentazione, così come previsto dal Protocollo, fino al completamento di tutte le schede raccolta dati per i pazienti inclusi nella Sperimentazione e sono quindi comprensivi delle spese sostenute per gli esami strumentali e/o di laboratorio effettuati localmente. Gli esami di laboratorio previsti dal Protocollo come centralizzati presso un laboratorio esterno saranno a totale carico della Società e, pertanto, nessun costo aggiuntivo graverà sull'Ente o sul Servizio Sanitario Nazionale.

La finalizzazione del presente contratto assolve l'obbligo della Società di non gravare sulla finanza pubblica come stabilito dal DLgs 211/2003, in quanto gli importi riportati coprono tutte le prestazioni effettuate nell'ambito dello studio clinico in oggetto presso l'Ente in cui si svolge la Sperimentazione. La Società non è responsabile dei costi sostenuti nel caso in cui attività previste dalla Sperimentazione vengano effettuate presso altre strutture a meno che gli stessi siano stati precedentemente concordati e regolamentati da specifico incarico.

Parte 2 – Rimborso spese vive per i pazienti/accompagnatori coinvolti nella Sperimentazione

Procedura di rimborso spese ai sensi del DM 21.12.2007
In accordo al Decreto Ministeriale 21 dicembre 2007, poiché la sperimentazione clinica riguarda una patologia particolare/rara e può determinare in taluni casi la necessità di lunghi tragitti (superiori ai 100 KM per viaggio di andata o ritorno) da parte dei pazienti per recarsi nei centri specializzati, la presente Sperimentazione prevede, da parte della Società, il rimborso delle spese "vive" sostenute e documentate dai pazienti arruolati per recarsi dal proprio domicilio al Centro di sperimentazione.
Il rimborso spese è applicabile, inoltre, per un eventuale accompagnatore, se, per le condizioni mediche o età del paziente, un accompagnatore è da ritenersi necessario, data la patologia e/o la popolazione in studio (es. pazienti minori).
Nel caso di pazienti minori, per la sola visita di inizio studio, il rimborso sarà previsto sia per il paziente che per entrambi i genitori, la cui firma sul consenso informato è necessaria per consentire la partecipazione allo studio del paziente; per le successive visite il rimborso sarà applicabile solo per uno dei due genitori. Nel caso in cui sussistano particolari motivazioni che rendano necessaria la presenza di entrambi i genitori anche nelle visite successive, previa autorizzazione scritta da parte della Società, il rimborso sarà applicabile ad entrambi i genitori anche nelle visite successive alla prima.

Tale rimborso potrà essere riconosciuto solo a fronte di presentazione di adeguati giustificativi delle spese effettivamente sostenute (scontrini, ricevute fiscali o fatture) e direttamente correlate agli accessi effettuati presso il Centro.
La raccolta dei giustificativi dovrà essere effettuata dallo Sperimentatore Responsabile che potrà avvalersi del "Modulo richiesta rimborso spese per pazienti inseriti nelle sperimentazioni" (trasmesso con la documentazione di studio) compilato e sottoscritto.
Lo Sperimentatore Responsabile controllerà la congruità dei giustificati raccolti con la presente procedura e li invierà unitamente al Modulo sottoscritto all'Ufficio competente amministrativo del Centro, che provvederà a predisporre la sua liquidazione.
I giustificativi di spesa devono far riferimento alle giornate corrispondenti ad ogni accesso al Centro per lo svolgimento dello studio, o al giorno precedente o successivo per la sola durata del trasferimento da e per il Centro.
Non verranno riconosciute richieste di rimborso al di fuori di quelle previste a meno di approvazione preventiva da parte della Società.
Il paziente verrà rimborsato solo dopo l'avvenuto versamento degli importi dovuti da parte della Società, che provvederà al pagamento a fronte dell'emissione da parte dell'Ente delle fatture relative anche alle altre attività inerenti la sperimentazione clinica secondo le scadenze concordate. Nelle fatture dovranno essere indicati i dettagli del rimborso al fine di individuare precisamente la prestazione resa, **senza indicazione alcuna dei dati del paziente**.

Voci di spesa di norma riconosciute e limiti di rimborso
Viaggi in treno: saranno rimborsati viaggi fino alla prima classe;
Viaggi in aereo: saranno rimborsati viaggi esclusivamente in classe economica;
Viaggi in taxi e autobus: saranno rimborsati viaggi da e per la stazione ferroviaria/aeroporto/albergo al Centro nonché da e per la stazione ferroviaria/aeroporto al domicilio;
Auto a noleggio: sarà rimborsato il costo del noleggio di una automobile (fino alla classe media) per le giornate corrispondenti ad ogni accesso al Centro e per i giorni precedente e successivo per la sola durata del trasferimento da e per il Centro;
Viaggi in auto:
• Il rimborso chilometrico con utilizzo di auto propria avverrà alla tariffa piena sulla base delle tariffe applicate per l'auto in questione dalla ACI (Automobile Club d'Italia): sito internet http://www.aci.it - costi chilometrici - "effettua il calcolo", con riferimento ad una percorrenza annua di 20.000 km (copia del modulo ricavato dovrà essere allegata al "Modulo richiesta rimborso spese per pazienti inseriti nelle sperimentazioni" quale giustificativo di spesa).
• il rimborso chilometrico con utilizzo di auto a noleggio avverrà alla tariffa carburante sulla base delle tariffe applicate per l'auto in questione dalla ACI (Automobile Club d'Italia): sito internet http://www.aci.it - costi chilometrici - "effettua il calcolo", con riferimento ad una percorrenza annua di 20.000 km (copia del modulo ricavato dovrà essere allegata al "Modulo richiesta rimborso spese per pazienti inseriti nelle sperimentazioni" quale giustificativo di spesa).
• saranno rimborsati i pedaggi autostradali.
• saranno rimborsati i costi del parcheggio.
Pernottamenti: sarà rimborsato il costo del pernottamento in albergo/casa accoglienza o altra struttura ricettiva convenzionata (riferibile alla giornata di avvicinamento precedente l'accesso al Centro qualora giustificato, al giorno della visita o alle giornate corrispondenti alle visite effettuate in più giorni consecutivi, oppure in caso di impossibilità del paziente a lasciare il sito

del Centro a causa del proprio stato di salute), fino ad un importo massimo di 120 Euro per persona per notte.
Nel caso fosse necessario un numero di pernottamenti superiori a quelli previsti sulla base delle visite previste da Protocollo, il rimborso delle spese di pernottamento avverrà a seguito di autorizzazione preventiva della Società tramite lo Sperimentatore.
N.B. per i pernottamenti presso locali in affitto: saranno rimborsati i costi riferibili alla giornata precedente l'accesso al Centro e alla giornata della visita o alle giornate corrispondenti alle visite effettuate in più giorni consecutivi, in misura proporzionale al canone di locazione concordato con il locatore.
Pasti da consumarsi obbligatoriamente presso Bar o Ristoranti:
• sarà rimborsato il pranzo nel giorno dell'accesso se il paziente e l'eventuale accompagnatore restano fuori casa per meno di 8 ore, fino ad un massimo di Euro 25,00, per persona.
• sarà rimborsata la cena se il paziente e l'eventuale accompagnatore effettuano il trasferimento il giorno precedente l'accesso al Centro, fino ad un massimo di Euro 30,00 per persona;
• saranno rimborsati la colazione, il pranzo e la cena se il paziente e l'eventuale accompagnatore soggiornano in albergo (o altra struttura ricettiva), fino ad un massimo di Euro 60,00, al giorno, per persona.
• saranno rimborsati la colazione ed il pranzo se il paziente e l'eventuale accompagnatore effettuano il ritorno al domicilio nel giorno successivo all'accesso al Centro, fino ad un massimo di Euro 30,00 per persona.
Pasti consumati in caso di pernottamenti presso locali in affitto/casa accoglienza/struttura ricettiva convenzionata
Solo ed esclusivamente in caso di pernottamento presso locali in affitto oppure casa accoglienza oppure presso struttura ricettiva convenzionata che prevedano esclusivamente alloggio e non vitto, saranno rimborsate eventuali spese sostenute in loco presso negozio/supermercato per i pasti se non forniti presso il locale in affitto/casa accoglienza/struttura ricettiva (es. cibo e bevande per colazione, pranzo, cena; tovaglioli e stoviglie usa e getta) ed eventuali beni di prima necessità per la cura della persona se non disponibili presso il locale in affitto/casa di accoglienza/struttura ricettiva (es. prodotti per igiene personale, prodotti per igiene del locale) per il paziente e l'eventuale accompagnatore/i autorizzato/i fino ad un massimo di Euro 60, al giorno per il nucleo familiare, riferibili alla giornata precedente l'accesso al Centro e alla giornata della visita o alle giornate corrispondenti alle visite effettuate in più giorni consecutivi, ovvero nelle stesse giornate in cui è previsto il rimborso proporzionale del canone di affitto in caso di locale in affitto.
Servizi speciali (per esempio trasporti protetti): saranno rimborsati solo ed esclusivamente previa autorizzazione specifica da parte della Società.
Tutti i costi relativi alle voci sopra non specificate non verranno rimborsati (esempio: televisione a pagamento, mini-bar, lavanderia, animazione, prodotti per la pulizia personale, servizi in camera diversi dai pasti rimborsabili, prodotti per la pulizia personale, giornali, tutti gli altri costi creatisi a casa in conseguenza dell'assenza per la visita nel Centro).
Qualsiasi richiesta di rimborso superiore agli importi di cui sopra dovrà essere sottoposta all'autorizzazione della Società prima di procedere al rimborso al paziente. Il Paziente farà il possibile per prenotare i biglietti aerei e di treno, gli alberghi, etc, più economici.

LIQUIDAZIONE FATTURE

- Il compenso deve essere liquidato entro 90 giorni data ricevimento fattura
- La fattura deve essere emessa con cadenza semestrale secondo quanto maturato nel periodo di riferimento, sulla base di apposita richiesta di emissione fattura da parte della Società con indicazione degli importi che risultano maturati dall'Ente;
- L'eventuale quota a saldo maturata al termine della Sperimentazione verrà corrisposta al momento della completa raccolta dei dati e risoluzione di eventuali chiarimenti relativi ai dati stessi
- In conformità a quanto previsto dal Decreto Semplificazioni (DL n. 76 del 16/07/2020) il pagamento della fattura emessa dall'Ente sarà effettuato esclusivamente attraverso l'utilizzo della piattaforma pagoPA;
- Ogni pagamento sarà identificato univocamente dal codice IUV (Identificativo Univoco di Versamento), generato in sede di creazione della fattura e notificato alla Società tramite un Avviso di Pagamento, che l'Ente si impegna ad allegare alla fattura, contenente anche il Codice Avviso di Pagamento, il Codice QR e il Codice Interbancario (codice CBILL: **ADZM2**) che consentono di effettuare il pagamento.

ALLEGATO B – GLOSSARIO RELATIVO ALLA PROTEZIONE DEI DATI PERSONALI
(terminologia riferita al GDPR – Reg. UE n. 2016/679 – ed alle norme attuative italiane)

- **Dato personale** – qualsiasi informazione riguardante una persona fisica identificata o identificabile ("interessato"); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale;
- **Trattamento** – qualsiasi operazione o insieme di operazioni, compiute con o senza l'ausilio di processi automatizzati e applicate a dati personali o insiemi di dati personali, come la raccolta, la registrazione, l'organizzazione, la strutturazione, la conservazione, l'adattamento o la modifica, l'estrazione, la consultazione, l'uso, la comunicazione mediante trasmissione, diffusione o qualsiasi altra forma di messa a disposizione, il raffronto o l'interconnessione, la limitazione, la cancellazione o la distruzione;
- **Pseudonimizzazione** – il trattamento dei dati personali tale che i dati non possano più essere attribuiti a un interessato specifico senza l'utilizzo di informazioni aggiuntive, a condizione che tali informazioni aggiuntive siano conservate separatamente e soggette a misure tecniche e organizzative intese a garantire che tali dati personali non siano attribuiti a una persona fisica identificata o identificabile;
- **Interessato** – la persona fisica cui si riferiscono i dati personali (art. 4 n.1 GDPR);
- **Titolare del trattamento** – la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che, singolarmente o insieme ad altri, determina le finalità e i mezzi del trattamento di dati personali; quando le finalità e i mezzi di tale trattamento sono determinati dal diritto dell'Unione o degli Stati membri, il titolare del trattamento o i criteri specifici applicabili alla sua designazione possono essere stabiliti dal diritto dell'Unione o degli Stati membri (art.4 n. 7 GDPR);
- **Responsabile del trattamento** – la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che tratta dati personali per conto del titolare del trattamento (art. 4 n.8 GDPR);
- **Altri soggetti che trattano dati personali** – le persone autorizzate al trattamento dei dati personali sotto l'autorità diretta del Titolare o del Responsabile (artt. 28, n. 3, lettera b, 29 e 32, n. 4 GDPR), ivi incluse quindi le persone fisiche alle quali il Titolare o il Responsabile abbiano attribuito specifici compiti e funzioni connessi al trattamento, che operano sotto l'autorità del Titolare e nell'ambito dell'assetto organizzativo, ai sensi dell'art. 2 *quaterdecies* del D.lgs. 196/2003 così come modificato dal D.lgs. 101/2018;
- **Consenso dell'interessato** - qualsiasi manifestazione di volontà libera, specifica, informata e inequivocabile dell'interessato, con la quale lo stesso manifesta il proprio assenso, mediante dichiarazione o azione positiva inequivocabile, che i dati personali che lo riguardano siano oggetto di trattamento;

- **Violazione dei dati personali** - la violazione di sicurezza che comporta accidentalmente o in modo illecito la distruzione, la perdita, la modifica, la divulgazione non autorizzata o l'accesso ai dati personali trasmessi, conservati o comunque trattati;
- **Dati relativi alla salute** - i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute;
- **Dati genetici** - i dati personali relativi alle caratteristiche genetiche ereditarie o acquisite di una persona fisica che forniscono informazioni univoche sulla fisiologia o sulla salute di detta persona fisica, e che risultano in particolare dall'analisi di un campione biologico della persona fisica in questione;
- **Campione biologico** - ogni campione di materiale biologico da cui possano essere estratti dati genetici caratteristici di un individuo;
- **Sponsor/Promotore** - la persona, società, istituzione oppure organismo che si assume la responsabilità di avviare, gestire e/o finanziare una sperimentazione clinica;
- **CRO** – organizzazione di ricerca a Contratto alla quale lo sponsor può affidare una parte o tutte le proprie competenze in tema di sperimentazione clinica;
- **Monitor** – il responsabile del monitoraggio della Sperimentazione individuato dallo sponsor/CRO;
- **Auditor** – il responsabile della esecuzione della verifica sulla conduzione della Sperimentazione, come parte integrante della assicurazione di qualità, individuato dallo sponsor/CRO.