EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 September 2025
EMA/325405/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Uplizna

International non-proprietary name: Inebilizumab

Procedure No. EMEA/H/C/005818/II/0012

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation or Term	Definition/Explanation
AC	Adjudication Committee
ACR	American College of Rheumatology
ADA	anti-drug antibodies
ADR	adverse drug reaction
AESI	adverse event of special interest
AUC_{SS}	area under the drug concentration-time curve at steady state
CD	cluster of differentiation
C_{oaxes}	maximum concentration observed and drug concentration at steady state
$C_{min,ss}$	minimum concentration observed and drug concentration at steady state
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
E-R	exposure response
EMA	European Medicines Agency
FDA	Food and Drug Administration
GC	glucocorticoid
HR	hazard ratio
IgE	immunoglobulin E
IgG4-RD	immunoglobulin G4-related disease
IgM	immunoglobulin M
IRR	infusion-related reactions
IV	intravenous
NMOSD	neuromyelitis optica spectrum disorders
ODD	orphan drug designation
OLP	open-label period
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
RCP	randomized-controlled period
SFUP	safety follow up period
TTTAF	the time-to-event variable of time to disease flare
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Horizon Therapeutics Ireland DAC submitted to the European Medicines Agency on 7 November 2024 an application for a variation.

The marketing authorisation of Uplizna was transferred to Amgen Europe B.V. during the procedure.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with Immunoglobulin G4-Related Disease (IgG4-RD) for UPLIZNA, based on the results from study MITIGATE. This is a pivotal phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab in adult subjects with IgG4-RD. As a consequence, sections 4.1, 4.2, 4.4 ,4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce editorial changes to the PI.

As part of the application, the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0217/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0217/2024 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

A request for Scientific advice (EMEA/H/SA/2664/2/2019/II) was received on 04 November 2019 from Viela Bio (former MAH) on the clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 November 2024
Start of procedure:	30 November 2024
CHMP Rapporteur Assessment Report	23 January 2025
PRAC Rapporteur Assessment Report	1 February 2025
PRAC Outcome	13 February 2025
CHMP members comments	12 February 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 February 2025
Request for supplementary information (RSI)	27 February 2025
Submission deadline	16 Apr 2025
Re-start of procedure	21 Apr 2025
CHMP Rapporteur Assessment Report	20 May 2025
PRAC Rapporteur Assessment Report	22 May 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	05 June 2025
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	11 June 2025
2nd Request for supplementary information (RSI)	19 June 2025
Submission deadline	19 August 2025
Re-start of procedure	20 August 2025
CHMP Rapporteur Assessment Report	02 September 2025
PRAC Rapporteur Assessment Report	25 August 2025
PRAC members comments	27 August 2025
Updated PRAC Rapporteur Assessment Report	28 August
PRAC Outcome	04 September 2025
CHMP members comments	08 September 2025
Updated CHMP Rapporteur Assessment Report	11 September 2025
Opinion	18 September 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Immunoglobulin G4-related disease (IgG4-RD) is a rare, systemic, chronic immune-mediated relapsing disorder that can cause fibrosing inflammatory lesions in nearly any organ (Kamisawa, 2022[1]; Maehara et al, 2020[2]; Perugino and Stone, 2020[3]; Zhang and Stone, 2019[4]; Stone et al, 2012[5]).

State the claimed therapeutic indication

The MAH initially applied for the following indication: *Uplizna is indicated for the treatment of adult patients with IgG4-RD (see section 5.1).*

Epidemiology

IgG4-RD tends to affect people in their fifth to seventh decades of life, but paediatric and older adult patients can also present with IgG4-RD. Most cohorts demonstrate a male predominance; however, this varies: pancreatobiliary disease and retroperitoneal disease more commonly affect males, whereas disease limited to the head and neck most commonly affects females. Population-based estimates of IgG4-RD incidence and prevalence are limited. Using a claims-based algorithm to identify cases in the USA, the estimated incidence was 0.78–1.39 per 100 000 person-years between 2015 and 2019, and the point prevalence as of 1 January 2019 was 5.3 per 100 000 persons. Patients with IgG4-RD may have an elevated risk of death compared with the general population, probably driven, in part, by irreversible organ damage from IgG4-RD in addition to treatment complications; the precise cause of excess mortality is unknown (Wallace et al, 2024[6]).

Biologic features, aetiology and pathogenesis

Immunoglobulin G4-related disease pathogenesis is complex and includes an extensive interplay between innate and adaptive immune mechanisms (Liu et al, 2020[7]). While many cell types have been implicated in disease pathogenesis, recent progress in the understanding of IgG4-RD immunopathology has delineated B cells, particularly plasmablasts and plasma cells, as key drivers of

[1] Kamisawa T. Immunoglobulin G4-related disease: a new systemic disease emerging in Japan. JMA J. 2022;5(1):23-35.
[2] Maehara T, Moriyama M, Nakamura S. Review of a novel disease entity, immunoglobulin G4-related disease. J Korean Assoc Oral Maxillofac Surg. 2020;46(1):3-11.
[3] Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020;16(12):702-714.
[4] Zhang W, Stone JH. Management of IgG4-related disease. Lancet Rheumatol. 2019;1(1):e55-e65.
[5] Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539-551.
[6] Wallace, Zachary S., et al. "Current and future advances in practice: IgG4-related disease." *Rheumatology Advances in Practice* 8.2 (2024): rkae020.
[7] Liu Z, Nie Y, Peng Y, Lu H, Zhang P, Li J, et al. The external validation of the 2019 ACR/EULAR classification criteria for IgG4-related disease in a large cohort from China. *Semin Arthritis Rheum*. 2023;61:152202.

disease via multiple different mechanisms of action (Della-Torre et al, 2020[8]; Perugino and Stone, 2020[9]).

Beyond IgG4+ plasma cells found in affected tissues, other B cell subsets found in the periphery, including circulating IgG4+ plasmablasts and memory B cells, also contribute to disease and have been used as measures of disease activity or as predictors of relapse (Lanzillotta et al, 2020[10]).

Clinical presentation, diagnosis and stage/prognosis

The clinical presentation of IgG4-RD is heterogeneous and the disease usually takes a chronic, relapsing-remitting course and is generally indolent and slowly progressive. The initial clinical presentation is often a mass lesion or organ enlargement that may be mistaken for malignancy. The slow pace of IgG4-RD in many patients is one of its most dangerous features, allowing for parenchymal injury and irreversible organ damage despite relatively few clinical symptoms (Katz et al, 2024[11]).

For example, IgG4-RD affecting the head and neck may result in orbital myositis, uveitis, scleritis, sialadenitis, chronic rhinosinusitis, Riedel's thyroiditis, and supraglottic stenosis. Involvement of the chest can manifest as parenchymal lung disease, pleural disease, pericarditis, coronary arteritis, fibrosing mediastinitis, and aortitis. Abdominal and pelvic manifestations include autoimmune pancreatitis type 1, sclerosing cholangitis, sclerosing mesenteritis, retroperitoneal fibrosis and aortitis, tubulointerstitial nephritis, membranous glomerulonephritis, and prostatitis. Finally, pituitary and central nervous system involvement can result in hypophysitis and hypertrophic pachymeningitis.

IgG4-RD has also been associated with increased mortality (Wallace et al, 2023[12]; Wallwork et al, 2019[13]; Huggett et al, 2014[14]).

Irreversible organ damage is observed in approximately 60% of IgG4-RD patients at the time of diagnosis (Abraham and Khosroshahi, 2017[15]; Wallace et al, 2020[16]).

The diagnosis of IgG4-RD requires clinicopathological correlation because there is no highly specific or sensitive test (Wallace et al, 2024[6]).

Management

The goal of treatment in IgG4-RD is to reduce disease activity and prevent irreversible damage, such as fibrosis, and most patients have significant reduction in the size of lesions and improvement in laboratory parameters with appropriate treatment. Worldwide, glucocorticoids (GC) are first-line therapy for IgG4-RD (Wallace et al, 2024[6]).

[8] Della-Torre E, Rigamonti E, Perugino C, Baghai-Sain S, Sun N, Kaneko N, et al. B lymphocytes directly contribute to tissue fibrosis in patients with IgG4-related disease. J Allergy Clin Immunol. 2020;145(3):968-981.
[9] Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020;16(12):702-714.
[10] Lanzillotta M, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ. 2020;369:m1067.
[11] Katz, Guy, et al. "Proliferative features of IgG4-related disease." *The Lancet Rheumatology* 6.7 (2024): e481-e492.
[12] Wallace ZS, Miles G, Smolkina E, et al. Incidence, prevalence, and mortality of IgG4-related disease in the USA: a claims-based analysis of commercially insured adults. *Ann Rheum Dis*. 2023;82(7):957.
[13] Wallwork R, Harkness T, Fu X, Perugino C, Choi HK, Stone J, et al. Early mortality in IgG4-related disease. Arthritis Rheumatol. 2019;71(Suppl 10).
[14] Huggett MT, Culver EL, Kumar M, Hurst JM, Rodriguez-Justo M, Chapman MH, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. 2014;109(10):1675-1683.
[15] Abraham M, Khosroshahi A. Diagnostic and treatment workup for IgG4-related disease. Expert Rev Clin Immunol. 2017;13:867-875.
[16] Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4 Related Disease. Arthritis Rheumatol. 2020;72(1):7-19.

Although nearly all patients with IgG4-RD respond to GCs, approximately 40% either fail to achieve complete remission or relapse within 1 year despite the use of maintenance prednisone. Moreover, the potential for GC toxicity is increased in IgG4-RD because these patients are typically middle-aged or older and frequently have comorbidities such as hypertension, glucose intolerance, and obesity. The potential for GC-related toxicity is heightened further by the tendency of IgG4-RD to cause damage in both the endocrine and exocrine pancreas. The major deficits in glucose tolerance acquired by many patients with IgG4-RD are compounded substantially by GC treatment. Thus, there is a clear need for effective GC-sparing treatment options in IgG4-RD (Perugino et al, 2023[17]).

Certain immunomodulatory agents have been used for steroid-sparing maintenance therapy in IgG4-RD. These include azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, tacrolimus, and cyclophosphamide (Khosroshahi et al, 2015[18]; reviewed in Lanzillotta et al, 2020[19]). However, the efficacy of these agents has not been rigorously evaluated in a double-blind, randomized, controlled study, and most studies have examined immunomodulatory agents in addition to GCs rather than as monotherapy (Omar et al, 2020[20]).

Surgery is also used, particularly in organs amenable to excision such as the pancreas, aorta, biliary ducts, and thyroid (Lee et al, 2019[21]), and some patients, particularly those with pancreatobiliary or renal disease, may require stenting for mechanical obstruction.

In conclusion, there is a high unmet medical need in IgG4-RD for steroid-sparing treatments for which clinically meaningful benefit and safety have been demonstrated in randomized, controlled, double-blind studies.

2.1.2. About the product

Inebilizumab (Uplizna) is a CD19-directed B cell-depleting antibody that binds to the B cell-specific cell surface antigen CD19, resulting in antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis of CD19+ B cells.

In clinical studies, inebilizumab provides rapid, deep, and durable B cell depletion (Bennett et al, 2022[22]; Cree et al, 2019[23]). B cells (particularly IgG4+ plasma cells and plasmablasts) are key drivers of disease in IgG4-RD. This provided a scientific rationale for the investigation of B cell-depleting therapy as a potential treatment modality for IgG4-RD. By targeting CD19, inebilizumab directly depletes a broader range of B cells compared with CD20-targeted agents. This is because CD19 expression begins earlier in B cell development than does CD20, starting at the pro-B cell phase, and is maintained through the differentiation of plasmablasts into plasma cells after CD20 expression has been lost.

[17] Perugino, C., Culver, E. L., Khosroshahi, A., Zhang, W., Della-Torre, E., Okazaki, K., ... & Stone, J. H. (2023). Efficacy and safety of inebilizumab in IgG4-related disease: protocol for a randomized controlled trial. *Rheumatology and Therapy*, *10*(6), 1795-1808.
[18] Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4 related disease. Arthritis Rheumatol. 2015;67(7):1688-1699.
[19] Lanzillotta M, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ. 2020;369:m1067.
[20] Omar D, Chen Y, Cong Y, Dong L. Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta analysis. Rheumatology (Oxford). 2020;59(4):718-726.
[21] Lee CM, Alalwani M, Prayson RA, Gota CE. Retrospective single-centre analysis of IgG4-related disease patient population and treatment outcomes between 2007 and 2017. Rheumato Adv Prac. 2019;3(1):1-10. doi: 10.1093/rap/rkz014
[22] Bennett JL, Katas O, Rees WA, Smith MA, et al. Association between B cell depletion and attack risk in neuromyelitis optica spectrum disorder: An exploratory analysis from N-MOmentum, a double-blind, randomised, placebo-controlled, multicentre phase 2/3 trial. EBioMedicine. 2022;86:104321.
[23] Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo controlled phase 2/3 trial. Lancet. 2019;394(10206):1352-1363.

Inebilizumab is approved in the European Union for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult patients who are anti-aquaporin-4 antibody positive.

IgG4-RD indication was proposed to use the same strength, dosage form, formulation, dosing regimen, and route of administration as for the currently authorised NMOSD indication: 300 mg on day 1 and day 15 and subsequently every 6 months.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant received Scientific Advice on the development of inebilizumab for the treatment of adults with IgG4-related disease from the CHMP on 30 January 2020. The Scientific Advice pertained to the following clinical aspects:
Agreement on design of a randomized (1:1), double-blind, placebo-controlled, parallel-cohort pivotal phase 3 study "MITIGATE" in approximately 160 patients with a 52-week randomized-controlled period (RCP), and an optional 52-week open-label period (OLP). Specific issues discussed included: proposed primary endpoint "time to disease flare" and secondary endpoints; definition of IgG4-RD flare to be included in the primary efficacy analysis using a novel set of organ/tissue-specific criteria and adjudication; use of the 2019 ACR/EULAR Classification Criteria to ensure accuracy of the diagnosis of IgG4-RD in the study population; single dosage level and fixed dosing interval; safety management plan and allowing patients to continue in the RCP after the first treated flare; eligibility to enter the OLP; sample size and statistical analyses; and a single pivotal study in support of MAA.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Inebilizumab by its nature as a protein (humanized antibody) is not posing a risk for the environment. The target of the monoclonal antibody (mAb) is not expected in living species, in water, sediment or sewage. mAb are considered naturally occurring products (i.e. they are proteins), which are not expected to remain either stable or biologically active in the environment for any significant period of time because of their susceptibility to chemical and physical degradation, as well as biodegradation by a wide range of microflora, and various physical removal mechanisms. Therefore, inebilizumab is not expected to pose a significant risk to the environment in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier	Objectives	Design and Type of Control	Test Product; Dosage Regimens; Route of Administration	Number of Subjects	Subject Population	Maximum Treatment Duration	Study Status; Type of Report
VIB0551.P3.S2 (MITIGATE; (20230068)	Primary: Efficacy Secondary: Safety and tolerability, efficacy	Phase 3, randomized, double-blind, placebo-controlled	RCP: 300 mg inebilizumab or placebo IV on day 1, day 15, and week 26. OLP: 300 mg inebilizumab IV on day 1, blinded 300 mg inebilizumab or placebo on day 15, then inebilizumab 300 mg IV every 6 months thereafter	135 randomized: • 68 to inebilizumab • 67 to placebo	Adults who had recently active IgG4-RD (initial diagnosis or recurrent disease) that required glucocorticoid treatment, had multiorgan disease, and who met the 2019 ACR/EULAR IgG4-RD Classification Criteria	RCP: 52 weeks OLP: 3 years	Ongoing; Full

2.3.2. Pharmacokinetics

Bioanalytical methods

Bioanalytical Method for Quantitation of Inebilizumab in Human Serum

A stepwise enzyme-linked immunosorbent assay method is used to quantitate the pharmacokinetic (PK) inebilizumab concentration in human serum samples. Inebilizumab in diluted standards, controls, and samples is captured by anti inebilizumab mouse mAb H5 coated on a microtiter plate. Addition of a second, biotinylated anti-inebilizumab mAb (A4) that binds to a region distinct from H5 and streptavidin-linked horseradish peroxidase complete the binding complex. Tetramethylbenzidene substrate addition results in a colorimetric reaction in which the amount of inebilizumab in a sample is directly proportional to color intensity. Inebilizumab concentration is determined by interpolation from a standard curve using a 4-parameter logistic curve without weighting.

The PK method was validated prior to testing clinical samples to establish the quantitative range, accuracy and precision, selectivity, dilution linearity, robustness, and sample stability. The lower limit of quantitation (LLOQ) and the upper limit of quantitation (ULOQ) were established. Accuracy and precision experiments were performed using the ULOQ, LLOQ, and 4 additional levels (high, mid, low, and back-up LLOQ quality controls [QCs]) within the quantitation range; each level had an absolute mean bias, and interassay precision (% coefficient of variation [CV]). The method was found to be

specific for inebilizumab through acceptable selectivity results in disease state sera including renal impairment and IgG4 RD. Each lot of the disease state matrices measured below the LLOQ, with 80% of inebilizumab-spiked samples meeting acceptance criteria at the back-up LLOQ concentration and the high QC (HQC) level. Acceptable selectivity was also demonstrated in hemolyzed sera and lipemic sera at the LLOQ and HQC levels. The method had acceptable dilution linearity and showed no evidence of a prozone effect.

The PK method was separately validated at another Laboratory for samples collected prior to testing clinical samples to establish the quantitative range, accuracy and precision, specificity, dilution linearity, robustness, and sample stability. Results are detailed in validation report. The main validation experiments were conducted by 3 analysts over approximately 4 weeks. The LLOQ w and the ULOQ were established. Accuracy and precision experiments were performed using the ULOQ, LLOQ, and 3 additional levels (high, mid, and low QCs) within the quantitation range; each level had an absolute mean bias, and interassay precision (%CV). The method was found to be specific for inebilizumab through acceptable selectivity results in healthy donor sera. Each lot of the healthy donor sera measured below the LLOQ, with 100% of inebilizumab-spiked samples meeting acceptance criteria at the LLOQ and the HQC level. Acceptable selectivity was also demonstrated in hemolyzed sera and lipemic sera at the LLOQ and HQC levels. The method had acceptable dilutional linearity and showed no evidence of a prozone effect.

Long-term stability assessment of QCs established stability when samples were stored at -80 ± 10°C. Additional long-term stability testing was performed and is documented in reagent qualification reports. The final established storage stability at -80°C has been determined.

Table 1 Bioanalytical Method Lifecycle Information (PK assay for Inebilizumab)

	Method Validation #1	Method Validation #2
Analyte	Inebilizumab	Inebilizumab
Validation type	Full	Full
Matrix	Serum	Serum
Platform	ELISA	ELISA
Format	A validated sandwich ELISA format using anti-inebilizumab antibody (H5) coated plates as capture and different anti-inebilizumab-biotinylated antibody (A4) followed by SA-HRP as detection.	A validated ELISA format using anti-inebilizumab antibody (H5) coated plates as capture and different anti-inebilizumab-biotinylated antibody (A4) followed by SA-HRP as detection.
Matrix study population	Healthy participants; participants with renal impairment; participants with IgG4-RD	Healthy participants
Synopsis of amendment history	Validation at new test site	Validation at new test site

The anti-drug antibody (ADA) method is a bridging assay format measured on the Meso Scale Discovery (MSD) electrochemiluminescence technology platform. The ADA method was validated prior to testing to determine the screening and confirmatory CPs as well as to establish precision, sensitivity, drug tolerance, and titration linearity using a goat polyclonal antibody (pAb) surrogate positive control (PC). Drug tolerance and sensitivity were also assessed using a rabbit polyclonal anti inebilizumab antibody. The main validation consisted of 40 assays performed by 3 analysts over

approximately 5 months. Each assay included the rabbit PC at multiple levels and at least 4 duplicate wells of the negative quality control (NQC).

The ADA method was separately validated at another Laboratory, LTD for samples collected prior to testing to determine the screening and confirmatory CPs as well as to establish precision, sensitivity, drug tolerance, and titration linearity using a goat pAb surrogate PC. The ADA method is an affinity capture elution (ACE) format measured on the MSD electrochemiluminescence technology platform. Drug tolerance and sensitivity were also assessed using a rabbit polyclonal anti-inebilizumab antibody. The main validation consisted of 40 assays performed by 5 analysts over approximately 3 months. Each assay included the rabbit PC at multiple levels and at least 4 duplicate wells of the NQC.

Pharmacokinetic data analyses

General pharmacokinetics

Study MITIGATE is a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of inebilizumab in adults with active IgG4-RD. Subjects were randomized 1:1 to receive either intravenous (IV) inebilizumab 300 mg or matching placebo on day 1, day 15, and week 26 of the 52-week randomised control period (RCP). Blood samples for assessment of serum concentrations of inebilizumab during the RCP were collected from all subjects on days 1, 15, 29, 57, 85, 183, 211, 267, and 365. On inebilizumab dosing days, samples were collected predose and 15 minutes (± 5 minutes) after the end of infusion. Samples were taken for assessment of ADA on days 1, 29, 85, 183, 267, and 365 of the RCP, and at weeks 0, 2, 12, 26, 38, 52, and then every 6 months during the open label period (OLP).

A noncompartmental analysis (NCA) was performed based on serum inebilizumab concentration vs time data from 135 IgG4-RD patients in the RCP. The PK Analysis dataset was comprised of 1489 concentration records in total, with 747 records from 68 subjects in the treatment cohort and 742 records coming from 67 subjects in the placebo cohort. Of these 747 sample results, 563 were measurable concentrations from 57 subjects and included in the validation data set. A total of 184 sample results (66 BLQs before dose, 117 BLQs after first dose and 1 "not applicable") were excluded.

The 2-week dosing interval between the Dose 1 and Dose 2 did not allow meaningful extrapolation of inebilizumab PK profile to infinity for derivation of AUC_{inf}, CL and V_{ss}. On the other hand, the PK of inebilizumab did not reach steady-state following only 2 doses of inebilizumab. Overall, inebilizumab PK in IgG4-RD patients was consistent with NMOSD, indicating disease setting did not alter the disposition or exposure of the drug.

For the IgG4 RD indication, pharmacokinetic parameter summary statistics are presented by dosing day in Table 2 and overall parameters based on cumulative exposure are presented in Table 3.

For the NMOSD indication, summary results for clinical pharmacokinetics studies are provided in Table 4.

Table 2 Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameter Estimates After IV Administration of 300 mg Inebilizumab to Subjects with IgG4-RD

NCA Day	Statistic	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-14d} (μg•day/mL)	AUC_{last} (μg•day/mL)
1	N	63	63	63	63
	Mean	0.084	108	820	827
	SD	0.012	32.9	253	256

	Min	0.072	63.4	408	408
	Median	0.081	104	783	796
	Max	0.15	209	1550	1560
	CV%	15	30	31	31
	GeoMean	0.084	104	784	791
15	N	64	64	64	64
	Mean	0.30	133	1150	2280
	SD	1.7	39.2	333	897
	Min	0.070	27.1	300	753
	Median	0.080	123	1130	2210
	Max	14	266	2180	5660
	CV%	580	30	29	39
	GeoMean	0.089	127	1100	2120
183	N	51	51	51	51
	Mean	0.085	100	951	1920
	SD	0.010	21.8	215	574
	Min	0.073	41.4	454	782
	Median	0.082	99.3	937	1860
	Max	0.13	142	1330	3180
	CV%	12	22	23	30
	GeoMean	0.085	97.9	926	1830

$AUC_{0\text{-}14d}$ = area under the curve from time 0 to 14 days postdose; AUC_{last} = area under the curve from time 0 to the last quantifiable time point; C_{max} = maximum concentration; CV = coefficient of variation; Geo = geometric; IgG4-RD = immunoglobulin G4-related disease; IV = intravenous; NCA = noncompartmental analysis; t_{max} = time to maximum concentration. Descriptive statistics are presented to 3 significant figures except for t_{max} and CV%, which are presented to 2 significant figures and the nearest integer, respectively.

Table 3 Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameter Estimates Based on Overall Exposure After IV Administration of 300 mg Inebilizumab to Subjects with IgG4-RD

Statistic	AUC_{cum} (μg•day/mL)	$t_{1/2,z}$ (day)
N	64	53
Mean	4620	18.4
SD	1720	4.21
Min	1470	10.9
Median	4410	18.0

Max	10 100	29.0
CV%	37	23
GeoMean	4290	17.9

Notes: Descriptive statistics are presented to 3 significant figures except for CV% which is presented to the nearest integer. Terminal half-life only represents day 15 as day 183 had insufficient sampling in too many subjects for accurate half-life estimates. AUC_{cum} = AUC from time zero of the first dose to the last quantifiable time point following the last dose and was calculated using the following formula: $AUC_{0\text{-}14d,\ Day1} + AUC_{last,\ Day\ 15} + AUC_{last,\ Day183}$; CV = coefficient of variation; Geo = Geometric; IgG4-RD =

Table 4 Summary results for clinical pharmacokinetics studies in NMSOD indication

Protocol No.	Study Objective(s)	Study Design	No. of Subjects;	Treatment Details (Drug/Dose/ Form/Route/ Frequency/Duration)	Summary Statistics [a]				
					C_{max} (µg/mL)	T_{max} (d)	AUC_{inf} (µg·d/mL)	$t_{½}$ (d)	V_{ss} (mL) [b]
Study 1155	To characterize the PK profile of inebilizumab in NMOSD subjects	R, DB, PLC	174	300 mg IV Inebilizumab on Day 1 and Day 15	[116] 108 (45.4%) [c]	0.07 (0.07-14.00) [c]	[3130] 2980 (34.3%)	[18.8] 18.0 (27.2%)	[4380] 4210 (27.3%)

AQP4-IgG = aquaporin-4 autoantibodies; AUC_{inf} = area under the plasma concentration-time curve from Time 0 to infinity; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; DB = double blind; DR = dose rising; IV = intravenous; NA = not applicable; PLC = placebo; R = randomized; SC = subcutaneous; SD = standard deviation; $t_{½}$ = terminal elimination half-life; T_{max} = time to maximum concentration; V_{ss} = volume of distribution.

All PK parameters are rounded to 3 significant figures except T_{max} (rounded to 2 decimal places)

a Parameters are summarized as arithmetic mean (CV%) for CP200 and Study 1102 apart from T_{max} displayed as median (range: min – max). Paramete for Study 1155 are summarized as [arithmetic mean] geometric mean (geometric CV%) apart from T_{max}, displayed as median (range: min – max).

b V_{ss} unit is mL/kg for CP200 and mL for Study 1155.

c Value is calculated from Dose 2 inebilizumab on Day 15 of AQP4-IgG Combined.

Figure 1 Individual serum inebilizumab concentration-time profiles for subjects following 3 doses IV administrations at 30 mg (Plot 1 of 4)

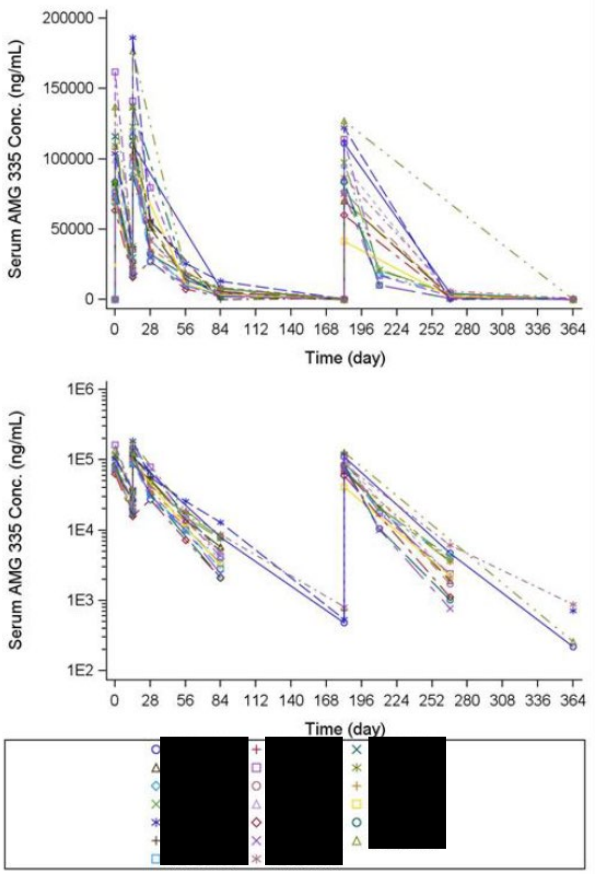


Figure 2 Individual serum inebilizumab concentration time-profiles for subjects following 3 IV administrations at 300 mg (Plot 2 of 4)

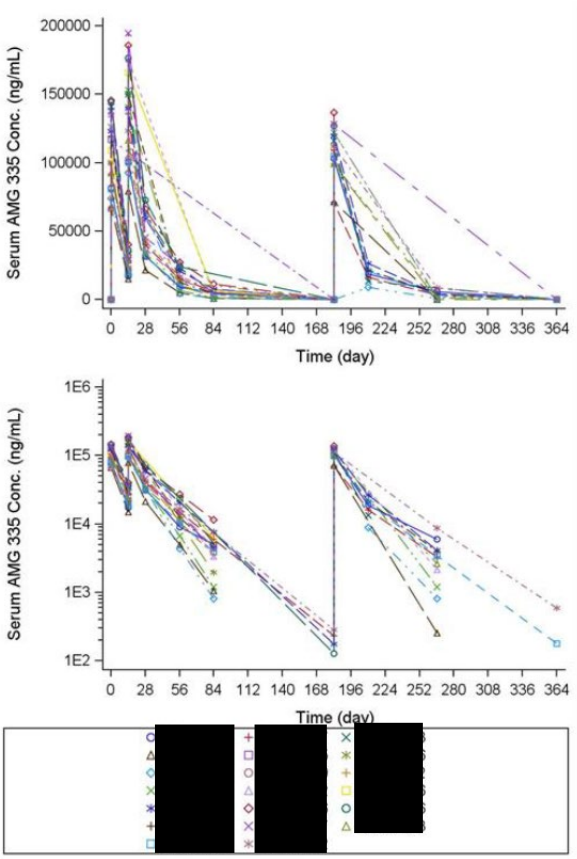


Figure 3 Individual serum inebilizumab concentration-time profiles for subjects following 3 IV administrations at 300 mg (Plot 3 of 4)

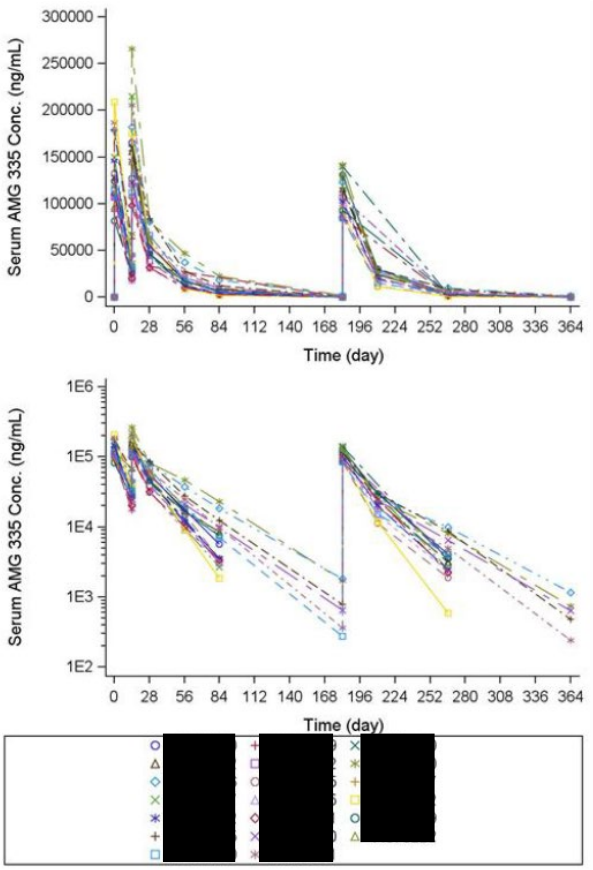
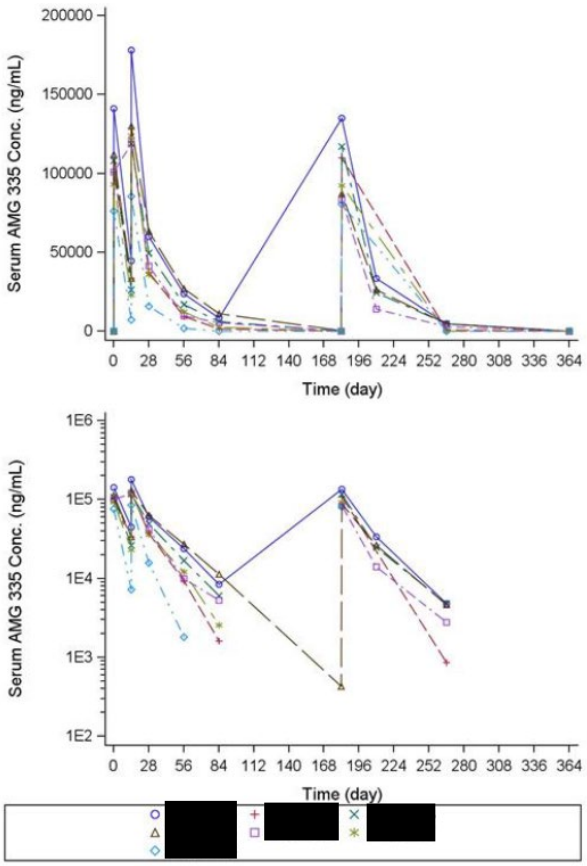


Figure 4 Individual serum inebilizumab concentration-time profiles for subjects following 3 IV administrations at 300mg (Plot 4 of 4)



Pop PK analysis

A Pop PK model for inebilizumab was previously developed based on data from 3 studies: MI-CP200, CD-IA-MEDI-551-1102, and CD-IAMEDI-551-1155. The model structure was two-compartmental with parallel first-order and time-dependent nonlinear elimination pathways. Baseline body weight was identified as a statistically significant covariate.

The PK data in study VIB0551.P3.S2 (MITIGATE) was analysed using the previous developed final inebilizumab PopPK model via an external validation approach. The MITIGATE study included PK data from patients with IgG4-related disease treated with inebilizumab (300 mg treatment on Day 1, Day 15, and Week 26) who had at least one measurable inebilizumab post-dose sample. Measurement of inebilizumab serum concentrations was performed using a validated immunoassay. The MITIGATE data set contained 747 inebilizumab concentrations from 68 patients of which 563 concentrations from 67 patients were included in the external validation. A total of 34 data points (6.04%) were excluded as outliers due to the absolute prediction errors that were 10 times over the calculated mean prediction error.

For external model validation, predicted inebilizumab serum concentrations for subjects in the validation dataset were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the previous final inebilizumab PopPK model using post hoc Bayesian forecasting with NONMEM 7.

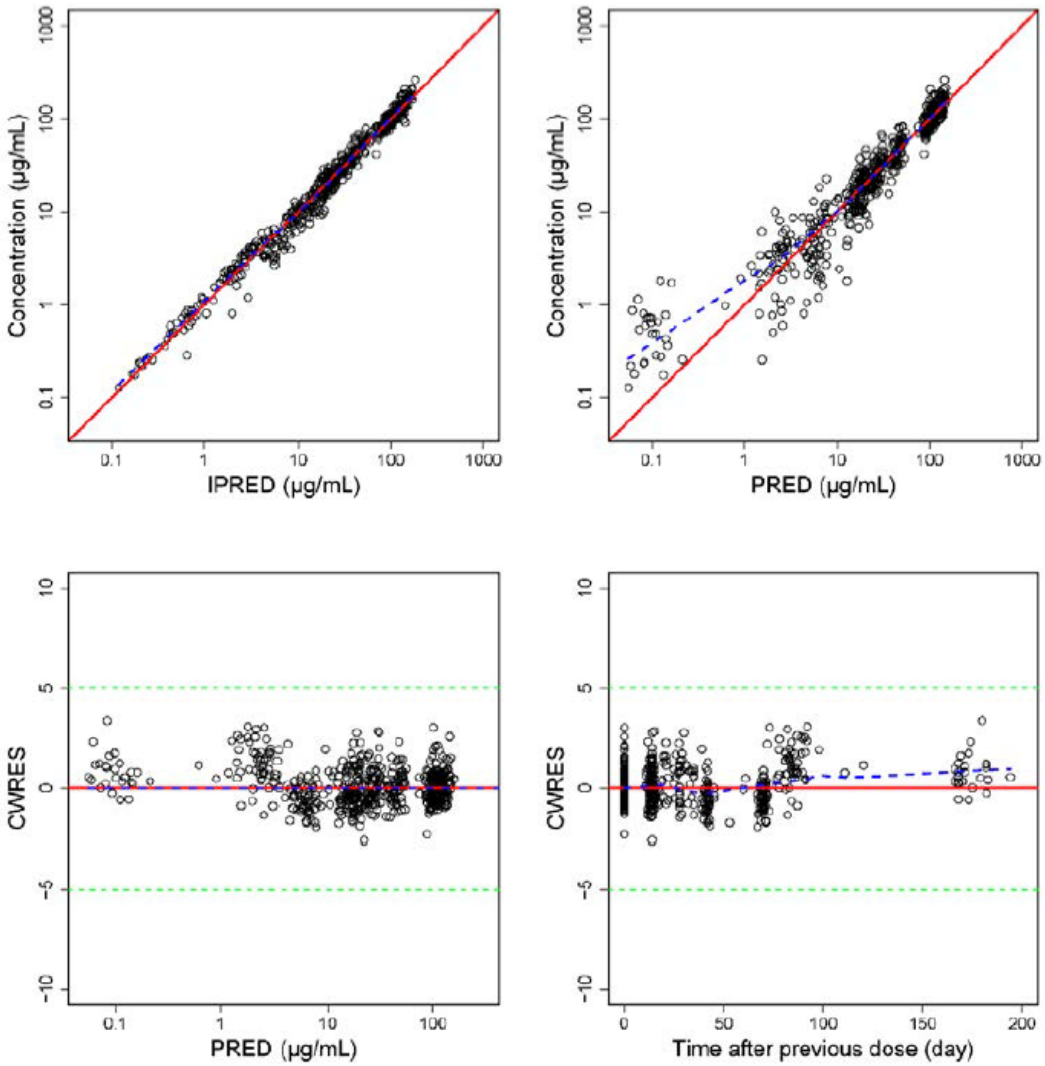
Table 5 Summary of *Post hoc* parameters

Descriptions	Geometric mean values of post hoc PK parameters	PK parameters estimate from the previous Model	% Change
Clearance, CL (mL/day)	190.42	188.22	1.17
Central volume, V_c (mL)	2977.83	2946.39	1.07
Inter-compartmental clearance, Q (mL/day)	367.89	363.23	1.28
Peripheral volume, V_p (mL)	2617.79	2569.43	1.88
Maximum velocity of the saturable clearance process, V_{max} (µg/day)	828.52	832.5	-0.477
Concentration to achieve half of V_{max}, K_m, (µg/mL)	5.89	5.89	0
First-order rate constant for decrease in V_{max}, K_{dec} (1/day)	0.00294	0.00294	0

% change = (geometric mean of post hoc value – previous model estimate)/ previous model estimate*100%

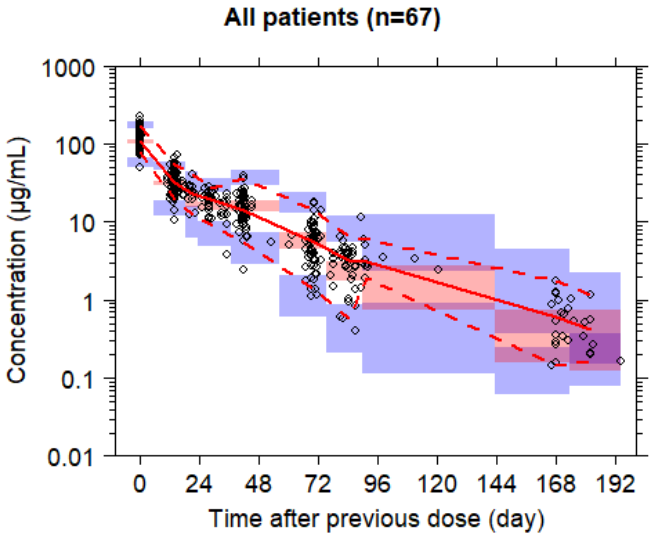
The mean bias in the population predictions for validation subjects was -0.453% (95% [CI -6.02%, 5.11%]). The mean imprecision was 30.8% (95% CI [28.0%, 33.7%]).

Figure 5 General goodness-of-fit plots for all inebilizumab validation subjects



Top: individual predicted serum inebilizumab concentrations (IPRED) versus observed inebilizumab concentrations (left) and population predicted serum inebilizumab concentrations (PRED) versus observed serum inebilizumab concentrations (right). Bottom: conditional weighted residuals (CWRES) versus time after the previous dose (left) and PRED (right). Points are individual data. Red solid lines represent the unit diagonal (top) or line at zero (bottom). Green dashed lines represent |CWRES| of 5. Blue dashed lines represent the lowess smooth curves.

Figure 6 pcVPC of inebilizumab concentration versus time for validation subjects



pvVPC = prediction-corrected visual predictive checks
Notes: Circles are observed inebilizumab serum concentrations, a solid red line represents the median observed value, and dashed red lines represent the 2.5 percentile and 97.5 percentile of the observed values. Pink-shaded areas represent the 95% CI of the predicted median concentrations, and the blue-shaded areas represent the 95% CI of the 2.5 percentile and 97.5 percentile of the predicted concentrations.

Table 6 Summary of numerical predictive check in inebilizumab validation subjects

Range	Observation (%)	
	Expected	All Subjects
Above 95th percentile	5.00	5.86
Above 75th percentile	25.0	27.9
Above 50th percentile	50.0	57.4
Below 50th percentile	50.0	42.6
Below 25th percentile	25.0	18.7
Below 5th percentile	5.00	1.42

Exposure-response analyses

The E-R analysis data file was created using R software.

Population E-R analysis was conducted to investigate potential relations between inebilizumab exposure metrics (AUCss, Cmin,ss, and Cmax,ss) and efficacy endpoints: time to disease flare; annualized flare rate for treated and AC-determined flare; and treatment-free complete remission at week 52. The data came from study MITIGATE and contained exposure and efficacy data from a total of 67 subjects.

Time-to-event data e.g time to disease flare was plotted using Kaplan-Meier survival curves. If an E-R trend was observed, further analysis with Cox proportional-hazards modelling was performed with exposure grouped in quartiles. Effect of various prognostic factors were evaluated: exposure (AUCss , Cmax,ss and Cmin,ss), age, age group (<65 years vs. ≥65 years), HGT, WT, BMI, BSA, CRCL, eGFR, AST, ALP, TB, sex, race, ADA, and HEPA.

Table 7 Summary of model parameters from the Cox regression model for time to disease flare in inebilizumab-treated patients

Exposure	Predictor	Parameter and HR Estimates				Wald p-value
		β	HR	95% CI for β		
				Lower	Upper	
AUC_{ss}	Q2	-1.71	0.182	0.0188	1.76	0.1407
	Q3	-1.23	0.292	0.042	2.03	0.2139
	Q4	NA	NA	NA	NA	NA
$C_{max,ss}$	Q2	NA	NA	NA	NA	NA
	Q3	-0.283	0.753	0.122	4.64	0.7601
	Q4	-0.756	0.469	0.0748	2.95	0.4197
$C_{min,ss}$	Q2	-0.419	0.658	0.11	3.95	0.6470
	Q3	-0.988	0.372	0.0387	3.58	0.3921
	Q4	NA	NA	NA	NA	NA

Hazard ratio (HR) is relative to Q1 and calculated using exp(β), with 'NA' indicating inability to estimate due to lack of events.

Table 8 Summary of the selected cox model

Model No	Predictor	Parameter and HR Estimates				Wald p-value
		β	HR	95% CI for β		
				Lower	Upper	
2	AUC_{ss}	-2.18	0.113	-4.46	0.1044	0.0614
3	$C_{min,ss}$	-0.322	0.725	-0.676	0.0316	0.0743
4	$C_{max,ss}$	-2.02	0.133	-6.26	2.23	0.3517
12#	AST	-0.189	0.827	-0.403	0.0244	0.8274

HR: hazard ratio is calculated by exp(β). #final covariate model.

For the binary response variables, boxplots of exposures stratified by responses were generated. If an E-R trend was observed, further analysis with linear logistic regression models was performed.

Table 9 Logistic model-building process for an annualized flare rate of 0 for treated and AC-determined flare versus exposures in inebilizumab-treated patients

Model No.	Model Description	Compare to	P-value
0	run0 only intercept	-	-
1	run0 + log(AUC_{ss})	0	0.1278
2	run0 + log($C_{min,ss}$)	0	0.1587

Table 10 Summary of logistic model parameters for an annualized flare rate of 0 for treated and AC-determined flare versus exposures in inebilizumab-treated patients

Model: $logit(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(X_i)$			
Exposure	**Parameter**	**Estimates (SE)**	**P-value**
AUC_{ss}	β_0	-12.3 (9.42)	0.193
	β_1	2.02 (1.33)	0.129
$C_{min,ss}$	β_0	3.36 (0.995)	0.000741
	β_1	0.304 (0.211)	0.149

Table 11 Logistic model-building process for treatment-free complete remission at week 52 versus AUCss in inebilizumab-treated patients

Model No.	Model Description	Compare to	P-value
0	run0 only intercept	-	-
1	run0 + log(AUC_{ss})	0	0.4576

Table 12 Summary of logistic model parameters for treatment-free complete remission at week 52 versus AUCss in inebilizumab-treated patients

Model: $logit(P(Y_i = 1)) = \beta_0 + \beta_1 \cdot \log(X_i)$			
Exposure	**Parameter**	**Estimates (SE)**	**P-value**
AUC_{ss}	β_0	-4.25 (6.21)	0.494
	β_1	0.636 (0.861)	0.461

Distribution

V_{ss} was not determined in the NCA due to the injection and sampling scheme. In the popPk analysis, V_c was estimated to be 2946.39 mL and V_p 2569.43 mL.

Elimination

The mean (SD) of terminal half-life for day 15, the most intense collection period, was 18.4 (4.21) days. PopPK analysis estimated CL to be 188.22 mL/day.

Special populations

Intrinsic Factors and Special Populations

Pediatric Use

Inebilizumab has not been studied in adolescents or children with IgG4-RD.

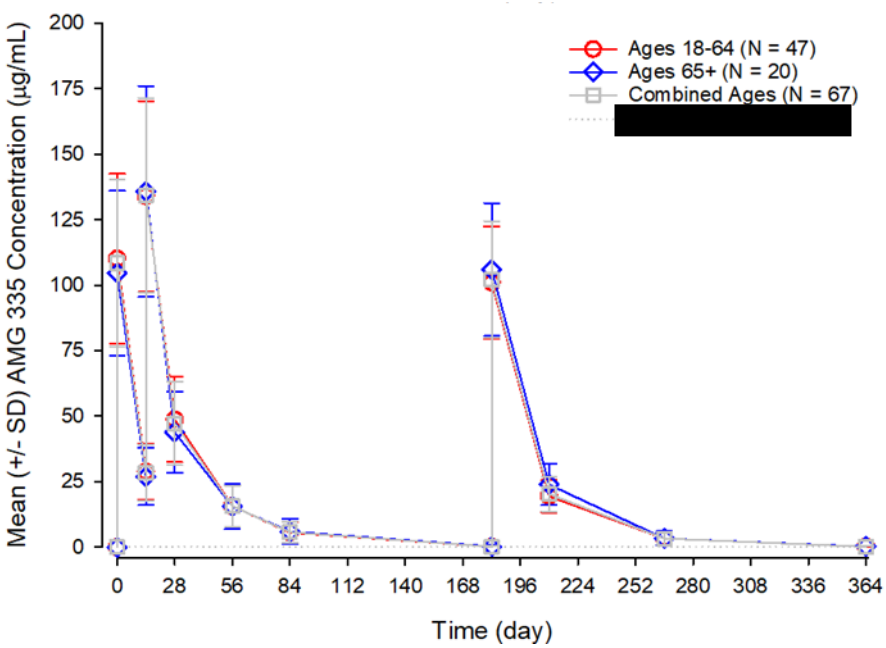
Geriatric Use

Of the 135 adult subjects enrolled and dosed with inebilizimab in clinical studies, 42 subjects were 65 years and older:

- In NMOSD study, across RCP and OLP, inebilizumab was administered in 10 elderly (≥65 years) patients (6 in inebilizumab group during the RCP and 4 in placebo group during the OLP).
- In IgG4-RD study, across RCP and OLP, inebilizumab was administered in 32 elderly patients (21 in inebilizumab group during the RCP and 11 in placebo group during the OLP).

Based on population PK analysis, age did not affect inebilizumab clearance. Mean concentration-time profiles for elderly subjects enrolled in the MITIGATE study in comparison with the rest of the population is presented in Figure 10.

Figure 10. Mean Concentration-Time Profiles of AMG 335 by Age Category in Subjects with IgG4-RD



IgG4-RD = immunoglobulin G4-related disease:
Error bars represent (±) standard deviation of the mean.

Gender, Race

The population PK analysis indicated that there was no significant effect of gender and race on inebilizumab clearance.

Renal Impairment

No formal clinical studies have been conducted to evaluate the PK of inebilizumab in patients with impaired renal function. Due to the large hydrodynamic size, monoclonal antibodies are not expected to be excreted in urine. The population PK analysis indicated that there was no significant effect of renal function on inebilizumab clearance.

Hepatic Impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on inebilizumab. IgG monoclonal antibodies are not primarily cleared via hepatic pathway; change in

hepatic function is not expected to influence inebilizumab clearance. The population PK analysis indicated that there was no significant effect of hepatic function on inebilizumab clearance.

Pharmacokinetic interaction studies

Formal drug-drug interaction studies have not been conducted for inebilizumab. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the system clearance (CL) of inebilizumab, a humanized IgG1κ monoclonal antibody. The primary elimination pathway for inebilizumab is clearance by the reticuloendothelial system in the same way as that for an endogenous IgG. Therefore, the potential risk of PK interactions between inebilizumab and other drugs is low. Based on population analysis, commonly used small molecule drugs by subjects with IgG4-RD (prednisolone and methylprednisolone) had no effect on inebilizumab PK.

2.3.3. Pharmacodynamics

Mechanism of action

Inebilizumab is a monoclonal antibody that specifically binds to CD19, a cell surface antigen present on pre-B and mature B-cell lymphocytes, including plasmablasts and some plasma cells. Following cell surface binding to B lymphocytes, inebilizumab supports antibody-dependent cellular cytolysis (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B cells are believed to play a central role in the pathogenesis of IgG4-RD. The precise mechanism by which inebilizumab exerts its therapeutic effects in IgG4-RD is unknown but is presumed to involve B cell depletion and may include the suppression of antibody secretion, antigen presentation, B -cell–T- cell interaction, and the production of inflammatory mediators.

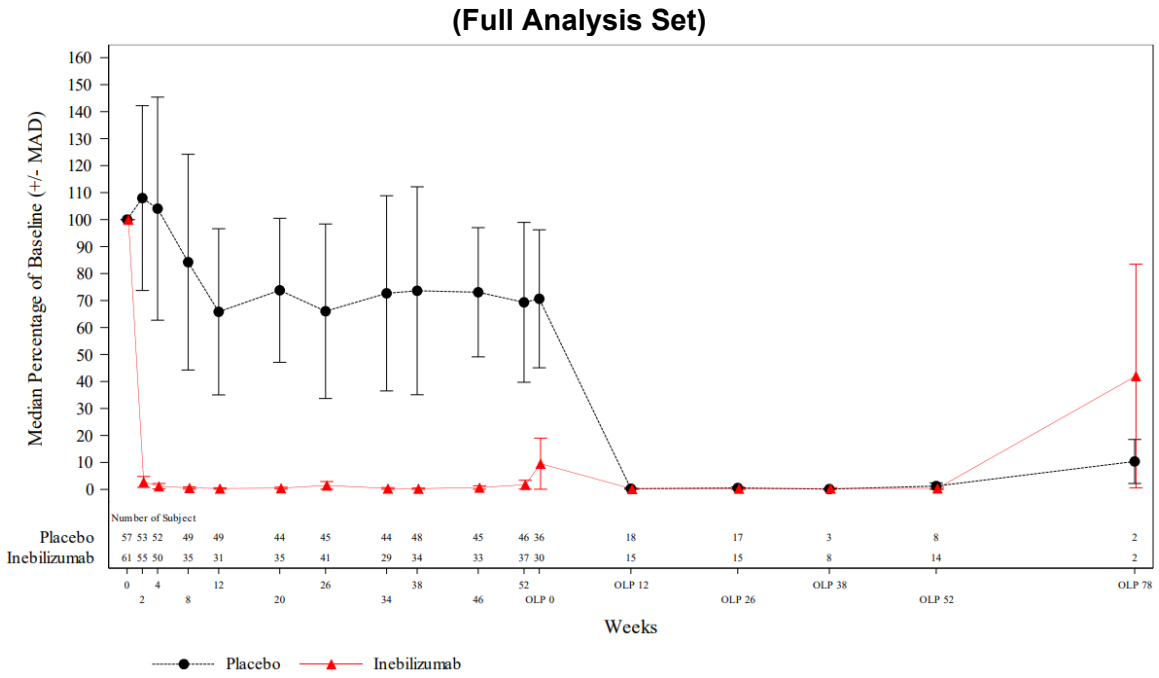
Primary and secondary pharmacology

B cell Counts

Inebilizumab treatment led to rapid sustained depletion of CD20+ B cells. A median reduction of > 90% in peripheral CD20+ B cell counts was observed 2 weeks after the initial infusion with inebilizumab and CD20+ B cell counts remained at that level of reduction throughout the 52 week Randomized controlled period (RCP). CD20+ B cells counts were significantly lower in the inebilizumab group compared with the placebo group at the earliest time point measured (2.78% of baseline in inebilizumab and 107.97% in placebo at week 2) and remained below the placebo group through week 52 (1.76% in inebilizumab and 69.33% in placebo) after initial treatment (Figure 7). CD20+ B cell counts did not significantly change from baseline across any RCP time points in the placebo group. CD20+ B-cell counts were reduced below the lower limit of normal by week 2 in 100% of patients treated with inebilizumab and remained below the lower limit of normal in 82% and 79% of patients at week 26 and 52, respectively.

During the OLP, CD20+ B cell counts remained at >90% reduction in the inebilizumab/inebilizumab groups and were rapidly reduced in subjects in the placebo/inebilizumab group upon initiation of the inebilizumab treatment, with both groups having similar B cell counts by OLP Week 12 (Figure 7).

Figure 7 Median Values for CD20+ B Cell Count As a Percentage of Baseline Over Time



CD = cluster of differentiation; MAD = Median Absolution Deviation.
Error bars represent MAD.

Plasmablast and Plasma Cell Count

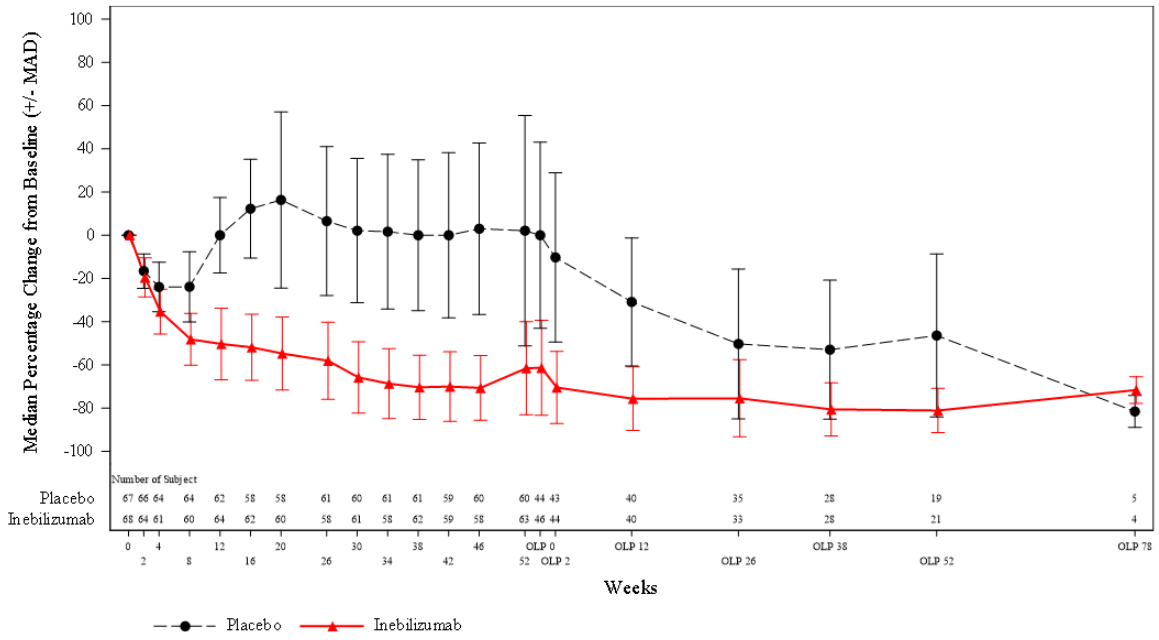
Plasmablast and plasma cell counts showed a significant reduction in the inebilizumab group by RCP Week 12 and remained low throughout the 52-week RCP.

During the OLP, plasmablast and plasma cell counts remained low in the inebilizumab/inebilizumab group and the placebo/inebilizumab group showed similar reductions in plasmablast and plasma cell counts by OLP Week 12. Generally, plasmablast and plasma cell counts remained lower in the inebilizumab/inebilizumab subjects compared with the placebo/inebilizumab subjects at all other RCP and OLP time points.

Immunoglobulin G4

IgG4 levels showed a >70% median reduction during the RCP in inebilizumab-treated subjects with levels remaining low throughout the OLP (Figure 8).

Figure 8 Median Values For Percent Change From Baseline In Immunoglobulin G4 (g/L) Over Time During Randomized Controlled Period (Full Analysis Set)



MAD = Median Absolution Deviation; RCP = randomized controlled period.
Notes: Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

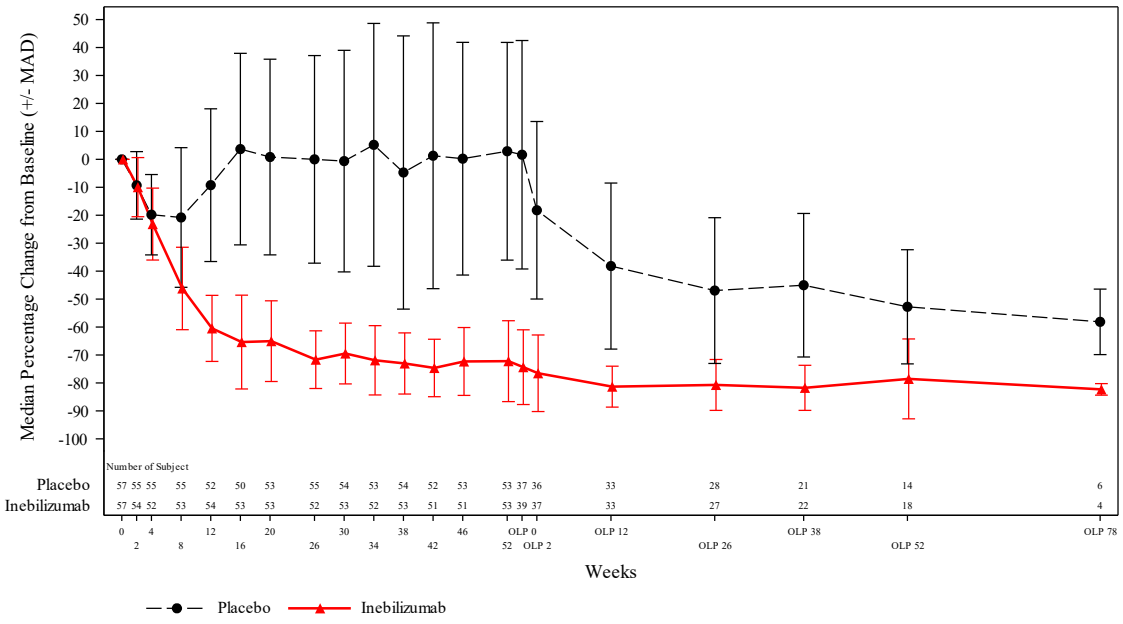
Immunoglobulin E

IgE levels showed a >72.2% median reduction during the RCP in inebilizumab-treated subjects with levels remaining low throughout the OLP (Figure 9).

Subjects in the placebo group had some apparent reductions in IgE levels during the first 8 weeks of the RCP coinciding with the steroid taper period, after which levels increased throughout the RCP. Beginning at week 12, there was a separation between the treatment arms with respect to their IgE levels. Subjects in the placebo/inebilizumab group in the OLP also showed decreases over time in IgE levels with a median reduction of 56.7%.

Figure 9 Median Values for Immunoglobulin E as a Percentage of Baseline Over Time

(Full Analysis Set)



MAD = Median Absolution Deviation; OLP = open-label period; RCP = randomized controlled period.
Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

Clinical Immunogenicity

The tabulated summary of inebilizumab immunogenicity by treatment group in the RCP is provided in Table 13.

Table 13 Anti-drug antibody response to investigational product (randomized controlled period, safety analysis set)

	Placebo N = 67	Inebilizumab N = 68
Subjects with at least one non-missing Anti-Drug Antibody (ADA) result during the study	67	68
ADA not detected (negative) during the study	60 (89.6%)	52 (76.5%)
ADA Incidence[a]	5 (7.5%)	6 (8.8%)
ADA detected (positive) during the study: ADA prevalence	7 (10.4%)	16 (23.5%)
Baseline[b] positive regardless of post-baseline status	4 (6.0%)	11 (16.2%)
Only baseline positive	0	8 (11.8%)
Post-baseline positive regardless of baseline status	7 (10.4%)	8 (11.8%)
Only post-baseline positive	3 (4.5%)	5 (7.4%)
Both baseline and post-baseline positive	4 (6.0%)	3 (4.4%)
Persistent positive[c]	2 (3.0%)	5 (7.4%)
Transient positive[d]	1 (1.5%)	0

ADA = anti-drug antibody.
[a]Incidence is the proportion of the subjects with ADA positive post-baseline only or boosted their preexisting ADA (at least 4-fold over the baseline titer) during the study period.
[b]Baseline is defined as the last valid value on or before the first dose of randomized controlled period.
[c]ADA post-baseline positive only and at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment.
[d]ADA post-baseline positive only and does not fulfil the criteria of persistent positive.

Inebilizumab PK parameter summary statistics are presented by dosing day and ADA status in Table 14. Summary statistics of PK parameters based on overall exposure are presented by ADA status in Table 15. Arithmetic mean (±SD) inebilizumab concentration-time figures by ADA status are presented in Figure 10. Comparable AUC and half-life between ADA positive and negative groups are depicted in Figure 11.

Table 14 Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameters by NCA Day after IV Administration of Inebilizumab to Subjects with IgG4-RD Stratified by Antibody Status

	Positive			**Negative**		
	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-14d} (μg•day/mL)	t_{max} (day)	C_{max} (μg/mL)	AUC_{0-14d} (μg•day/mL)
Day 1						
N	13	13	13	50	50	50
Geo. Mean (CV% Geo. Mean)	0.08 (5.5)	109 (28.7)	843 (33.5)	0.08 (13.5)	102 (30.1)	770 (30.2)

Median [Min-Max]	0.08 [0.07; 0.09]	109 [63.4; 162]	863 [408; 1290]	0.08 [0.07; 0.15]	99.9 [67.1; 209]	722 [411; 1550]
Day 15						
N	13	13	13	51	51	51
Geo. Mean (CV% Geo. Mean)	0.12 (259.1)	135 (58.7)	1180 (50.4)	0.08 (8.1)	125 (25.0)	1080 (27.2)
Median [Min-Max]	0.08 [0.07; 14.02]	141 [27.1; 266]	1290 [300; 2180]	0.08 [0.07; 0.10]	122 [79.1; 206]	1060 [575; 1740]
Day 183						
N	10	10	10	41	41	41
Geo. Mean (CV% Geo. Mean)	0.08 (8.2)	104 (27.3)	955 (29.5)	0.09 (11.1)	96.5 (23.4)	919 (23.5)
Median [Min-Max]	0.08 [0.07; 0.09]	112 [59.9; 142]	1040 [522; 1330]	0.08 [0.07; 0.13]	97.6 [41.4; 140]	936 [454; 1330]

$AUC_{0\text{-}14d}$ = area under the curve from time 0 to 14 days postdose; C_{max} = maximum concentration; Geo = geometric; IgG4-RD = immunoglobulin G4-related disease; IV = intravenous; NCA = noncompartmental analysis; t_{max} = time to maximum concentration

Pharmacokinetic parameters are presented as geometric mean (geometric CV%) and median [Min; Max]

Data are presented to 3 significant figures for all summary statistics with the exception of CV% (% coefficient of variation), which is rounded to 1 decimal place.

Table 15 Descriptive Statistics of Serum Inebilizumab Pharmacokinetic Parameters Based on Overall Exposure After IV Administration of Inebilizumab to Subjects with IgG4-RD

	AUC_{cum} (μg•day/mL)			$t_{1/2}$ (day)
ADA Positive				
N	13			10
Geo. Mean (CV% Geo. Mean)	4510 (40.8)			17.2 (25.8)
Median [Min-Max]	4480 [2130; 10100]			17.2 [11.7; 26.4]
ADA Negative				
N	51			43
Geo. Mean (CV% Geo. Mean)	4230 (42.8)			18.1 (23.0)
Median [Min-Max]	4390 [1470; 9360]			18.0 [10.9; 29.0]
ADA Combined				
N	64			53
Geo. Mean (CV% Geo. Mean)	4290 (42.2)			17.9 (23.4)
Median [Min-Max]	4410 [1470; 10100]			18.0 [10.9; 29.0]

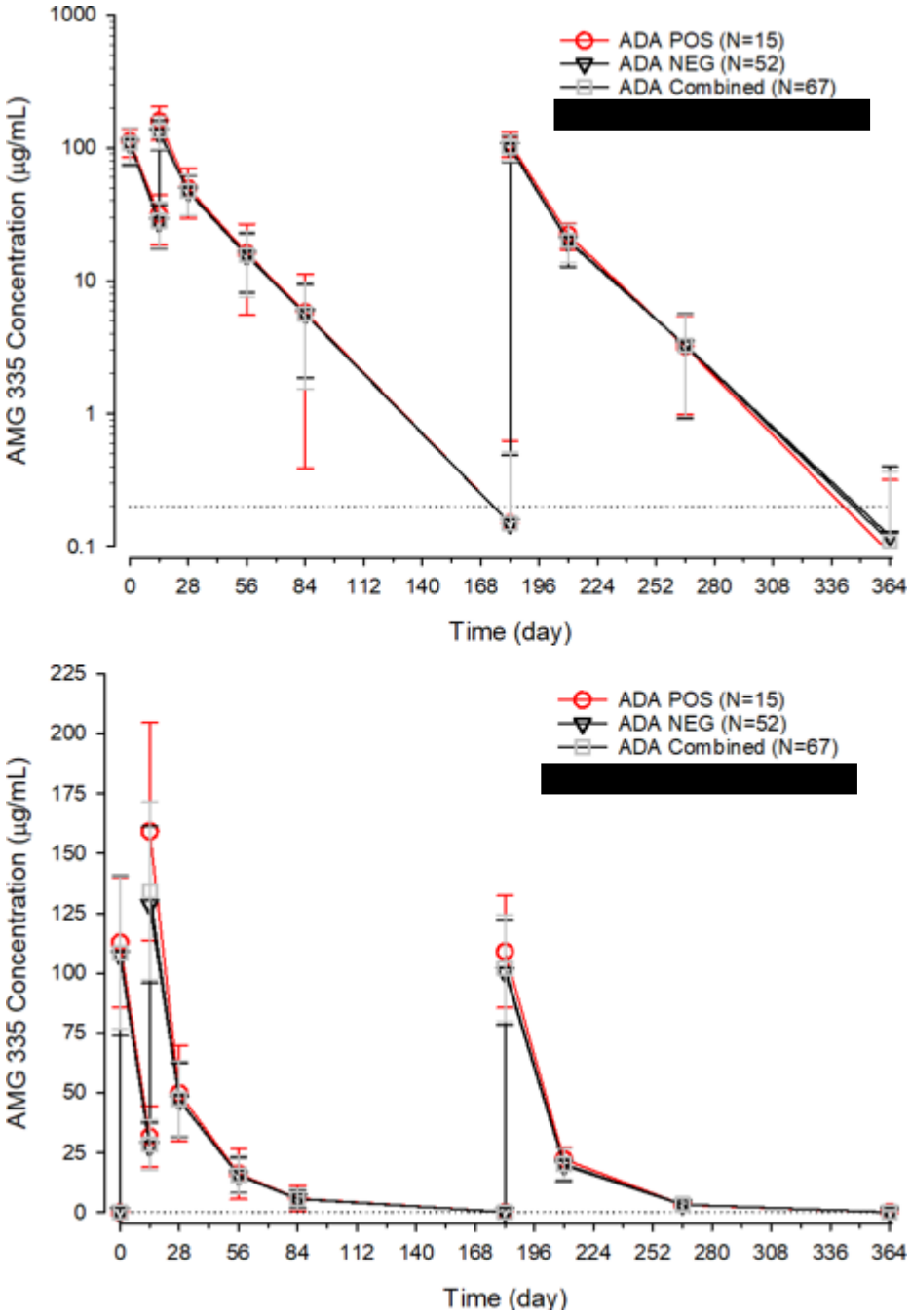
ADA = anti-drug antibody; AUC_{cum} = AUC from time zero of the first dose to the last quantifiable time point after the last dose and was calculated using the following formula: $AUC_{0\text{-}14d,\ Day1} + AUC_{last,\ day\ 15} + AUC_{last,\ day183}$;; $t_{1/2}$ = terminal half-life

Notes: Terminal half-life ($t_{1/2}$) only represents day 15 as day 183 had insufficient sampling in too many subjects for accurate half-life estimates.

Pharmacokinetic parameters are presented as geometric mean (geometric CV%) and median [Min; Max]

Data are presented to 3 significant figures for all summary statistics with the exception of CV% (% coefficient of variation), which is rounded to 1 decimal place.

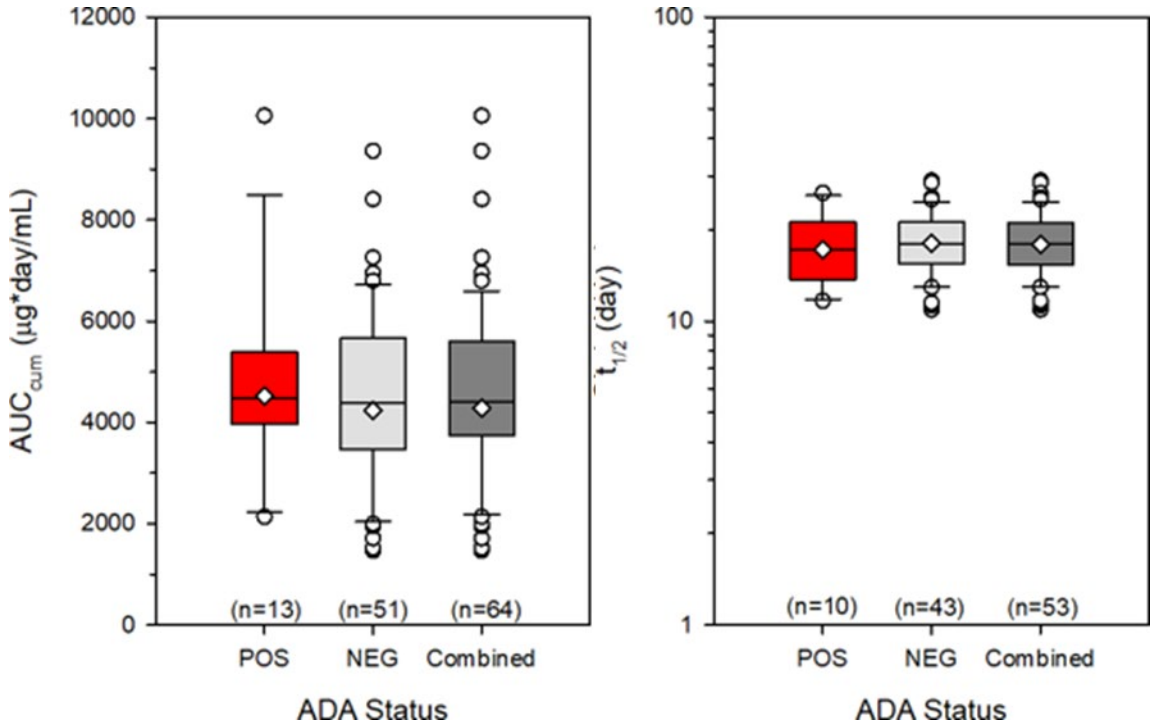
Figure 10 Arithmetic Mean Concentration-Time Profiles of Inebilizumab by ADA Status in Subjects with IgG4-RD



ADA = anti-drug antibody; ADA POS = ADA positive subject; ADA NEG = ADA negative subject; AMG 35 = inebilizumab;

Notes: Error bars represent (±) standard deviation of the mean. Top: log; bottom: linear.

Figure 11 Impact of ADA on Exposure and Half-Life in Subjects with IgG4-RD



ADA = anti-drug antibody; AUC_{cum} = AUC from time zero of the first dose to the last quantifiable time point following the last dose CL = system clearance; IgG4-RD = immunoglobulin G4-related disease; POS = ADA positive subject; NEG = ADA negative subject.

Notes: The boxes indicate the first and third quartile of observations. The black horizontal bar within each box indicates the median (second quartile). The upper and lower whiskers indicate the maximum and minimum observations, respectively, that lie within the 1.5 inter-quartile range of the first and third quartiles.

Circles = outliers; Diamonds = geometric mean.

Based on the summary of B-cell counts (primary PD marker) by ADA status in the RCP, there was no impact of ADA status on B-cell depletion.

2.3.4. Discussion on clinical pharmacology

The bioanalytical programme, performed in support of this application, was acceptable to the CHMP.

The data set from MITIGATE was fitted using external validation with structural parameters and etas fixed to values from a previous model for inebilizumab. A large number of post-dose samples (>10%) were excluded. This did not affect the model as no parameters were re-estimated. Exposure-efficacy relations were explored based on data from Study MITIGATE. Exposure metrics AUCss, Cmin,ss, and Cmax,ss were generated by the previous Pop PK model for inebilizumab. Cox regression models were used for the time-to-flare endpoint and for univariate evaluation of various covariates. Only AST was included in the final covariate model but did not have significant influence on the hazard. Logistic regression models were used to evaluate annualized flare rate of 0 for treated and AC-determined flare versus AUCss, Cmin,ss and treatment-free remission at week 52 versus AUC,ss. Only one dose level of inebilizumab (300 mg iv) in 67 treated patients was investigated. Therefore, potential exposure-efficacy relations, if any, were not clear from this data alone and the results should be interpreted with caution.

The pharmacokinetic data from the MITIGATE study were consistent with an IV administrated monoclonal antibody. CV% was within the expected margins for all parameters, which is reflected in

the individual serum concentration curves. The lack of NCA-derived AUC_{inf}, CL and Vss was adequately justified.

When accounting for the extra dose at 6 months included in the MITIGATE PK analysis, AUC_{cum} was comparable between the two patient populations (2980 v. 4290 μg•day/mL). Some of the variability in individual PK parameters such as t_{max}, AUC_{last} and $AUC_{cumulative}$ could be ascribed to missing data.

Inebilizumab is a mAb which mostly resides in the plasma compartment. V_{ss} was not determined in the NCA due to the injection and sampling scheme. In the popPk analysis, V_c was estimated to be 2946mL and V_p 2569 mL. This resulted in a V_{Total} of 5510 mL which is consistent with a distribution confined to the blood. The half-life of inebilizumab was calculated for Day 15 only. There was insufficient sampling after Day 183 dosing to estimate half-life. Half-life is within expected margins for an IgG monoclonal antibody and comparable to NMOSD patients (approximately 18 days). Due to the injection and sampling scheme, CL could not be determined in the NCA. The PopPK estimated CL was consistent with the NCA half-life and Vtotal ($t_{1/2.IV} = \frac{0{,}693 * V_d}{Cl}$) and results from the previous study in NMOSD patients (app. 200 ml/day).

Only one dose level was included in MITIGATE study. The dosing schedule was slightly different from the NMOSD clinical phase II/III study as the 6-months dose was included in the analysis in the MITIGATE study. This was reflected in relevant PK parameters (see above).

The lack of studies in renal and hepatic impairment populations was adequately justified. When combining all clinical studies with inebilizimab, a total of 42 enrolled subjects were 65 years or older. Of these, a total of 27 subjects were enrolled in inebilizumab arm and the remaining 15 were allocated to the placebo with subsequent open label treatment. No clinical meaningful difference in exposure was observed in the elderly compared to the rest of the population. SmPC Section 4.2 was updated accordingly.

The CHMP agreed that pharmacokinetic interaction with other products is not likely for inebilizimab as the clearance pathway is the same as for other IgGs.

The SmPC section 5.2, paragraph on absorption, was updated to include the mean maximum values and cumulative AUC for the NMOSD and IgG4-RD studies, respectively.

Pharmacodynamics

Inebilizumab is a monoclonal antibody that binds to the B cell-specific surface antigen CD19, resulting in the depletion of B cells, including plasmablasts and some plasma cells. The exploratory PD endpoints were changes from baseline in peripheral B cell counts, including total B cells and B cell subsets change from baseline.

In the phase 3 Study MITIGATE, inebilizumab treatment led to a major reduction in peripheral CD20+ B-cell counts, plasmablast and plasma cell counts, consistent with the mechanism of action and known primary pharmacodynamics.

IgG4 and IgE levels were assessed as biomarkers of IgG4-RD activity. Both IgG4 and IgE levels decreased with inebilizumab treatment as an indicator of disease response to treatment.

The incidence of ADA was 8.8% for inebilizumab-treated participants and 7.5% for placebo treated participants. Time-concentration curves PK parameters were not significantly affected by ADA status. No impact of ADA status was seen on B-cell depletion (primary PD-marker). ADA status was not found to have an impact on the efficacy. No firm conclusions can be made due to the small numbers in the ADA subgroup (Section 2.4.2.). Furthermore, ADA status was not found to have an impact on the safety (Section 2.5.).

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology package was overall adequate and supported the posology in the treatment of active IgG4-RD of a loading dose of 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion. The recommended maintenance dose is 300 mg intravenous infusion every 6 months.

2.4. Clinical efficacy

2.4.1. Dose response study

The selected dose for IgG4-RD subjects was identical to the Phase 3 study in adults entitled N-MOmentum: A Clinical Research Study of Inebilizumab in Neuromyelitis Optica Spectrum Disorders (NCT02200770) which demonstrated a rapid and sustained depletion of CD19+ B cells. Since there was no expected difference in inebilizumab PK between subjects with NMOSD and IgG4-RD, the proposed dosing regimen was expected to be well-tolerated and to achieve a similar deep and durable B cell depletion in subjects with IgG4-RD.

The regimen of inebilizumab (300 mg IV [which ensures 3 mg/kg for adult subjects weighing 100 kg], at a schedule of day 1, day 15, and every 6 months thereafter) selected for this study was supported by data from phase 1 studies in multiple sclerosis and scleroderma. In these studies, B cell depletion was less complete and/or less durable at doses lower than 3 mg/kg.

The 300 mg dose resided at the efficacy plateau for NMOSD, minimising the impact of PK variability. The second dose of inebilizumab on day 15 was timed to deplete newly circulating B cells mobilised out of lymphoid and other tissues. Subsequent doses administered at 6-month intervals were timed to maintain the PD effect based on observations in Study N-MOmentum in which CD20+ B cell counts were significantly reduced 8 days after the initial infusion and remained below the lower limit of normal (LLN) in 100% of subjects at 4 weeks and 94% of subjects at 28 weeks. Both efficacy and safety outcomes in subjects with NMOSD supported this dose regimen. In aquaporin-4 IgG seropositive subjects in Study N-MOmentum, inebilizumab reduced the risk of NMOSD attack by 77% compared with placebo. At the 300 mg dose level, the safety profile was acceptable for further development.

2.4.2. Main study

Study MITIGATE: a Phase 3, Randomized, Double-blind, Multicenter, Placebo-Controlled Study of Inebilizumab Efficacy and Safety in IgG4 Related Disease

Study MITIGATE was a multicentre, randomized, double-blind (Investigator, subject, and applicant were blinded to treatment assignment), placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab for prevention of disease flare in adults with active IgG4-RD who are at high risk of recurrent flare.

Methods

The study consisted of a screening period (up to 28 days), a 52-week RCP, an optional 3-year OLP, and a 2-year safety follow-up period (SFUP) after the last investigational product administration for subjects who did not participate in the OLP or discontinued from treatment during the OLP.

Subjects were randomized 1:1 to receive either intravenous (IV) inebilizumab 300 mg or placebo on day 1, day 15, and week 26 of the 52-week RCP. Treatment assignment was stratified by first or subsequent IgG4-RD manifestation (i.e., newly diagnosed vs recurrent). Subjects who completed the RCP were given the option to enter a 3-year OLP. Those who were assigned to placebo during the preceding RCP received inebilizumab on OLP days 1 and 15. Subjects who were assigned to inebilizumab in the RCP received inebilizumab on OLP day 1 and matching placebo on day 15 to maintain blinding of sites and subjects to the RCP treatment assignment. Both groups then received inebilizumab every 6 months for the duration of the OLP.

During the screening period, all subjects had to have received at least 3 weeks of GC treatment for their recent flare. This GC treatment could either be newly initiated or be increased from a prior maintenance dose of ≤10 mg/day of prednisone or equivalent. The GC treatment for recent flare had not to have exceeded 60 mg/day prednisone or equivalent at any point. Subjects who received GCs for treatment of recent flare at the time of consent were not eligible if this treatment had exceeded 4 weeks in duration.

Subjects were normalized to a dose of 20 mg/day prednisone or equivalent before randomization, and upon randomization, all subjects began a mandatory, prescribed taper leading to GC discontinuation at the end of 8 weeks. Other immunomodulatory or immunosuppressive medications were prohibited during the study, except for medications required to treat on study IgG4-RD flares. Treatment of flares was at the discretion of the investigator. Receipt of prohibited medication required discontinuation of investigational product.

This study was conducted in participants randomized at 46 sites in Argentina, Australia, Canada, China, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Poland, Spain, Turkey, United Kingdom and US.

Study participants

Approximately 160 subjects were planned to be randomized in a 1:1 ratio to 2 treatment groups (inebilizumab group and placebo group).

Inclusion Criteria

To be included in the study, each individual had to satisfy all of the following criteria:

1. Male or female adults who have reached the age of consent in the applicable region (eg, ≥18 years in the US)

2. Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3. Clinical diagnosis of IgG4-RD.

4. Fulfilment of the 2019 ACR/EULAR classification criteria as determined by the Eligibility Committee. Specifically, subjects must meet the classification criteria entry requirements (including involvement of one of the following organs: pancreas, bile ducts/biliary tree, orbits, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, pachymeninges, or thyroid gland [Riedel's thyroiditis]), must not meet any of the classification criteria exclusions, and must achieve at least 20 classification criteria inclusion points.

5. Experiencing (or recently experienced) an IgG4-RD flare that requires initiation or continuation of GC treatment at the time of informed consent. This criterion may be met in two ways:

- On GC therapy for recent IgG4-RD flare, having received a maximum of 4 weeks of treatment prior to informed consent at a dose no higher than 60 mg/day prednisone or equivalent, and at 20 mg/day prednisone or equivalent on the day prior to randomization, or
- Experiencing active disease not currently being treated at the time of informed consent, with planned initiation of treatment for flare with GC at a maximum dose of 60 mg/day prednisone (or equivalent) and with a plan to be treated at a dose of 20 mg/day of prednisone (or equivalent) on the day prior to randomization, for a total duration of GC treatment during screening period of at least 3 weeks at the time of randomization.
  This GC therapy can either be newly initiated or be increased from a maintenance dose of ≤ 10 mg/day of prednisone or equivalent.
  Subjects unable to be tapered to 20 mg/day of prednisone or equivalent by Visit 2 may not be randomized.
  Total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks prior to randomization.

6. IgG4-RD affecting at least 2 organs/sites at any time in the course of IgG4-RD with documentation to confirm. One organ must meet the requirements for the ACR/EULAR classification criteria (inclusion 4); the second organ is as defined by the investigator.

7. Willing and able to comply with the protocol, complete study assessments, and complete the study period.

8. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide (where spermicide is available) from Day 1 through to the end of the study and must agree to continue using such precautions for at least 6 months after the final dose of IP. Females of childbearing potential must have a negative serum pregnancy test at screening. Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception.

Exclusion Criteria

Any of the following excluded an individual from participation in the study:

1. Severe cardiovascular, respiratory, endocrine, gastrointestinal, haematological, neurological, psychiatric, or systemic disorder, or any other condition that, in the opinion of the Investigator, would place the patient at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of patient safety or study results.

2. History of solid organ or cell-based transplantation.

3. Known immunodeficiency disorder

4. Active malignancy or history of malignancy that was active within the last 10 years, except as follows:

- In situ carcinoma of the cervix following apparently curative therapy > 12 months prior to screening,
- Cutaneous basal cell or squamous cell carcinoma following apparently curative therapy,
- Prostate cancer treated with radical prostatectomy or radiation therapy with curative intent > 3 years prior to screening and without known recurrence or current treatment, or
- Thyroid cancer for which surgery has been performed and there is no evidence of active disease.

5. Receipt of any biologic B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, inebilizumab) in the 6 months prior to screening.

6. Receipt of non-depleting B-cell-directed therapy (eg, belimumab), abatacept, or other biologic immunomodulatory agent within 6 months prior screening.

7. Receipt of non-biologic DMARD or immunosuppressive agent other than GCs (eg, azathioprine, mycophenolate mofetil, methotrexate, others) within 4 weeks prior to screening.

8. Receipt of any investigational agent < 12 weeks or < 5 half-lives of the drug (whichever is longer) prior to screening.

9. Inability to be tapered off of GC therapy by 8 weeks post-randomization (other than ≤ 2.5 mg/day prednisone or equivalent for treatment of adrenal insufficiency or intolerance of taper) in the opinion of the Investigator.

10. Receipt of live vaccine or live therapeutic infectious agent within the 2 weeks prior to screening.

11. Pregnancy, lactation, or planning to become pregnant within 6 months of the last dose of IP.

12. Positive test for, or prior treatment for, hepatitis B or HIV infection. A positive test for hepatitis B is detection of either (1) hepatitis B surface antigen (HBsAg); or (2) hepatitis B core antibody (anti-HBc); and in Japan only (3) hepatitis B surface antibody (HBsAb)

13. History of untreated hepatitis C infection, or positive antibody test for hepatitis C virus (HCV) unless patient is considered to be cured following antiviral therapy and has a HCV viral load below the limit of detection at least 24 weeks after completion of treatment at site or central lab.

14. Evidence of active tuberculosis (TB) or being at high risk for TB based on:

- History of active TB or untreated/incompletely treated latent TB. Patients with a history of active or latent TB who have documentation of completion of treatment according to local guidelines may be enrolled.
- History of recent (≤ 12 weeks of screening) close contact with someone with active TB (close contact is defined as ≥ 4 hours/week or living in the same household or in a house where a person with active TB is a frequent visitor).
- Signs or symptoms that could represent active TB by medical history or physical examination.
- Positive, indeterminate, or invalid interferon-gamma release assay test result at screening, unless previously treated for TB. Patients with an indeterminate test result can repeat the test once, but if the repeat test is also indeterminate, the patient is excluded.
- Chest radiograph, chest computed tomography (CT) or MRI scan that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all patients must have had lung imaging with an acceptable reading within 6 months prior to consent, or during screening.

15. History of > 1 episode of herpes zoster (any grade) and/or any other definite or probable opportunistic infection in the 12 months prior to screening (see Appendix A) for details on opportunistic infections that require exclusion).

16. Known history of allergy or reaction to any component of inebilizumab formulation or history of anaphylaxis to any human gamma globulin therapy.

17. Allergy to or intolerance of protocol-required treatment, including medications for prophylaxis of infusion reactions (antipyretic such as paracetamol/acetaminophen or equivalent, diphenhydramine or equivalent, and methylprednisolone or equivalent).

18. Estimated glomerular filtration rate < 30 mL/min/1.73 m2 by Modification of Diet in Renal Disease Study (MDRD) equation (NIDDK).

19. Blood tests at screening that meet any of the following criteria:

- Hemoglobin < 7.5 g/dL
- Neutrophils < 1200/mm3
- Platelets < 110 × 109/L
- Eosinophil count > 3000/mm3
- Prothrombin time > 1.2 x upper limit of normal (ULN); however, subjects who are anticoagulated due to atrial fibrillation and who have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 2 x ULN are not excluded
- Total immunoglobulins < 600 mg/dL
- CD19+ B cells at screen < 40 cells/□L; an exclusionary value may be repeated.

20. Subjects with the following abnormal liver function tests in the absence of hepatobiliary IgG4-RD activity:

- Aspartate aminotransferase (AST) > 2 × ULN
- Alanine aminotransferase (ALT) > 2 × ULN
- Total bilirubin (TBL) > 2 × ULN unless AST, ALT, and haemoglobin are within central laboratory normal range and the patient has a known history of Gilbert syndrome

OR Subjects with the following abnormal liver function tests in the presence of hepatobiliary IgG4-RD activity:

- AST > 10 × ULN
- ALT > 10 × ULN
- TBL > 5 × ULN
- Screening liver function tests may be repeated prior to randomization to permit abnormal values due to hepatobiliary IgG4-RD activity to respond to GC treatment.

21. Known positive anti-neutrophil cytoplasmic antibodies (ANCA) targeted against proteinase 3 or myeloperoxidase based on patient records.

22. History of alcohol or drug abuse that, in the opinion of the Investigator, might affect patient safety or compliance with visits or interfere with safety or other study assessments.

23. Active, clinically significant infection at the time of randomization (IP administration may be delayed until recovery, if within screening window, otherwise subject may be rescreened).

24. Participation in any clinical trial that includes use of any pharmacologic intervention.

The following criteria applied for eligibility to the OLP:

1. Have completed the RCP Week 52 visit (end of RCP).

2. Must not have had IP discontinued for any of the following safety reasons:

   - Anaphylaxis or a serious hypersensitivity reaction that occurred within 7 days after IV dosing and cannot be attributed to another known allergen exposure (see Appendix B).
   - Any adverse event (AE) or significant laboratory abnormality that, in the opinion of the Investigator, Sponsor, or SDMC, warrants discontinuation of dosing.
   - Any life-threatening (Grade 4) infection.
   - Any event of sepsis or febrile neutropenia.
   - Any infection listed as either a definite or probable opportunistic infection in Appendix A.
   - Any Grade 3 IRR.
   - Any Grade 4 serious adverse event (SAE).
   - Pregnancy or a decision to become pregnant.

- Malignancy.
- Absolute neutrophil count < 800 cells/μL confirmed by repeat testing.
- Determination that the subject was ineligible for study participation and continuation of IP could pose a safety risk to the subject in the judgment of the Investigator or Sponsor.
- Significant noncompliance with the study protocol, as judged by the Investigator or Sponsor.
- Receipt of any B cell-depleting therapy (eg, rituximab, ocrelizumab, obinutuzumab, ofatumumab, commercially available inebilizumab).

3. Have completed a 28-day washout period after discontinuation of non-B cell-depleting, non-GC immunosuppressive therapy initiated during the RCP, if relevant.
4. Receive Dose 1 in the OLP within the window of 1-38 days after the RCP Week 52 visit (the final visit for the RCP and the first visit for the OLP cannot occur on the same day).
5. Have a planned taper of GCs to discontinuation by 8 weeks after OLP Dose 1, if receiving GC at the time of OLP entry.

Treatments

Study duration was designed to approximately 4.1 years for subjects who chose to enter the optional OLP: screening (4 weeks), RCP (52 weeks), and OLP (3 years). Subjects who chose not to participate in the OLP, or who discontinued investigational product during the OLP, entered the SFUP for 2 years after the last dose of investigational product.

Investigational product (inebilizumab 300 mg or placebo) was administered as an IV infusion on day 1, day 15, and week 26 of the RCP. In the OLP, those who were assigned to placebo during the preceding RCP received inebilizumab on OLP days 1 and 15. Subjects who were assigned to inebilizumab in the RCP received inebilizumab on OLP day 1 and matching placebo on day 15 to maintain blinding of sites and subjects to the RCP treatment assignment. Both groups then received inebilizumab every 6 months for the duration of the OLP.

Inebilizumab was supplied as a sterile liquid drug product (100 mg inebilizumab per vial, nominal) intended for IV infusion after dilution in normal saline. Placebo was a sterile liquid product intended for IV infusion after dilution in normal saline. Both inebilizumab and placebo were supplied as a clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles.

Premedication (from commercial supplies) with a corticosteroid (eg, methylprednisolone 100 mg IV or equivalent), an antihistamine (eg, diphenhydramine 25-50 mg orally or equivalent), and an anti-pyretic (eg, acetaminophen 500-650 mg orally or equivalent) were administered approximately 30-60 minutes prior to each IP infusion.

Vital signs were obtained prior to the start of each IP infusion. An experienced and qualified staff member placed the IV access.

Unless an infusion reaction occurred resulting in discontinuation of infusion, the entire infusion bag contents was administered and the tubing flushed with a volume of saline at least as large as that of the tubing to ensure complete delivery of the IP infused at a rate not to exceed 333 mL/hour.

After completion of the infusion, subjects were observed for at least one hour.

Medically qualified personnel were immediately available to respond to emergencies during administration of IP. Appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions had to be immediately available, and study personnel

trained to recognize and treat these reactions. Additionally, appropriate drugs and medical equipment to treat IRRs were to be immediately available, and study personnel trained to recognize and treat IRRs.

If an infusion reaction occurred, the site could stop or slow the infusion. Resumption of the infusion was at the discretion of the site. Management of infusion reactions depended on the type and severity of the reaction and was at the discretion of the Investigator. For life-threatening infusion reactions, IP was to be immediately and permanently stopped and appropriate supportive treatment administered. For less severe infusion reactions, management could involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

The requirement for prednisone (or equivalent) treatment for 3 to 8 weeks before randomization reflects the standard of care for the treatment of IgG4-RD flares. All subjects tapered prednisone to discontinuation at the end of the eighth week following randomization, in keeping with standard flare treatment practices. The introduction of inebilizumab prior to completion of the steroid taper also aligns with typical clinical practice in which steroid-sparing agents are introduced prior to or during the taper of GC flare treatment.

Concomitant and rescue therapies:

The Sponsor recommended that Investigators ensure that all patients were up to date with required vaccinations prior to entry into the study.

Prohibited Medications

Patients had to receive all treatments that were considered necessary for their health in the judgment of their physician(s). The following prohibited medications required the discontinuation of IP, but subjects who received prohibited medications remained in the study through the final Week 52 RCP visit. Generally, GC treatment for reasons other than new or worsening IgG4-RD activity was prohibited, but exceptions were described below (*Permitted Glucocorticoid Uses*). The per-protocol limitations on dose and duration of GC treatment for IgG4-RD flare were also described below (*Management of Flare of IgG4-RD During the Study*). The Investigator provided the indication for each use of GC or other immunosuppressive therapy.

Additional prohibited medications in the RCP and OLP included:

- Biologic or non-biologic immunosuppressive agents other than GCs, including but not limited to, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, leflunomide, cyclophosphamide, rituximab, etanercept, adalimumab, infliximab, certolizumab pegol, golimumab, abatacept, and tocilizumab.
- Live viral vaccines or live therapeutic infectious agents.

Permitted Glucocorticoid Uses

Aside from the required 8-week GC taper, GCs are generally only permitted in this study to treat IgG4-RD flares. However, the following were permitted GC use for indications other than IgG4-RD flare:

- Oral GC treatment for $\leq$ 2 weeks (for any purpose).
- GCs at a dose of $\leq$ 2.5 mg of prednisone or equivalent for treatment of adrenal insufficiency (mineralocorticoids are permitted) or intolerance of steroid taper (in this case, continued tapering of steroids should be performed as tolerated). GCs at any dose should not be continued for the purpose of prevention of IgG4-RD related flare.
- Inhaled, intranasal or topical corticosteroids.
- Up to 2 intra-articular steroid injections that do not exceed 40 mg methylprednisolone or equivalent per injection.

Management of Flare of IgG4-RD During the Study

Treatment of flares was at the discretion of the Investigator. Subjects would be managed in accordance with best medical practice for their condition regardless of whether protocol-defined flare criteria were met. Stenting or other procedures were permitted as medically warranted per the judgment of the Investigator. Unless treatment was urgent, in which case medically appropriate therapy would be instituted without delay, Investigators would conduct flare assessments according to the organ(s) affected prior to initiation of treatment, if possible.

Choice of flare treatment was at the discretion of the Investigator. The use of GCs at a dose exceeding 40 mg/day of prednisone or equivalent, or for a duration exceeding 8 weeks including taper to discontinuation, required discontinuation of IP. Use of any prohibited immunosuppressive treatment for flares required discontinuation of IP.

Objectives

Primary objective and primary estimand:

To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with immunoglobulin G4-related disease (IgG4-RD).

Primary Hypothesis:

By depleting CD19+ B cells, including plasmablasts and some plasma cells, inebilizumab will reduce IgG4-RD activity by preventing disease flares i.e., this is a superiority study in which inebilizumab is compared to placebo with regard to protection against flares.

Primary Endpoint

Time to disease flare, defined as the time in days from day 1 (dosing) to the date of the first treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week randomized controlled period (RCP). The date of disease flare is defined as the date of initiation of any flare treatment (new or increased glucocorticoids [GCs] treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.

Primary estimand

The estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS (Randomized adults with a diagnosis of IgG4-RD who meet the 2019 ACR/EULAR classification criteria (Wallace et al, 2019[24]; who have had recent active disease (initial diagnosis or flare))
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as date of onset of treatment (medication or procedure).
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. Subjects who do not complete the RCP and who have not had a treated and AC-determined flare during the RCP will be censored at the time of discontinuation.

[24] Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH; ACR/EULAR IgG4-RD Classification Criteria Committee. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. Ann Rheum Dis. 2019;78(3):406-412.

- Population-level summary: Hazard ratio (HR) between inebilizumab versus placebo and its associated 95% CI.

The Full Analysis Set (FAS) includes all subjects who receive any dose of IP during the RCP. Subjects will be analyzed according to the treatment assignment. The efficacy analyses will be based on the Full Analysis Set.

Secondary Objectives

Secondary Hypotheses:

1. Inebilizumab will reduce disease activity in patients with IgG4-RD as assessed by additional measures of efficacy.
2. Inebilizumab will be well-tolerated and have an acceptable safety profile in patients with IgG4-RD.

Key Secondary objective:

1. To evaluate the effect of inebilizumab on other measures of disease activity.

Key Secondary Endpoint

1. Annualized flare rate for treated and AC-determined flares during the RCP
2. The proportion of subjects achieving flare-free, treatment-free complete remission at week 52, defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no treatment for flare or IgG4-RD disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018[25]) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence
3. The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52, defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018[25]) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence.

Endpoints 1, 2, and 3 are key secondary endpoints to be considered for study-wise Type I error control.

Estimands for key secondary endpoints:

The estimand for the first key-secondary endpoint, annualized flare rate, is defined by the following:

- Target population: Subjects in the FAS
- Variable: The number of treated AC-determined IgG4-RD flares experienced during 52-week RCP
- Intercurrent event (Treatment policy strategy): No intercurrent events will be taken into account. All data captured during the 52-week RCP will be used for analysis.
- Population-level summary: Rate ratio between inebilizumab versus placebo and its associated 95% CI.

[25] Wallace ZS, Khosroshahi A, Carruthers MD, et al. An international multispecialty validation study of the IgG4-related disease responder index. Arthritis Care Res (Hoboken). 2018;70(11):1671-1678.

The estimand for the second key secondary endpoint, proportion of subjects achieving flare-free, treatment-free complete remission at week 52, is defined by the following:

- Target population: Subjects in the FAS
- Variable: Proportion of subjects achieving flare-free, treatment-free complete remission at Week 52
- Intercurrent event: Subjects who receive treatment for flare or disease control except the required 8-week GC taper will be treated as not achieving complete remission at Week 52.
- Population-level summary: Odds ratio between inebilizumab versus placebo and its associated 95% CI.

The estimand for the third key-secondary endpoint, proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, is defined by following:

- Target population: Subjects in the FAS
- Variable: Proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52
- Intercurrent event: Subjects who receive corticosteroid for flare or disease control except the required 8-week GC taper will be treated as not achieving complete remission at Week 52.
- Population-level summary: Odds ratio between inebilizumab versus placebo and its associated 95% CI.

Secondary objectives:

1. To evaluate the safety and tolerability of inebilizumab in patients with IgG4-RD
2. To evaluate the effect of inebilizumab on other measures of disease activity

Secondary Endpoints

1. Incidence of treatment-emergent adverse events, treatment-emergent serious adverse events, and treatment-emergent adverse events of special interest during the 52-week RCP and during the open-label period (OLP).
2. The incidence of antidrug antibodies (ADAs) directed against inebilizumab during the RCP.
3. Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the investigator within the RCP, regardless of AC determination of flare
4. Annualized flare rate for AC-determined IgG4-RD flares, whether or not treated, during the RCP.
5. GC use, calculated as the cumulative GC dose taken for the purpose of IgG4-RD disease control during the RCP.

Exploratory objectives

1. To characterize the PK of inebilizumab in patients with IgG4-RD
2. To characterize the primary pharmacodynamic effect of inebilizumab in patients with IgG4-RD
3. To explore the effect of inebilizumab on other measures of disease activity.
4. To assess the effect of inebilizumab on health resource utilization in patients with IgG4-RD

5. To assess the effect of inebilizumab on circulating immunoglobulins (Ig)s
6. To assess effect of inebilizumab on complement components and the ELF score
7. To evaluate the effects of inebilizumab on other disease-relevant measures, including other immune cell populations, biomarkers, and gene expression in patients with IgG4-RD
8. To assess the relationship between genetic variations, disease activity, and efficacy

Exploratory Endpoints

1. Serum concentration of inebilizumab and noncompartmental PK parameters
2. Changes from baseline in peripheral B cell counts, including total B cells and B cell subsets
3. Change from baseline to week 52 in the Physician Global Assessment of Disease Activity.
4. Changes in patient functioning and health-related quality of life, as measured by changes from baseline to week 52 in the following: SF-36v2; FACIT-fatigue; Patient Global Assessment of Disease Activity
5. Annualized flare rate for treated and AC-determined flares during the OLP
6. Number of inpatient hospitalizations, days of hospitalization, days in an intensive care unit, emergency department visits, non-study related physician visits, home-health visits (physician or nurse), disease-related imaging procedures, and disease-related procedures/surgeries (stenting, other).
7. Change from baseline in Ig levels (IgG, IgG subclasses including IgG4, IgM, IgA, IgE, and total immunoglobulins).
8. Changes from baseline in serum levels of complement components C3and C4 and the ELF score.
9. Changes from baseline in: Blood gene expression profiles: Serum biomarker expression (eg, inflammation-related cytokines/chemokines)
10. Analysis of genetic alterations associated with disease activity and response to treatment.

Outcomes/endpoints

Baseline was defined as the last non-missing valid observation before the first investigational product administration during RCP. In cases where measurements were taken on the same day as the first administration of investigational product and no time was reported, it was assumed that these measurements are taken before the first administration of investigational product.

Investigator Assessment of Flare: If a subject's symptoms, physical examination, laboratory parameters, or other clinical finding suggested the possibility that a disease flare would be occurring, the Investigator evaluated the subject, conducted any medically indicated assessments, and reviewed any relevant data collected at facilities other than the investigational site (eg. Symptoms, Physical examination findings, Laboratory results, Imaging results, and biopsy results). Assessments were per local standard of care and at the discretion of the Investigator. Flare assessments were conducted prior to the initiation of treatment for flare, if possible.

Flare Diagnosis: To promote uniformity and objectivity in the diagnosis of flare, the Investigator used the flare criteria to determine whether the event met the definition of flare for this study.

Flare Treatment: Flare treatment was at the discretion of the Investigator and nitiated after completion of assessments and flare diagnosis, if possible. Flare treatment was not dependent on protocol-specified flare criteria being met.

Flare Adjudication: An independent AC), composed of experts in the field, reviewed the data available to the Investigator or used by the Investigator for decision-making (including any available and relevant imaging reports, laboratory testing, biopsy reports, description of patient symptoms, and a narrative) and used the same study-specific definition of flare that used by the Investigator. The AC was blinded and independent, and composed of physicians with expertise in the care of patients with IgG4-RD. AC members reviewed and adjudicated cases individually but permitted to discuss cases as a committee as needed. A majority vote is required for AC decisions.

The AC, in a similar process, was also charged with determining whether sequential IgG4-RD activity events represented a single or more than one flare for the purpose of secondary efficacy endpoints. In general, for treated flares, disease manifestations present prior to flare diagnosis or treatment initiation represented a single flare. New or worsening disease activity that presented during treatment for a flare represented a separate flare. If the flare was not treated, new or worsening of IgG4-RD activity occurring prior to resolution of the presenting flare manifestations did not constitute a new flare.

IgG4-RD Responder Index: The IgG4-RD RI is a validated instrument for longitudinal assessment of IgG4-RD disease activity, developed and refined by an international team of IgG4-RD experts specifically to permit structured assessment of response to treatment by clinical investigators. The RI captures disease activity and damage in 25 domains, with higher weights for disease manifestations that require urgent treatment or that worsen despite treatment. The RI incorporates an activity score for each organ/site of disease, a score for symptomatic disease at each of these sites, and a score amendment for a need for urgent treatment. Serum IgG4 concentration and presence of organ-specific damage were collected but not part of the overall RI. Because visit-to-visit consistency is important, whenever possible, the same Investigator completed the IgG4-RD RI for the same subject across all visits.

Cumulative Glucocorticoid Use: Cumulative GC use was calculated as the total GC dose in mg of prednisone or prednisone equivalent taken for the purpose of IgG4-RD disease control during the RCP.

Physician and Patient Global Assessments of Disease Activity: The Physician Global Assessment of Disease Activity and Patient Global Assessment of Disease Activity (PGA) are scales commonly used in the assessment of rheumatologic diseases. For the physician's global assessment, Investigators indicated the patient's level of disease activity due to IgG4-RD today, from no disease activity to maximum disease activity, on a 100 mm visual analog scale (VAS).

For the PGA, the subject was asked to rate their current quality of life by making a mark on a 100 mm VAS, labeled "very poorly" to "very well", in response to these instructions: *Considering all the ways that your IgG4-related disease affects you, please rate how well you are doing today*.

Patient-reported Outcomes: PROs in this study were measured using 2 instruments: the 36-Item Short Form Survey Version 2 (Acute Recall) Questionnaire (SF-36v2) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale.

SF-36 v2: The SF-36v2 (acute recall) is a 36-item general health status assessment that captures information about 8 health domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The SF-36v2 provides scores for each domain as well as 2 psychometrically-based summary scores: physical component score and mental

component score. The recall period for the acute version is one week (ie, "last week"). The instrument can be completed in approximately 10-18 minutes.

FACIT-Fatigue Scale: The FACIT-Fatigue Scale is a 13-item subject-completed questionnaire used to assess the impact of fatigue (FACIT.org [website]). Its recall period is 7 days. The responses range from 0 (Not at all) to 4 (Very much).

Health Resource Utilization: The following health resource utilization variables were recorded by the Investigator on an eCRF: Inpatient hospitalization, Days of hospitalization, Days in an intensive care unit, Emergency department visits, Non-study-related physician visits, Home-health visits (physician or nurse), Disease-related imaging procedures, Disease-related procedures/surgeries (stenting, etc).

Randomized-Controlled Period Assessments and Procedures:

Study Period	**Randomized-Controlled Period**													
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**26**	**30**	**34**	**38**	**42**	**46**	**52 or EDV [d]**
Nominal Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**183**	**211**	**239**	**267**	**295**	**323**	**365**
Window	**--**	**± 1 Day**	**± 3 Days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**
Assessment of AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Completion of PROs (SF-36v2, FACIT-Fatigue) and PGA [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (prior to IP administration)	X							X						X
Vital Signs	X [b]	X [b]	X	X	X	X	X	X [b]	X	X	X	X	X	X
Weight	X							X						X
Full physical examination	X							X						X
Symptom-driven physical exam		X	X	X	X	X	X		X	X	X	X	X	
IgG4-RD RI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test in women capable of pregnancy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (microscopic if abnormal) and urine protein/creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety labs (chemistry, hematology, coagulation)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inebilizumab PK [c]	X	X	X	X	X			X	X		X			X
ADA	X		X		X			X			X			X
Complement levels (C3, C4)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ELF score	X							X						X
IgG4 and IgE levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SPEP	X													X
Total Ig, IgA, IgM, IgG, and IgG subclasses	X				X			X			X			X
Whole blood for B cell flow cytometry	X	X	X	X	X		X	X		X	X		X	X
Exploratory biomarkers (plasma and serum; plasma sample not obtained in China)	X	X	X	X	X		X	X		X	X		X	X
RNA PAXgene tube (for gene expression; not obtained in China)	X	X	X	X	X		X	X		X	X		X	X
DNA PAXgene (optional, with consent; not obtained in China)	X													
Verify eligibility	X													
Randomization	X													
IP administration [e]	X	X						X						
Provide oral GCs	X													

Assess GC compliance		X	X	X										

AE = adverse event; ADA = anti-drug antibodies; AESI = adverse event of special interest; ECG = electrocardiogram; EDV = early discontinuation visit; ELF = enhanced liver fibrosis score; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; GC = glucocorticoid; Ig = immunoglobulin(s); IgG4-RD RI = IgG4-RD Responder Index; IP = investigational product; PGA = patient global assessment; PK = pharmacokinetic; PRO = patient-reported outcome; SAE = serious adverse event; SF-36v2 = 36-Item Short Form Survey Version 2 (Acute Recall) Questionnaire; SPEP = serum protein electrophoresis; V = visit.

Note: On days of IP administration, all procedures and blood sampling, except for post-dose PK, must be collected before IP administration.

A) Subjects should complete all PRO assessments prior to other procedures. B) Vital signs obtained as per Section 7.1.1.5. C) On infusion IP dosing days, inebilizumab PK serum samples are to be collected predose and approximately 15 minutes (± 5 minutes) after completion of the infusion. On nondosing days, only 1 PK serum sample is required. D) Subjects who have indicated their intent to withdraw consent during the RCP should be asked to complete an EDV visit. E) Premedication will be administered approximately 30-60 minutes prior to each IP infusion (see Section 7.1.1.4). If IP administration at Visit 9 (Day 183) is unavoidably delayed, for example due to COVID travel restrictions, the dosing visit may be delayed upon discussion and agreement with the Sponsor.

Adjustment of the timing of the subsequent OLP IP doses will be discussed on a case-by-case with the Sponsor. If a subject discontinues IP during the RCP, they should complete all RCP visits. If they do not subsequently enter the OLP, they should then enter the SFUP.

Table 16 Open-Label Period Assessments and Procedures:

Study Period	**Open-Label Period**												
OLP Visit Number	**OLP V1**	**OLP V2**	**OLP V3, V4**	**OLP V5**	**OLP V6, V7**	**OLP V8**	**OLP V9, V10**	**OLP V11**	**OLP V12, V13**	**OLP V14**	**OLP V15, 17, 19, 21**	**OLP V16, 18, 20,**	**OLP V22/EDV**
OLP Week(s)	**0**	**2**	**4, 8**	**12**	**16, 20**	**26**	**30, 34**	**38**	**42, 46**	**52**	**61, 87, 113, 139**	**78, 104, 130**	**156**
Window	**1-38 days after last RCP visit**	**± 2 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**± 10 days**	**Phone contact ±10 days [b]**	**±10 days**	**Phone contact ±10 days [b]**	**+10 days**	**Phone contact ±20 days [b]**	**±20 days**	**±20 days**
Assessment of AEs/SAEs/AESIs	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment of Disease Activity	X	X		X		X		X		X		X	X
Vital signs	X [d]	X [d]		X		X [d]		X		X [d]		X [d]	X
Physical exam													X
Symptom-driven physical exam	X	X		X		X		X		X		X	
IgG4-RD RI	X	X		X		X		X		X		X	X
Urine pregnancy test in women capable of pregnancy [e]	X	X		X		X		X		X		X	X
Safety labs [f]	X	X		X		X		X		X		X	X
ELF score	X					X				X		X	X
Urinalysis [g]	X	X		X		X		X		X		X	X
ADA	X	X		X		X		X		X		X	X
IgG4 and IgE	X	X		X		X		X		X		X	X
Total immunoglobulins, IgA, IgM, IgG, and IgG subclasses	X					X				X		X	X
B cell flow cytometry panel	X			X		X		X		X		X	X
RNA PAXgene tube (for gene expression; not obtained in China)	X			X		X		X		X		X	X
Assessment of eligibility for OLP	X												
IP administration [h]	X	X				X				X		X	

AE = adverse event; ADA = anti-drug antibodies; AESI = adverse event of special interest; EDV = early discontinuation visit; ELF = enhanced liver fibrosis score; Ig = immunoglobulin; IgG4-RD RI = IgG4-RD Responder Index; IP = investigational product, OLP = open-label period; RCP = randomized-controlled period; SAE = serious adverse event; SPEP = serum protein electrophoresis; V = visit. Note: All procedures and blood sampling must be collected before IP administration on days when IP is administered.

A) Subjects who have received immunosuppressive therapy other than glucocorticoid treatments must have a washout period of at least 28 days prior to Dose 1 of inebilizumab in the OLP. B) Monthly telephone calls in months without in-person visits. If, during the telephone contact, a safety event or possible flare that requires further follow-up is identified, the subject should be evaluated in the clinic as an unscheduled visit. C) AEs and SAEs occurring after completion of the RCP must be collected at OLP Visit one. D) Vital signs obtained. E) Perform on days of dosing; confirm negative prior to dose. F) Safety labs include chemistry, hematology, and coagulation; SPEP will not be performed during the OLP. G) Microscopic if abnormal. H) Premedication will be administered approximately 30-60 minutes prior to each IP infusion. If a subject discontinues IP during the OLP, they should enter the SFUP.

Sample size

A total of 39 flares were required to detect a relative reduction of 65% in risk for time from Day 1 (dosing) to onset of flare during the RCP with at least 90% power, two-sided α = 0.05, and a 1:1 randomization ratio based on log-rank test for comparison. Assuming the probability of having a treated and AC-determined IgG4-RD flare during the RCP in the placebo group is 0.35 (Yunyun et al, 2017[26]; Yunyun et al, 2019[27]; Wang et al, 2018[28]), a total of 160 subjects (80 subjects per treatment group) were expected to be randomized and dosed.

The hypothesized 65% reduction in risk was an estimate based on the observed treatment effect for attack reduction with inebilizumab in the phase 3 NMOSD trial (77% reduction in risk), and limited published clinical data on the efficacy of the B cell-depleting agent rituximab in IgG4-RD.

A total of 135 subjects (68 inebilizumab group, 67 placebo group) were randomized into the study.

Randomisation

Subjects were randomized 1:1 to receive either intravenous (IV) inebilizumab 300 mg or placebo on day 1, day 15, and week 26 of the 52-week RCP.

An interactive voice/web response system was used for randomisation to a treatment group and assignment of IP kit numbers. A subject was considered randomized into the study when the Investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group. Treatment assignment was stratified by first or subsequent IgG4-RD manifestation (ie, newly diagnosed vs recurrent)

Blinding (masking)

Blinding

This was a double-blind study in which inebilizumab and placebo were matched in appearance. The Sponsor remained blinded until after the database lock for primary efficacy analysis, which occured after all subjects had completed the Day 365 visit (Visit 15) or discontinued early from the RCP. Subjects, site staff, and contract research organization (CRO) personnel remained blinded to individual subject treatment assignment until final database lock at the conclusion of the study. Potentially unblinding laboratory data will not be available to investigative site personnel until after final database lock.

[26] Yunyun, F., Yu, C., Panpan, Z., Hua, C., Di, W., Lidan, Z., ... & Wen, Z. (2017). Efficacy of cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. *Scientific reports*, *7*(1), 6195.
[27] Yunyun, F., Yu, P., Panpan, Z., Xia, Z., Linyi, P., Jiaxin, Z., ... & Wen, Z. (2019). Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: a randomized clinical trial. *Rheumatology*, *58*(1), 52-60.
[28] Wang, L., Zhang, P., Wang, M., Feng, R., Lai, Y., Peng, L., ... & Zhang, W. (2018). Failure of remission induction by glucocorticoids alone or in combination with immunosuppressive agents in IgG4-related disease: a prospective study of 215 patients. *Arthritis research & therapy*, *20*, 1-12.

If treatment allocation for a subject became known to the Investigator or other study staff involved in the management of study subjects, the Sponsor had to be notified immediately.

Unblinding

In the event of a medical emergency, the Investigator could unblind an individual subject's IP allocation. Unblinding should only occur if management of the medical emergency would be different based on the subject having received IP. In the majority of cases, the management of a medical emergency would be the same whether or not IP was received by the subject. If this was the case, the IP allocation should not be unblinded.

Statistical methods

Analysis sets

Full Analysis Set (FAS)

The FAS included all subjects who receive any dose of IP during the RCP. Subjects are analyzed according to the treatment assignment. The efficacy analyses are based on the FAS.

Safety Analysis Set (Randomized-controlled Period)

The Safety Analysis Set includes all subjects who received any dose of IP during the RCP, and is used for safety, PD, and ADA analyses. For the analyses in the RCP, subjects are analyzed according to the treatment that they actually received. Specifically, subjects randomized to the inebilizumab group who received all placebo dose are included in the placebo group; conversely, subjects randomized to the placebo group who received at least one dose of inebilizumab are included in the inebilizumab group.

Open-label Analysis Set

The Open-Label Analysis Set includes all subjects who received any dose of inebilizumab during the OLP.

Main analysis methods for primary and (key) secondary endpoints

Primary endpoint:

For the primary efficacy endpoint, the hazard ratio (HR) and its associated 95% CI between inebilizumab versus placebo were estimated using the Cox proportional hazards model with the treatment indicator (inebilizumab or placebo) and the stratification factor as the explanatory variables. Subjects who discontinued prematurely from the RCP and had not had a treated and AC-determined flare were censored at the discontinuation date. Subjects who completed the RCP but had not had a treated and AC-determined flare during the RCP were censored at the end of the RCP.

Key Secondary Efficacy Analyses

"Annualized Flare Rate for Treated and AC-determined IgG4-RD Flares": The number of treated and AC-determined flares during the RCP were compared between the inebilizumab group and the placebo group using a negative binomial model. The model included covariates of treatment group (inebilizumab or placebo) and stratification factor. The logarithm of the subject's corresponding follow-up time was used as an offset variable in the model to adjust for subjects having different exposure times during which the events occurred.

"Flare-free, Treatment-free Complete Remission at Week 52 and Flare-free Corticosteroid-free Complete Remission at Week 52": The proportion of subjects achieving flare-free treatment-free complete remission at week 52 and the proportion of subjects achieving flare-free corticosteroid-free

complete remission at week 52 were analyzed using a logistic regression model. The response variable in the model was whether a subject achieved the corresponding flare-free treatment-free or corticosteroid-free complete remission at week 52. The model had treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables. The results of the analyses were presented using odds ratios, together with associated 95% CI and two-sided p-value, for inebilizumab versus placebo. For both analyses, subjects who did not complete the RCP or were missing IgG4-RD disease activity assessment at week 52 were treated as not achieving complete remission at week 52.

(Important) Secondary endpoints:

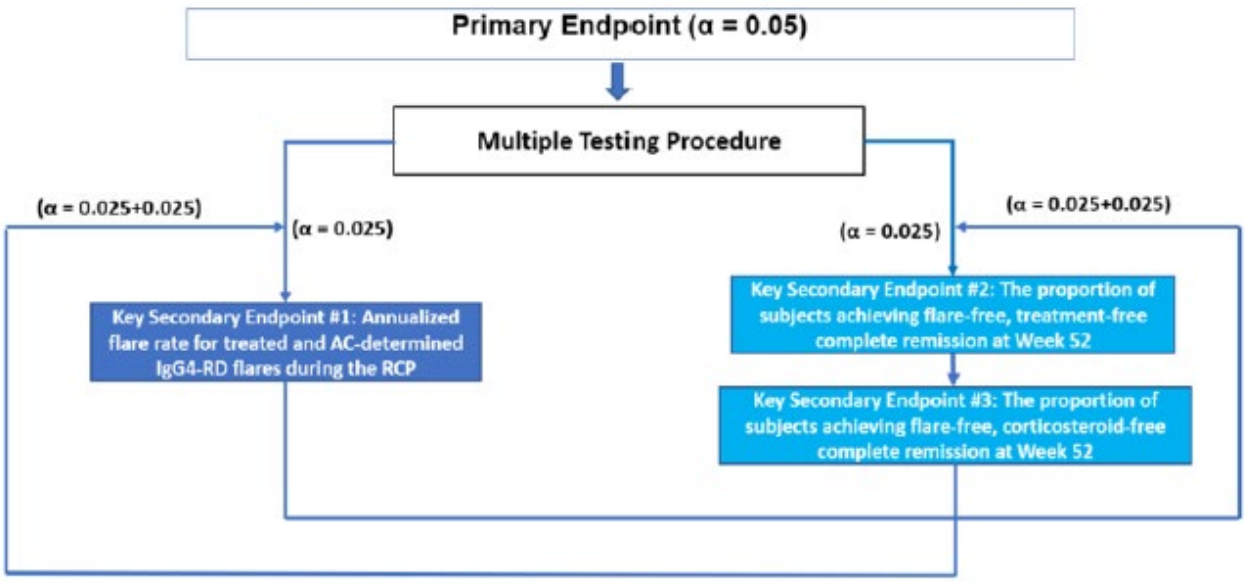
"Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the investigator within the RCP, regardless of AC determination of flare": Statistically treated as primary endpoint.

"Annualized flare rate for AC-determined IgG4-RD flares, whether or not treated, during the RCP": Statistically treated as first key secondary endpoint.

Multiplicity adjustment

Null hypotheses for the key secondary endpoint #1 and #2 were tested in parallel with alpha=0.025. The key secondary endpoint #2 and #3 were tested sequentially: if the null hypotheses was rejected for the key secondary endpoint #2, the null hypothesis for the key secondary endpoint #3 was tested with alpha=0.025. If the null hypothesis for the key secondary endpoint #1 was rejected, the alpha was recycled to test the key secondary endpoint #2 and #3 sequentially. On the other hand, if both the null hypotheses for the key secondary endpoint #2 and #3 were rejected, the alpha was recycled to test the null hypothesis for the key secondary endpoint #1 (Figure 12).

Figure 12 Multiple Testing Procedure for Key Secondary Endpoints



AC = Adjudication Committee, IgG4-RD = immunoglobulin G4-related disease, RCP=randomized controlled period.

Sensitivity analyses:

Support of primary analysis:

To assess the robustness towards violations of the assumption of non-informative censoring of subjects who did not complete the RCP, the following sensitivity analysis was to be performed (analysis set, variable and summary measure were like primary analysis):

Intercurrent event:

- All data captured during the 52-week RCP were used for analysis. Subjects who did not complete the RCP due to IgG4-RD related death or due to subject perception of lack of efficacy and who had not had a treated and AC-determined flare were considered as having a flare with onset at the time of discontinuation / withdrawal from the RCP. Subjects who did not complete the RCP due to other reasons and who have not had a treated and AC-determined flare were censored at the time of discontinuation / withdrawal from RCP.

Additional Analysis on the Primary Efficacy Endpoint:

Intercurrent events:

- Subjects who did not complete the RCP and who had not had a treated and AC-determined flare were be censored at the time of discontinuation.
- Subjects, who 1) received any treatment for IgG4-RD, including GC or immunosuppressive treatment (other than GC tapered in accordance with the protocol-specified schedule during the first 8 weeks of the RCP) and/or 2) received any prohibited GC or immunosuppressive treatment prior to experiencing a treated and AC-determined flare, were censored at the time when relevant treatment was first received.

The robustness towards violations of the assumption of non-informative censoring on subjects who did not complete the RCP and / or subjects who received prohibited GC or immunosuppressive treatment prior to experiencing a treated and AC-determined flare were assessed with the following sensitivity analysis (analysis set, variable and summary measure are like primary endpoint):

Intercurrent events:

- Subjects who did not complete the RCP due to IgG4-RD related death or due to subject perception of lack of efficacy and who have not had a treated and AC-determined flare were considered as having a flare at the time of discontinuation / withdrawal from RCP. Subjects who did not complete the RCP due to other reasons and who have not had a treated and AC-determined flare were censored at the time of discontinuation / withdrawal from RCP.
- Subjects who received the treatment for IgG4-RD, including GC or immunosuppressive treatment (other than GC tapered in accordance with the protocol-specified schedule during the first 8 weeks of the RCP) related to IgG4-RD prior to experiencing a treated and AC-determined flare were considered as having a flare at the time of treatment.
- Subjects who received any prohibited GC or immunosuppressive treatment not related to IgG4-RD prior to experiencing a treated and AC-determined flare were censored at the time when those treatment were first received.

Furthermore, an immortal time bias analysis was performed with following variable and treatment of intercurrent events:

- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset was defined as earliest date of subject reported new/worsening symptoms, new/worsening physical exam findings, new/worsening laboratory findings, new/worsening findings imaging, or other findings as data collected on flare assessment page.

- All data captured during the 52-week RCP were used for analysis. Subjects who did not complete the RCP and who had not had a treated and AC-determined flare during the RCP were censored at the time of discontinuation.

Planned subgroup analyses

Consistency of treatment effect measured by primary and 3 key secondary endpoints in the following subgroups was investigated:

- Age (< 65 vs 65)
- Sex (male vs female)
- Region (US vs non-US; EU vs non-EU; and Asia vs non-Asia)
- Serum IgG4 concentrations at baseline
- Enhanced liver fibrosis (ELF) score at baseline
- Racial/ethnic subgroups as needed for national/regional regulatory filings
- First or subsequent IgG4-RD manifestation (i.e., newly diagnosed vs. recurrent)
- Anti-drug antibody (ADA) status at any time during RCP including baseline (positive vs. negative) if data allows

Results

Participant flow

Subject disposition for this study is provided in Table 17.

Table 17 Subject Disposition with Discontinuation Reason (All Enrolled Subjects)

	Placebo n (%)	Inebilizumab n (%)	Total n (%)
Subjects screened			227
Screen failures			92
Adverse Event			1
Failure To Meet Randomization Criteria			75
Physician Decision			4
Protocol Deviation			3
Withdrawal By Subject			4
Other			5
Subjects randomized	67	68	135
Subjects randomized, not treated	0	0	0
Subjects randomized and treated	67 (100%)	68 (100%)	135 (100%)
Subjects who completed the RCP	63 (94.0%)	64 (94.1%)	127 (94.1%)
Subjects who did not complete the RCP	4 (6.0%)	4 (5.9%)	8 (5.9%)
Adverse Event	0	2 (2.9%)	2 (1.5%)
Lost To Follow-Up	1 (1.5%)	0	1 (0.7%)
Withdrawal By Subject	1 (1.5%)	1 (1.5%)	2 (1.5%)
Event			
Other	2 (3.0%)	1 (1.5%)	3 (2.2%)
Subjects who completed the RCP treatment	52 (77.6%)	58 (85.3%)	110 (81.5%)
Subjects who discontinued RCP treatment	15 (22.4%)	10 (14.7%)	25 (18.5%)
Subjects who discontinued RCP treatment but completed the RCP	11 (16.4%)	6 (8.8%)	17 (12.6%)
Adverse Event	0	2 (2.9%)	2 (1.5%)
Covid-19 Pandemic	1 (1.5%)	0	1 (0.7%)
Protocol Violation: Ineligible Subject	0	1 (1.5%)	1 (0.7%)
Protocol Violation: Receipt Of Prohibited Medications	6 (9.0%)	2 (2.9%)	8 (5.9%)
Other	4 (6.0%)	1 (1.5%)	5 (3.7%)
Subjects who discontinued RCP treatment but did not complete the RCP	4 (6.0%)	4 (5.9%)	8 (5.9%)
Adverse Event	1 (1.5%)	3 (4.4%)	4 (3.0%)
Discontinuation Of Dosing By Subject	2 (3.0%)	0	2 (1.5%)
Protocol Violation: Receipt Of Prohibited Medications	1 (1.5%)	0	1 (0.7%)
Other	0	1 (1.5%)	1 (0.7%)
Subjects who completed the RCP and rolled over to OLP[a]	49 (73.1%)	53 (77.9%)	102 (75.6%)
Subjects who completed the RCP but did not roll over to OLP	12 (17.9%)	7 (10.3%)	19 (14.1%)
Not Eligible: Did Not Complete 28 day Washout	2 (3.0%)	0	2 (1.5%)
Not Eligible: investigational product Discontinued For Safety	3 (4.5%)	2 (2.9%)	5 (3.7%)
Not Eligible: Not Able To Receive Dose 1	1 (1.5%)	1 (1.5%)	2 (1.5%)
Subject Decision	2 (3.0%)	3 (4.4%)	5 (3.7%)
Other	4 (6.0%)	1 (1.5%)	5 (3.7%)
Subjects who completed the OLP	0	0	0
Subjects who did not complete the OLP	3 (6.1%)	5 (9.4%)	8 (7.8%)
Adverse Event	1 (2.0%)	4 (7.5%)	5 (4.9%)
Lost To Follow-Up	0	1 (1.9%)	1 (1.0%)
Other	2 (4.1%)	0	2 (2.0%)
Subjects who completed OLP treatment	0	0	0
Subjects who discontinued OLP treatment	5 (10.2%)	6 (11.3%)	11 (10.8%)
Adverse Event	3 (6.1%)	5 (9.4%)	8 (7.8%)
Discontinuation Of Dosing By Subject	2 (3.2%)	0	2 (1.6%)
Noncompliance With Study Procedures	0	1 (1.9%)	1 (1.0%)
Enrolled into Safety Follow-up	17 (34.7%)	13 (24.5%)	30 (29.4%)

COVID-19 = coronavirus disease 2019; OLP = open-label period; RCP = randomized controlled period. First subject enrolled: 7 December 2020; Database snapshot: 09 April 2024 for the RCP, 09 February 2024 for the OLP. a) Subjects who did not complete 'Continuing to OLP' page by primary analysis data cutoff date are not included.

Recruitment

04 December 2020 (first subject enrolled) to 09 April 2024 for the randomized controlled period (RCP) and 09 February 2024 for the open-label period (OLP) (data cutoff date; the study is ongoing)

The analyses presented are based on a database cutoff date of 09 April 2024 for the completed randomized controlled period and 09 February 2024 for the ongoing open-label period, and a snapshot date of 29 May 2024.

Conduct of the study

The study began in December 2020 and was ongoing at time of submission of this variation. The study was conducted during the coronavirus disease 2019 (COVID-19) pandemic. The study was at the stage of recruitment of the RCP when the pandemic occurred. Contingency measures were implemented to manage study conduct during the COVID-19 pandemic.

These measures included allowing remote subject visits, allowing screening laboratory assessments to be performed locally, and that RCP Visit 9 (day 183, a dosing visit) could have been delayed in certain circumstances, with prior approval of the sponsor.

All changes in the conduct of the study were implemented by protocol amendment(s):

Table 18 Protocol Amendment Summary Table - main major changes

Amendment	Major Changes
Amendment 7 6 August 2021	Updated text regarding sample size to "approximately 160 subjects will be randomized and dosed". Updated text to allow for remote visits in exceptional circumstances (due to COVID-19 restrictions or other reasons). Added that "Total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks before randomization". Added that "One organ must meet the requirements for the ACR/EULAR classification criteria (inclusion #4); the second organ is as defined by the Investigator". Updated text for inclusion #8 to "A condom with spermicide (where spermicide is available)". Amended exclusion #5 to delete requirement to have B cell counts ≥lower limit of normal (LLN) in subjects who received a B cell-depleting agent in the period 6 - 12 months before screening. Exclusion 19 excludes subjects with CD19+ B cells at screen <40 cells/L; an exclusionary value may be repeated. Updated prothrombin time exclusion criteria ☐ 1.2 x upper limit of normal (ULN) and added that subjects who are anticoagulated due to atrial fibrillation and who have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ☐ 2 x ULN are not excluded. Subjects are excluded for total immunoglobulins <600 mg/dL. Added IgG, IgM, IgA, and total immunoglobulins to screening tests. Updated exclusion #21 to clarify that subjects are excluded for known positive anti-neutrophil cytoplasmic antibodies (ANCA) targeted against proteinase 3 or myeloperoxidase based on patient records. Deleted ANCA from laboratory tests obtained at screening and deleted other references to ANCA testing.

	Added IgG4 levels and B cell testing to tests that do not have to be completed for rescreening. Updated Rescreening and Procedures to "Subjects will not be replaced". Updated the Schedule of OLP Assessments and Procedures. Modified OLP eligibility criterion #2 to state that subjects "must not have had investigational product discontinued for any of the following reasons" and to exclude subjects who received any B cell-depleting therapy in the 6 months before enrollment in the OLP. Updated text to specify that in certain instances, safety laboratory tests may be run in a licensed local laboratory with approval of the sponsor even where the exclusion criterion specifies use of the central laboratory. Instances of use of local laboratory with approval of the sponsor will not be considered protocol deviations. Added text "Subjects who discontinue investigational product duringthe RCP may be eligible to enroll in the OLP, if they meet criteria outlined in Section 6.2.3.1". Changed manufacturer legal entity name. Added an alternate placebo manufacturer. Updated text regarding use of GCs to "GCs at a dose of ≤ 2.5 mg of prednisone or equivalent for treatment of adrenal insufficiency (mineralocorticoids are permitted) or intolerance of steroid taper (in this case, continued tapering of steroids should be performed as tolerated). Glucocorticoids at any dose should not be continued for the purpose of prevention of IgG4-RD related flare". Updated the Serious Adverse Event definition to include "A hospitalization for elective or pre-planned treatment of a preexisting condition thatdid not worsen from baseline will not be considered an SAE". Updated the Severity or Intensity definition to include "The determination of severity for eventsnot listed in the Common Terminology Criteria for Adverse Events (CTCAE) should be made by the Investigator based upon medical judgment and the severity categories of grade 1 to grade 5 as defined here, with the maximum severity recorded". IgG4-RD Flare Evaluation and Criteria document added to protocol.
Amendment 8 30 June 2022	Lengthened OLP from 365 days to 1095 days; follow-up for 730 days after investigational product discontinuation; total maximum duration now is equal to 2273 days. Added criterion allowing for patients with thyroid-cancer for which surgery has been performed and there is no evidence of active disease for Criterion 4. Added language that Visit 9 (D183, a dosing visit) may be delayed in certain circumstances, with prior approval of sponsor, and added instructions for subjects who discontinue investigational product during the RCP. Removed language allowing participants who received prohibited B cell-depleting therapy during the RCP to participate in the OLP, with some conditions.

	Extended SFUP to 2 years(from 90 days) after investigational product discontinuation. Added language that permits, in exceptional circumstances, the use of local laboratory results for screening purposes with prior approval by the sponsor. Extended follow-up after investigational product discontinuation for certain labs and safety events. Removed completion of OLP as the time point for study completion and specified that the studywill end when the last subject has completed all protocol-specified visits. Added text that AESIs must be reported within 24 hours of awareness regardless of seriousness or relationship to investigational product.
Amendment 9 15 June 2023	Updated name and address of sponsor, as Viela Bio, Inc. was acquired by Horizon Therapeutics. Updated definition of flare-free complete remission to include either a Responder Index score of 0, or determination by the investigator that there is no active disease, at the week 52 visit. For the secondary endpoint "The proportion of subjects achieving flare-free complete remission at week 52," added the phrase "treatment-free". Added a new key secondary endpoint, The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52. Changed the analyses for the flare-free complete remission related endpoints. Redesignated a key secondary endpoint (time to treatment for new or worsening disease activity by the investigator regardless of AC determination of flare) as a non-key secondary. A new secondary (flare-free, corticosteroidfree complete remission) was made a key secondary endpoint in its place.
Amendment 9 15 June 2023	For the secondary endpoint "The proportion of subjects achieving flare-free complete remission at week 52," added the phrase "treatment-free." Added a new key secondary endpoint, "The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52". Changed the analyses for the flare-free complete remission related endpoints. Redesignated a key secondary endpoint (time to treatment for new or worsening disease activity by the investigator regardless of AC determination of flare) as a non-key secondary. A new secondary (flare-free, corticosteroidfree complete remission) was made a key secondary endpoint in its place.

Protocol Deviations

Critical and major protocol deviations are summarized in for the RCP in Table 19.

13 (9.6%) critical deviations were timing deviations related to SAEs, AESIs and pregnancy not being reported within 24 hours of awareness by the study center as required by the protocol. Of these 13 critical deviations, 12 were AESI reporting deviations and 1 was a SAE reporting deviation. All subjects

continued in the study. Sites were retrained according to the protocol deviation plan and no under-reporting of SAEs occurred.

The most common major protocol deviations in the RCP were related to informed consent (17 [12.6%]), study procedures (15 [11.1%]), and glucocorticoid tapering regimen (13 [9.6%]).

Informed consent deviations included subjects who did not sign the informed consent prior to study assessments being performed, and subjects who did not sign a revised informed consent at the next study visit. In such cases, all subjects signed the informed consent at the next available visit and sites were retrained according to protocol deviation plan.

Study procedure deviations were related to the infusion premedication regimen (IV steroid, antihistamine, and antipyretic) not being administered, or the dose of IV steroid administered being lower than that specified in protocol. In all such cases, subjects continued in the study and sites were retrained according to protocol deviation plan.

Each deviation related to the protocol-specified 8-week GC taper regimen (eg, missed dose, particular dose level continued too long, etc) was captured as a minor deviation. These minor deviations were then assessed in aggregate per subject. If the cumulative dose of GC received varied by more than 20% from the nominal cumulative dose of 700 mg prednisone, a major deviation was recorded. Likewise, if the total duration of GC treatment during the tapering period varied by more than 20% from the nominal 56 days, a major deviation was recorded.

A total of 13 (14.4%) subjects experienced 1 or more critical or major protocol deviations in the OLP. The most common critical or major protocol deviations across both groups in the OLP were AESI/SAE reporting (7 [10.3%]), study procedures (6 [8.8%]) and major protocol deviations from tapering regimen (6 [8.8%]).

Table 19 Summary of Critical or Major Protocol Deviations in the Randomized-controlled Period

	Placebo (N = 67) n (%)	Inebilizumab (N = 68) n (%)	Total (N = 135) n (%)
Subjects with any critical and/or major protocol deviation	24 (35.8%)	20 (29.4%)	44 (32.6%)
Subjects with critical protocol deviations	6 (9.0%)	7 (10.3%)	13 (9.6%)
SAE reporting[b]	6 (9.0%)	7 (10.3%)	13 (9.6%)
Subjects with major protocol deviations	22 (32.8%)	16 (23.5%)	38 (28.1%)
Entry criteria not met	0	4 (5.9%)	4 (3.0%)
Excluded medication received	2 (3.0%)	3 (4.4%)	5 (3.7%)
Informed consent	12 (17.9%)	5 (7.4%)	17 (12.6%)
Investigational product	3 (4.5%)	2 (2.9%)	5 (3.7%)
Not withdrawn but developed withdrawal criteria	3 (4.5%)	2 (2.9%)	5 (3.7%)
Study procedures	9 (13.4%)	6 (8.8%)	15 (11.1%)
Subjects with major protocol deviation[a] from tapering regimen	7 (10.4%)	6 (8.8%)	13 (9.6%)

AESI = adverse events of special interest; N = number of subjects that were enrolled; SAE = serious adverse event. a) The total dose or duration for steroid tapering is more than 20% deviation from the protocol-specified tapering regimen. b) SAE reporting deviations include SAE, AESI and pregnancy reporting deviations.

Baseline data

Subject demographics and baseline disease characteristics are provided in Table 20 and baseline flare summary in Table 21.

Table 20 Demographics and baseline Demographics, full analysis set

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Age (year)			
Mean	58.2	58.2	58.2
SD	12.2	11.5	11.8
Median	58.0	59.5	59.0
(Min, Max)	(32, 80)	(24, 80)	(24, 80)
Age category			
< 65	46 (68.7%)	47 (69.1%)	93 (68.9%)
≥ 65	21 (31.3%)	21 (30.9%)	42 (31.1%)
Sex			
Female	18 (26.9%)	29 (42.6%)	47 (34.8%)
Male	49 (73.1%)	39 (57.4%)	88 (65.2%)
Race			
American Indian or Alaska Native	0 (0.0%)	2 (2.9%)	2 (1.5%)
Asian	25 (37.3%)	38 (55.9%)	63 (46.7%)
Black or African American	1 (1.5%)	0 (0.0%)	1 (0.7%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (1.5%)	1 (0.7%)
White	32 (47.8%)	21 (30.9%)	53 (39.3%)
Other	2 (3.0%)	2 (2.9%)	4 (3.0%)
Multiple Categories Checked	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	1 (1.5%)	0 (0.0%)	1 (0.7%)
Not Reported	6 (9.0%)	4 (5.9%)	10 (7.4%)
Ethnicity			
Hispanic or Latino	8 (11.9%)	8 (11.8%)	16 (11.9%)
Not Hispanic or Latino	53 (79.1%)	56 (82.4%)	109 (80.7%)
Not Reported	6 (9.0%)	4 (5.9%)	10 (7.4%)
Region			
US	14 (20.9%)	7 (10.3%)	21 (15.6%)

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Non-US	53 (79.1%)	61 (89.7%)	114 (84.4%)
EU	26 (38.8%)	20 (29.4%)	46 (34.1%)
Non-EU	41 (61.2%)	48 (70.6%)	89 (65.9%)
Asia	18 (26.9%)	34 (50.0%)	52 (38.5%)
Non-Asia	49 (73.1%)	34 (50.0%)	83 (61.5%)
Japan	7 (10.4%)	20 (29.4%)	27 (20.0%)
Non-Japan	60 (89.6%)	48 (70.6%)	108 (80.0%)
IgG4-RD manifestation			
Newly diagnosed	31 (46.3%)	31 (45.6%)	62 (45.9%)
Recurrent	36 (53.7%)	37 (54.4%)	73 (54.1%)
Disease duration (years)			
Mean	2.54	2.64	2.59
SD	3.06	3.73	3.40
Median	0.90	0.80	0.90
(Min, Max)	(0.1, 12.5)	(0.1, 20.5)	(0.1, 20.5)
	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Number of organs ever affected by IgG4-RD			
2	7 (10.4%)	15 (22.1%)	22 (16.3%)
3	15 (22.4%)	12 (17.6%)	27 (20.0%)
4	19 (28.4%)	12 (17.6%)	31 (23.0%)
5	9 (13.4%)	10 (14.7%)	19 (14.1%)
6	8 (11.9%)	10 (14.7%)	18 (13.3%)
7	1 (1.5%)	4 (5.9%)	5 (3.7%)
8	2 (3.0%)	4 (5.9%)	6 (4.4%)
9	1 (1.5%)	0 (0.0%)	1 (0.7%)
10	2 (3.0%)	0 (0.0%)	2 (1.5%)
11	2 (3.0%)	1 (1.5%)	3 (2.2%)
13	1 (1.5%)	0 (0.0)	1 (0.7%)
Prior non-glucocorticoid therapy for IgG4-RD			

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Yes	20 (29.9%)	17 (25.0%)	37 (27.4%)
No	47 (70.1%)	51 (75.0%)	98 (72.6%)

BMI = body mass index; EU = European Union; IgG4-RD = immunoglobulin G4-related disease; US = United States. Each race category counts subjects who selected only that category. 'Multiple Categories Checked' counts subjects who selected more than 1 race category. a Race and ethnicity data was not collected in France per French regulation

ACR/EULAR Classification Criteria mean (SD) score was overall 39.2 (11.9) (placebo group: 38.3 (11.7); inebilizumab group: 40.1 (12.1)).

Mean (SD) baseline IgG4-RD Responder Index score was overall 5.7 (4.0) (placebo group: 6.0 (4.0); inebilizumab group: 5.4 (4.0))

The sponsor was not aware of any published data clearly demonstrating geographic differences in IgG4-RD disease phenotype or outcomes. Cohorts from the US and China, for example, were remarkably similar with respect to key disease characteristics such as age, sex, and organ distributions (Jha et al, 2024[29]; Wang et al, 2019[30]). A systematic review reported some differences by region (Brito-Zerón et al, 2016[31]), but these findings were likely confounded by several biases, including the fact that many cohorts were reported by researchers from a single medical specialty and/or at a single center, and therefore the pool of participants is unlikely to be representative of the disease as a whole. The existence of international consensus treatment guidelines that lack region- or race-specific recommendations provided strong support for the uniformity of treatment and treatment responses around the world (Khosroshahi et al, 2015[32]). Further characterization of the disease through multi-specialty, international research efforts were needed to fully understand whether disease phenotypes or outcomes differ by region, but at present this seemed to not be the case. In fact, the major features of the disease – late onset, male preponderance, multiorgan involvement, patterns of organ involvement, responsiveness to steroids, tendency to relapse, and even the underlying pathophysiology – were all remarkably similar around the world.

In Study MITIGATE, the baseline demographics and disease characteristics were generally similar between the US and non-US subjects. A higher proportion of US subjects had obesity or were overweight and had recurrent IgG4-RD compared with non-US subjects.

Table 21 Baseline Flare Summary Study MITIGATE Full Analysis Set

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Number of organs affected by baseline flare			
N	67	68	135
1	5 (7.5%)	4 (5.9%)	9 (6.7%)
2	21 (31.3%)	23 (33.8%)	44 (32.6%)

[29] Jha, I., McMahon, G. A., Perugino, C. A., Katz, G., Wallace, Z. S., Fernandes, A., ... & Stone, J. H. (2024). Sex as a predictor of clinical phenotype and determinant of immune response in IgG4-related disease: a retrospective study of patients fulfilling the American College of Rheumatology–European League Against Rheumatism classification criteria. *The Lancet Rheumatology*, *6*(7), e460-e468.
[30] Wang, L., Zhang, P., Zhang, X., Lin, W., Tang, H., Li, J., ... & Zhang, W. (2019). Sex disparities in clinical characteristics and prognosis of immunoglobulin G4–related disease: a prospective study of 403 patients. *Rheumatology*, *58*(5), 820-830.
[31] Brito-Zerón, P., Kostov, B., Bosch, X., Acar-Denizli, N., Ramos-Casals, M., & Stone, J. H. (2016). Therapeutic approach to IgG4-related disease: a systematic review. *Medicine*, *95*(26), e4002.
[32] Khosroshahi, A., Wallace, Z. S., Crowe, J. L., Akamizu, T., Azumi, A., Carruthers, M. N., ... & Stone, J. H. (2015). International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis & rheumatology*, *67*(7), 1688-1699.

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
3	17 (25.4%)	16 (23.5%)	33 (24.4%)
4	13 (19.4%)	6 (8.8%)	19 (14.1%)
5	2 (3.0%)	10 (14.7%)	12 (8.9%)
6	6 (9.0%)	4 (5.9%)	10 (7.4%)
7	2 (3.0%)	3 (4.4%)	5 (3.7%)
8	1 (1.5%)	1 (1.5%)	2 (1.5%)
11	0	1 (1.5%)	1 (0.7%)
List of organs affected by baseline flare			
N	67	68	135
Abdominal aorta	3 (4.5%)	5 (7.4%)	8 (5.9%)
Bile ducts	15 (22.4%)	13 (19.1%)	28 (20.7%)
Extra-ocular muscle	5 (7.5%)	5 (7.4%)	10 (7.4%)
Kidney	19 (28.4%)	21 (30.9%)	40 (29.6%)
Lacrimal Glands	18 (26.9%)	27 (39.7%)	45 (33.3%)
Liver	3 (4.5%)	2 (2.9%)	5 (3.7%)
Lungs	15 (22.4%)	10 (14.7%)	25 (18.5%)
Lymph Node(s)	26 (38.8%)	26 (38.2%)	52 (38.5%)
Mastoid sinus or middle ear	2 (3.0%)	1 (1.5%)	3 (2.2%)
Mesentery (sclerosing mesenteritis)	1 (1.5%)	1 (1.5%)	2 (1.5%)
Nasal cavity	7 (10.4%)	5 (7.4%)	12 (8.9%)
Orbital mass (not including pituitary gland)	8 (11.9%)	5 (7.4%)	13 (9.6%)
Pancreas	24 (35.8%)	27 (39.7%)	51 (37.8%)
Parotid glands	10 (14.9%)	17 (25.0%)	27 (20.0%)
Pericardium	0	1 (1.5%)	1 (0.7%)
Pituitary Gland	0	1 (1.5%)	1 (0.7%)
Pleura	4 (6.0%)	2 (2.9%)	6 (4.4%)
Retroperitoneum	7 (10.4%)	7 (10.3%)	14 (10.4%)
Sinus	12 (17.9%)	12 (17.6%)	24 (17.8%)
Skin	2 (3.0%)	1 (1.5%)	3 (2.2%)
Sublingual glands	3 (4.5%)	4 (5.9%)	7 (5.2%)
Submandibular glands	20 (29.9%)	31 (45.6%)	51 (37.8%)
Thoracic Aorta	1 (1.5%)	0	1 (0.7%)
Thyroid	0	2 (2.9%)	2 (1.5%)
Other Organs	13 (19.4%)	10 (14.7%)	23 (17.0%)

IgG4-RD = immunoglobulin G4-related.

Numbers analysed

Of the 227 subjects screened for eligibility, 92 subjects were considered screen failures. In total, 135 subjects (68 inebilizumab group, 67 placebo group) were randomized at 46 participating sites in 16 countries. A total of 127 subjects (64 inebilizumab group, 63 placebo group) completed the 52-week RCP, and 102 of these subjects (53 inebilizumab group, 49 placebo group) rolled over to the OLP. Of the 4 subjects in the inebilizumab group who did not complete the RCP, 2 discontinued due to AEs and 2 subjects withdrew consent.

Among the 135 subjects randomized and treated in the RCP, 102 subjects entered the OLP, including 53 subjects from the inebilizumab group and 49 from the placebo group. The reasons for discontinuation from the OLP were AE (8 subjects and 2 subjects withdrew consent). No subjects have completed the study since the study is still ongoing.

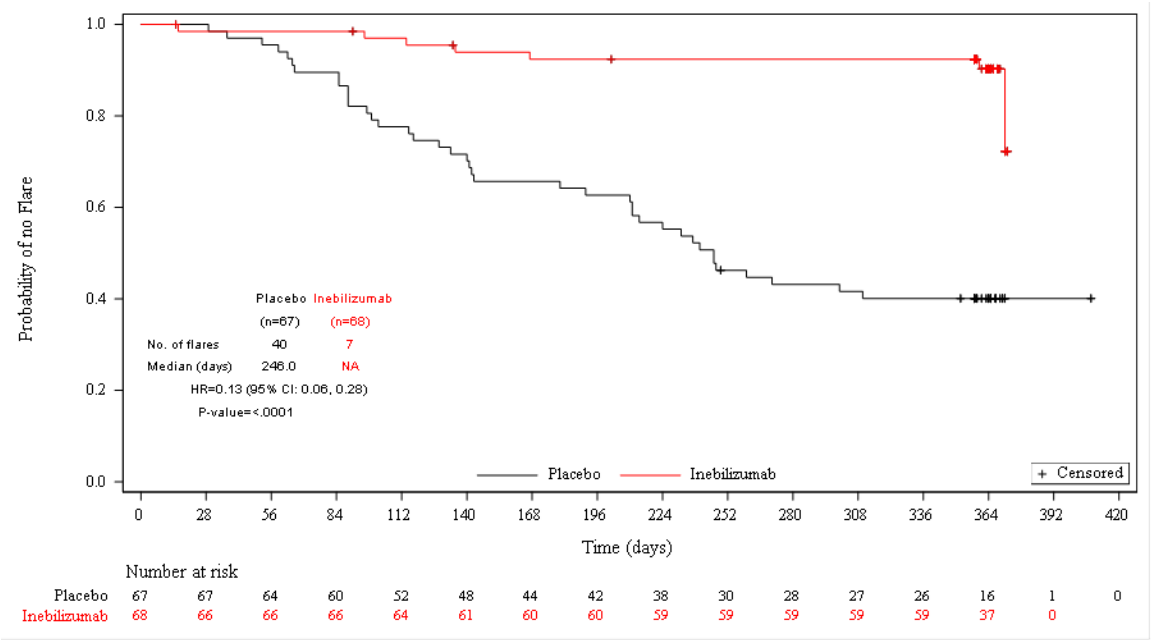
In total, 46 subjects in the inebilizumab group and 44 subjects in the placebo group received any dose of inebilizumab during the OLP and were included in the Open-label Analysis Set. The mean (SD) duration of exposure for the Open-label Analysis Set was 320.9 (173.7) days for the inebilizumab/inebilizumab group and 325.5 (161.7) days for the placebo/inebilizumab group. A total of 14 subjects were exposed to inebilizumab for more than 2 years.

Outcomes and estimation

Primary Efficacy Endpoint

Inebilizumab statistically significantly reduced the risk of treated and AC-determined IgG4-RD flare during the RCP compared with placebo (HR 0.13 [95% CI: 0.06, 0.28; p < 0.0001]) and demonstrated a significantly longer time to first treated and AC-determined IgG4-RD flare. The median time to flare was 246 days in the placebo group and could not be estimated in the inebilizumab group due to the low flare rate in this treatment group (Figure 13). A total of 7 subjects (10.3%) in the inebilizumab group and 40 subjects (59.7%) in the placebo group had at least 1 treated and AC-determined IgG4-RD flare during the RCP.

Figure 13 Kaplan Meier Plot: Time to First Treated and AC-determined IgG4-RD Flare During Randomized-controlled Period, Full Analysis Set



AC = Adjudication Committee; HR = hazard ratio; IgG4-RD = immunoglobulin G4-related disease; NA = not applicable; No = Number; RCP = randomized-controlled period. Subjects who do not complete the RCP and who have not had a treated and AC-determined flare during the RCP were be censored at the time of discontinuation.

Table 22 provides a full accounting of all flares that occurred in the study, including those that were untreated by the investigator, those that were negatively adjudicated by the AC, and those that were both untreated and negatively adjudicated.

Table 22 Summary of Flares: Treated- and untreated by investigator

	Placebo	Inebilizumab	Total
Flares evaluated by investigator	73	12	85
Duplicate flares[a]	8	0	8
Unique flares evaluated by investigator	65	12	77
Investigator treated flares	55	7	62
Treated and positively-adjudicated flares	49	7	56
First treated and positively-adjudicated flares[b]	40	7	47
Treated and negatively-adjudicated flares	6	0	6
Investigator untreated flares	10	5	15
Untreated and positively-adjudicated flares	3	4	7
Untreated and negatively-adjudicated flares	7	1	8

[a] Flares deemed by the AC to represent the same event as a prior flare. See Section 8.2.5.
[b] Flares that contributed to the primary efficacy endpoint

Additional Analyses of the Primary Endpoint

The results of 4 additional analyses of time to first treated and AC-determined IgG4-RD flare were consistent with the results of the primary analysis.
Inebilizumab reduced the risk of treated and AC-determined IgG4-RD flare during the RCP compared with placebo for the following analyses (all achieving an HR 0.13 and nominal $p < 0.0001$):

- Time to first treated and AC-determined IgG4-RD flare, with IgG4-RD-related death and early withdrawal due to patient perception of lack of efficacy included as flares.
- Time to first treated and AC-determined IgG4-RD flare, censoring subjects with any treatment for IgG4-RD or any prohibited treatment prior to having a flare.
- Time to first treated and AC-determined IgG4-RD flare, with IgG4-RD related death, early withdrawal due to patient perception of lack of efficacy, and any IgG4-RD-related treatment included as flares.
- Time to first treated and AC-determined IgG4-RD flare when flare onset date was defined as the earliest date of symptoms/findings.

Onset of Efficacy for the Primary Endpoint

The Kaplan Meier plot for time to first treated and AC-determined IgG4-RD flare presented in Figure 13 shows clear separation between the inebilizumab and placebo groups starting at approximately 56 days (8 weeks).
Ad hoc analyses were carried out to determine the earliest timepoint at which the benefit of inebilizumab versus placebo became significant. The results of these analysis showed that the HR for time to first treated and AC-determined IgG4-RD flare during the RCP became significant starting from study day 91 (week 13; nominal $p = 0.0143$). The difference in the proportion of subjects experiencing at least 1 treated and AC-determined IgG4-RD flare became significant between the 2 treatment groups starting from day 70 (week 10) of the RCP (nominal $p = 0.0278$). Thus, the data show that the treatment effect of inebilizumab on decreased flare risk is evident as early as 10 to 13 weeks after treatment initiation.

During the procedure, upon the CHMP's request, the MAH provided further analysis of organs affected by IgG4-RD in Study MITIGATE participants:

Table 23 On-Study Primary Endpoint-related Flare Summary Study MITIGATE Full Analysis Set

	Placebo (N = 67)	Inebilizumab (N = 68)	Total (N = 135)
Number of organs affected by primary-endpoint related flare			
N	40	5[a]	45
1	16 (40.0%)	2 (40.0%)	18 (40.0%)
2	14 (35.0%)	2 (40.0%)	16 (35.6%)
3	4 (10.0%)	1 (20.0%)	5 (11.1%)
4	3 (7.5%)	0	3 (6.7%)
5	3 (7.5%)	0	3 (6.7%)
List of organs affected by primary-endpoint related flare			
N	40	5[a]	45
Aorta and large blood vessels	2 (5.0%)	0	2 (4.4%)
Biliary tree (IgG4-RD sclerosing cholangitis)	12 (30.0%)	1 (20.0%)	13 (28.9%)
Kidney	5 (12.5%)	0	5 (11.1%)
Lacrimal glands	9 (22.5%)	1 (20.0%)	10 (22.2%)
Lungs, including pleura and parenchyma	6 (15.0%)	0	6 (13.3%)
Lymph node(s)	10 (25.0%)	0	10 (22.2%)
Orbits	6 (15.0%)	3 (60.0%)	9 (20.0%)
Pancreas and common bile duct	11 (27.5%)	1 (20.0%)	12 (26.7%)
Salivary glands	11 (27.5%)	2 (40.0%)	13 (28.9%)
Skin	2 (5.0%)	0	2 (4.4%)
Other sclerosis/mass formation	9 (22.5%)	1 (20.0%)	10 (22.2%)

The analysis is based on organs deemed by the investigators to meet flare criteria.
[a] For 2 primary endpoint-related flares, investigator did not indicate which organs were involved.

Table 24 Primary Analysis of Time to the First Treated and AC-determined IgG4-RD Flare by Most Common Baseline Organs (Randomized-controlled Period) (Full Analysis Set)

Subgroup	Placebo N = 67	Inebilizumab N = 68
The most common baseline organ (³ 20% in overall) - Bile ducts		
Number of participants with an IgG4-RD flare	12 (80.0%)	0
Number of censored participants	3 (20.0%)	13 (100%)
Hazard ratio[b]		0.00
95% CI[b]		(0.00, NA)
Nominal P-value[b]		NA
The most common baseline organ (³ 20% in overall) - Kidney		
Number of participants with an IgG4-RD flare	12 (63.2%)	2 (9.5%)
Number of censored participants	7 (36.8%)	19 (90.5%)
Hazard ratio[b]		0.08

Subgroup	Placebo N = 67	Inebilizumab N = 68
95% CI[b]		(0.02, 0.36)
Nominal P-value[b]		0.0012
The most common baseline organ (³ 20% in overall) - Lacrimal Glands		
Number of participants with an IgG4-RD flare	10 (55.6%)	2 (7.4%)
Number of censored participants	8 (44.4%)	25 (92.6%)
Hazard ratio[b]		0.10
95% CI[b]		(0.02, 0.47)
Nominal P-value[b]		0.0035
The most common baseline organ (³ 20% in overall) - Lymph Node(s)		
Number of participants with an IgG4-RD flare	18 (69.2%)	3 (11.5%)
Number of censored participants	8 (30.8%)	23 (88.5%)
Hazard ratio[b]		0.13
95% CI[b]		(0.04, 0.44)
Nominal P-value[b]		0.0011
The most common baseline organ (³ 20% in overall) - Pancreas		
Number of participants with an IgG4-RD flare	17 (70.8%)	1 (3.7%)
Number of censored participants	7 (29.2%)	26 (96.3%)
Hazard ratio[b]		0.03
95% CI[b]		(0.00, 0.21)
Nominal P-value[b]		0.0005

Subgroup	Placebo N = 67	Inebilizumab N = 68
The most common baseline organ (³ 20% in overall) - Parotid glands		
Number of participants with an IgG4-RD flare	6 (60.0%)	2 (11.8%)
Number of censored participants	4 (40.0%)	15 (88.2%)
Hazard ratio[b]		0.16
95% CI[b]		(0.03, 0.79)
Nominal P-value[b]		0.0244
The most common baseline organ (³ 20% in overall) - Submandibular glands		
Number of participants with an IgG4-RD flare	9 (45.0%)	3 (9.7%)
Number of censored participants	11 (55.0%)	28 (90.3%)
Hazard ratio[b]		0.17
95% CI[b]		(0.05, 0.63)
Nominal P-value[b]		0.0078

AC = Adjudication Committee; IgG4-RD = immunoglobulin G4-related disease; NA = not applicable.
[a] Based on Kaplan-Meier method.
[b] Based on Cox regression method, with Placebo as the reference group

Secondary Efficacy Endpoints

After multiplicity adjustment, 3 key secondary endpoints met statistical significance (Table 25).

Table 25 Overview of the Key Secondary Efficacy Endpoint Results Randomized-controlled Period, Full Analysis Set

	Placebo N = 67	Inebilizumab N = 68
Annualized Flare Rate[a]	0.71	0.10
95% CI of annualized flare rate[a]	(0.53, 0.94)	(0.05, 0.21)
Rate ratio[a]		0.14
95% CI of rate ratio[a]		(0.06, 0.31)
p-value[a]		<0.0001
Proportion of Subjects Achieving Flare-Free, Treatment-free Complete Remission at Week 52		
Flare-free, treatment-free, complete remission at week 52[b]	15 (22.4%)	39 (57.4%)
Odds ratio[c]		4.68
95% CI of odds ratio[c]		(2.21, 9.91)
p-value[c]		<0.0001

	Placebo N = 67	Inebilizumab N = 68
Proportion of Subjects Achieving Flare-Free, Corticosteroid-free Complete Remission at Week 52		
Flare-free, corticosteroid-free, complete remission at week 52[d]	15 (22.4%)	40 (58.8%)
Odds ratio[c]		4.96
95% CI of odds ratio[c]		(2.34, 10.52)
p-value[c]		<0.0001

AC = Adjudication Committee; GC = glucocorticoid; IgG4-RD = immunoglobulin G4-related disease; RCP = randomized-controlled period
[a] Based on negative binomial model with covariates of treatment group and stratification factors.
[b] Defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper. Subjects who did not complete the RCP or missed the IgG4-RD disease activity assessment at week 52 were treated as not achieving complete remission at week 52.
[c] Based on logistic regression model with covariates of treatment group and stratification factors.
[d] Defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Subjects who did not complete the RCP or missed the IgG4-RD disease activity assessment at week 52 were treated as not achieving complete remission at week 52.

Other efficacy endpoints:

Time to Initiation of First Treatment for New or Worsening Disease Activity, Regardless of AC Determination of Flare Efficacy

Table 26 Time To Initiation Of First Treatment For New or Worsening Disease Activity Within The RCP, Regardless Of AC Determination Of Flare (Randomized-Controlled Period) Full Analysis Set

	Placebo N = 67	Inebilizumab N = 68
Number of subjects with an IgG4-RD flare	42 (62.7%)	7 (10.3%)
Number of censored subjects	25 (37.3%)	61 (89.7%)
Median time to flare[a]	237.0	NA
95% CI[a]	(143.0, 310.0)	(371.0, NA)
Hazard ratio[b]		0.12
95% CI[b]		(0.05, 0.26)
P-value[b]		<.0001

Annualized Flare Rate for AC-determined Flares, Whether or Not Treated

Table 27 Annualized Flare Rate For AC-Determined IgG4-RD Flares, Whether Or Not Treated (Randomized-Controlled Period) Full Analysis Set

	Placebo N = 67	Inebilizumab N = 68
Number of AC-determined IgG4-RD flares		
n	41	9
Mean	1.3	1.2
SD	0.5	0.4
Median	1.0	1.0
(Q1, Q3)	(1.0, 1.0)	(1.0, 1.0)
(Min, Max)	(1, 3)	(1, 2)
Annualized flare rate per subject		
n	67	68
Mean	0.79	0.15
SD	0.76	0.41
Median	0.94	0.00
(Q1, Q3)	(0.00, 1.01)	(0.00, 0.00)
(Min, Max)	(0.0, 2.8)	(0.0, 2.0)
Annualized flare rate[a]	0.75	0.16
95% CI of annualized flare rate[a]	(0.57, 0.99)	(0.09, 0.29)
Rate difference[a]		-0.60
95% CI of rate difference[a]		(-0.82, -0.37)
Rate ratio[a]		0.21
95% CI of rate ratio[a]		(0.11, 0.40)
p-value[a]		<.0001

Glucocorticoid Use

Table 28 Glucocorticoid Use For IgG4-RD Flare or Maintenance (Randomized-Controlled Period) Full Analysis Set

	Placebo N=67	Inebilizumab N=68
Total Glucocorticoid use[a] (mg) per subject		
n	67	68
Mean	1384.53	118.25
SD	1723.26	438.97
Median	1040.00	0.00
(Q1, Q3)	(0.00, 1995.00)	(0.00, 0.00)
(Min, Max)	(0.0, 9125.0)	(0.0, 2490.0)
LSMEAN (SE)	1396.18 (152.70)	132.03 (151.66)
LSMEAN difference (SE)		-1264.16 (214.86)
95% CI		(-1689.16, -839.15)
P-value		<.0001
Daily Glucocorticoid use[a] (mg) per subject		
n	67	68
Mean	3.740	0.344
SD	4.408	1.200
Median	3.020	0.000
(Q1, Q3)	(0.000, 6.070)	(0.000, 0.000)
(Min, Max)	(0.00, 21.17)	(0.00, 6.82)
LSMEAN (SE)	3.76 (0.39)	0.37 (0.39)
LSMEAN difference (SE)		-3.39 (0.55)
95% CI		(-4.49, -2.30)
P-value		<.0001

The mean (SD) daily GC use during the RCP per patient using GC was 3.34 (2.09) mg prednisone equivalent in the inebilizumab group versus 5.97 (4.20) mg prednisone equivalent in the placebo group. The mean (SD) total GC use during the RCP per patient using GC was 1148.71 (877.92) mg prednisone equivalent in the inebilizumab group versus 2208.65 (1707.56) mg prednisone equivalent in the placebo group.

Exploratory Endpoints

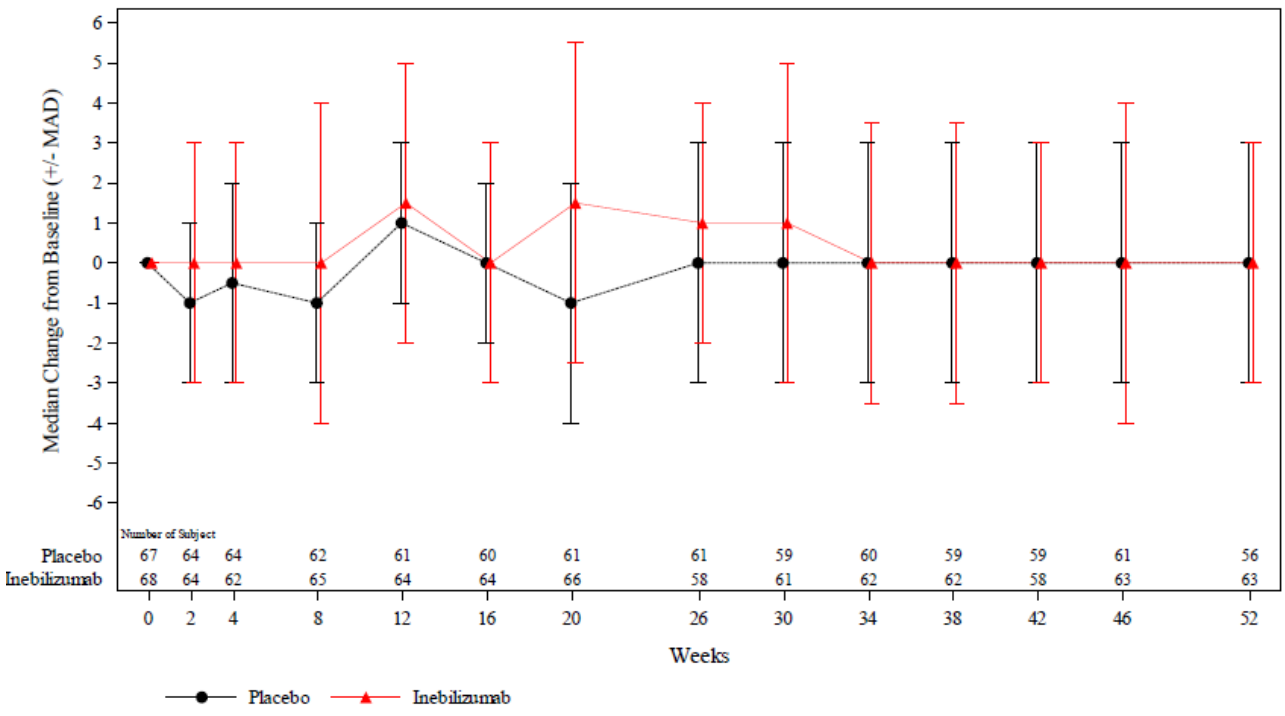
SF-36v2 Change from Baseline

Table 29 Change From Baseline In SF-36v2 By Visit (Randomized-Controlled Period) Full Analysis Set

	Placebo N=67	Inebilizumab N=68
Physical Functioning Norm-Based Score		
Week 52		
n	58	63
Mean	50.479	51.383
SD	8.181	6.814
Median	53.740	53.740
(Q1, Q3)	(47.950, 57.590)	(46.020, 57.590)
(Min, Max)	(28.67, 57.59)	(36.38, 57.59)
Change from baseline		
n	58	63
Mean	-0.819	0.148
SD	7.218	7.020
Median	0.000	0.000
(Q1, Q3)	(-3.850, 3.850)	(-3.850, 1.920)
(Min, Max)	(-28.92, 15.43)	(-11.57, 21.38)

FACIT-Fatigue Median Values (RCT, FAS)

Figure 14 Median Values For Change From Baseline In FACIT-Fatigue Over Time During Randomized-Controlled Period Full Analysis Set



Physician and Patient Global Assessment Median Change From Baseline (RCT, FAS)

Figure 15 Median Values For Change From Baseline In Physician's Global Assessment Of Disease Activity Over Time Full Analysis Set

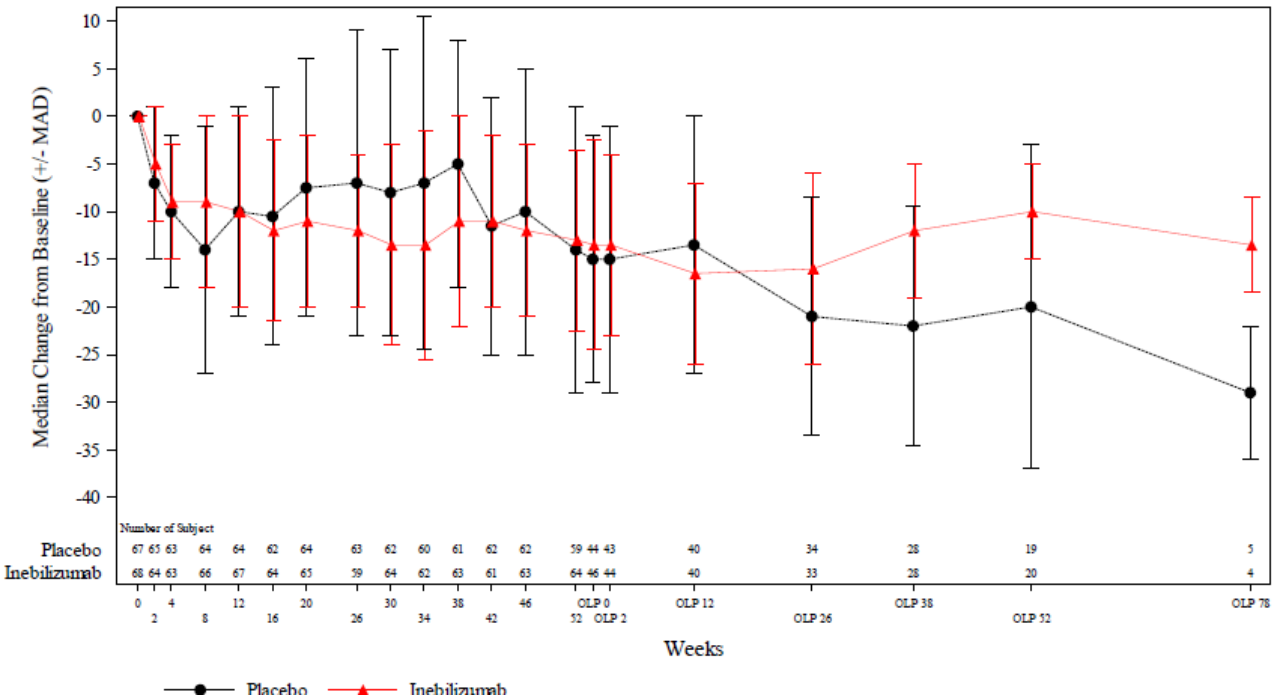


Figure 16 Median Values For Change From Baseline In Patient Global Assessment Of Disease Activity Over Time During Randomized-Controlled Period Full Analysis Set

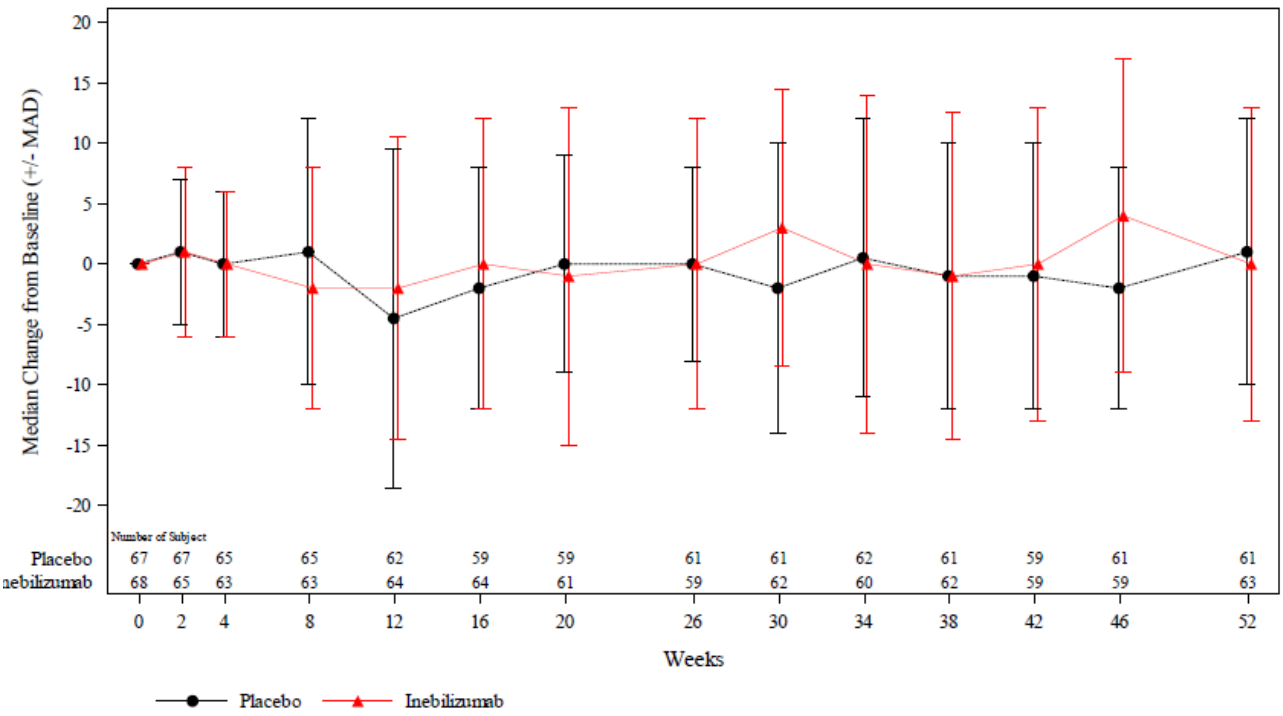


Table 30 Change From Baseline In Physician's Global Assessment Of Disease Activity At Week 52 Using Mixed Effect Model Repeated Measures (Randomized-Controlled Period) Full Analysis Set

	Placebo N=67	Inebilizumab N=68
n	59	64
LSMEAN (SE)	-16.5 (2.17)	-19.5 (2.13)
LSMEAN difference		-3.1
95% CI		(-9.1, 2.9)
P-value		0.3124

Table 31 Change From Baseline In Patient Global Assessment Of Disease Activity At Week 52 Using Mixed Effect Model Repeated Measures (Randomized-Controlled Period) Full Analysis Set

	Placebo N=67	Inebilizumab N=68
n	61	63
LSMEAN (SE)	-1.4 (2.34)	1.8 (2.33)
LSMEAN difference		3.1
95% CI		(-3.4, 9.7)
P-value		0.3423

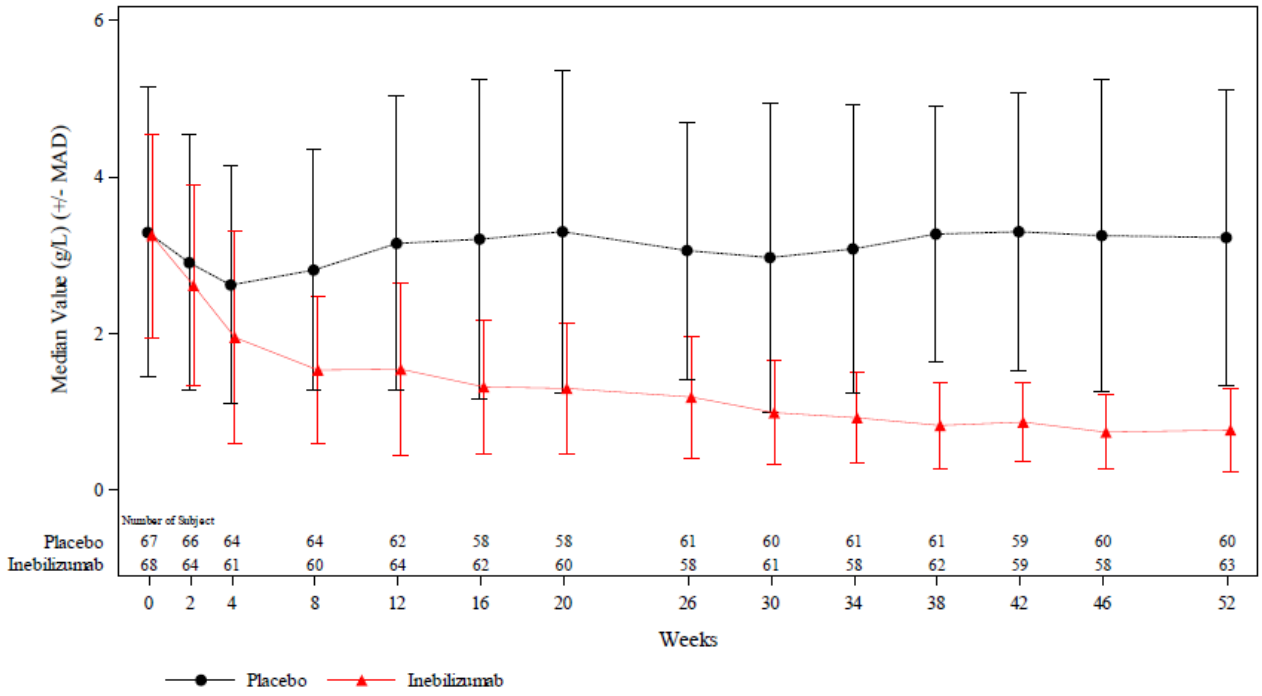
Inpatient Hospitalisations

Table 32 Healthcare Resource Utilization (Randomized-Controlled Period) Full Analysis Set

	Placebo N=67	Inebilizumab N=68
Total number of inpatient hospitalization		
n	8	4
Mean	1.1	1.8
SD	0.4	1.0
Median	1.0	1.5
(Q1, Q3)	(1.0, 1.0)	(1.0, 2.5)
(Min, Max)	(1, 2)	(1, 3)
Annualized hospitalization rate per subject		
n	8	4
Mean	1.15	1.70
SD	0.40	0.98
Median	1.00	1.45
(Q1, Q3)	(0.90, 1.25)	(0.95, 2.45)
(Min, Max)	(0.9, 2.0)	(0.9, 3.0)
Annualized hospitalization rate[a]	1.15	1.63
95% CI of annualized hospitalization rate[a]	(0.59, 2.25)	(0.73, 3.63)
Rate ratio[a]		1.41
95% CI of rate ratio[a]		(0.47, 4.21)
p-value[a]		0.5359

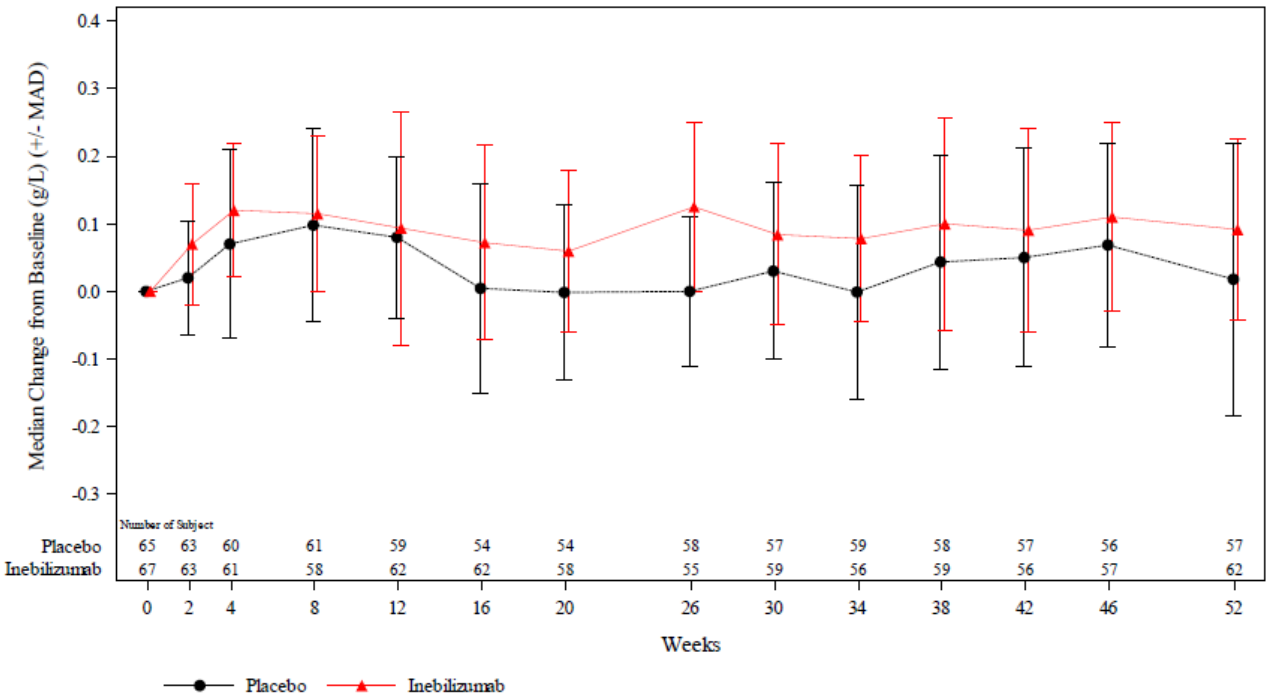
Immunoglobulin G4 Median Values (RCT, FAS)

Figure 17 Median Values For Immunoglobin G4 (g/L) Over Time During Randomized-Controlled Period Full Analysis Set



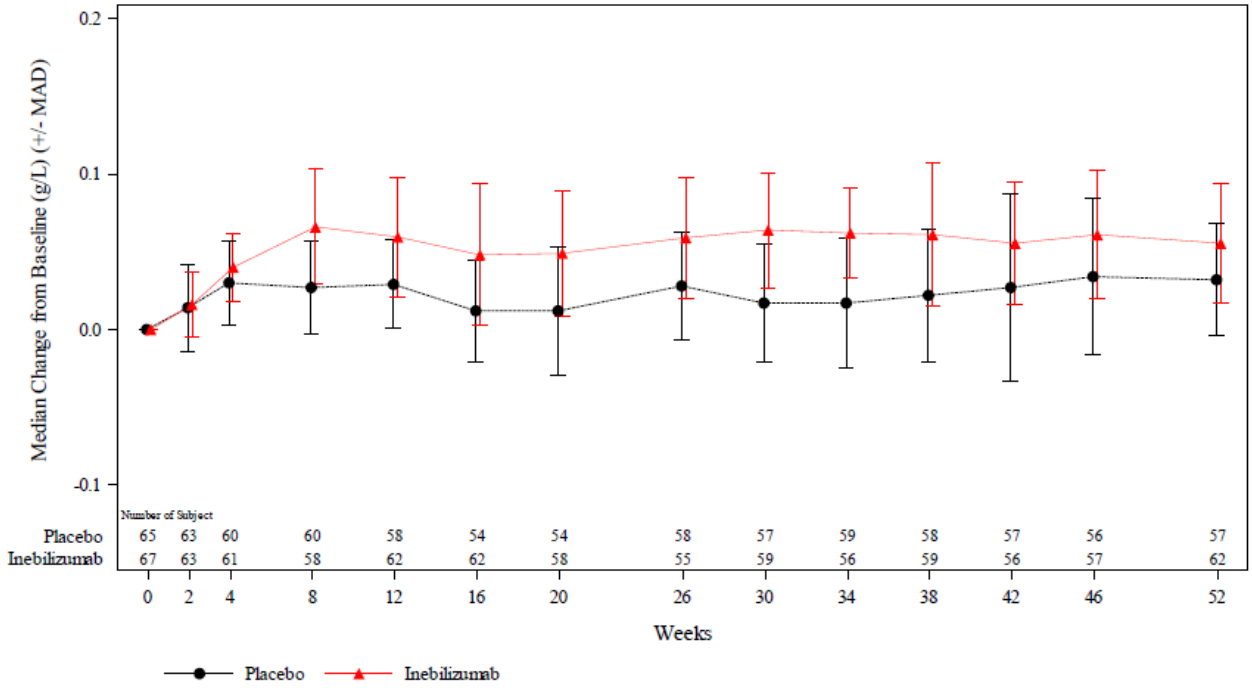
Complement Component C3 Median Change from Baseline

Figure 18 Median Values For Change From Baseline In C3 (g/L) Over Time During Randomized-Controlled Period Full Analysis Set



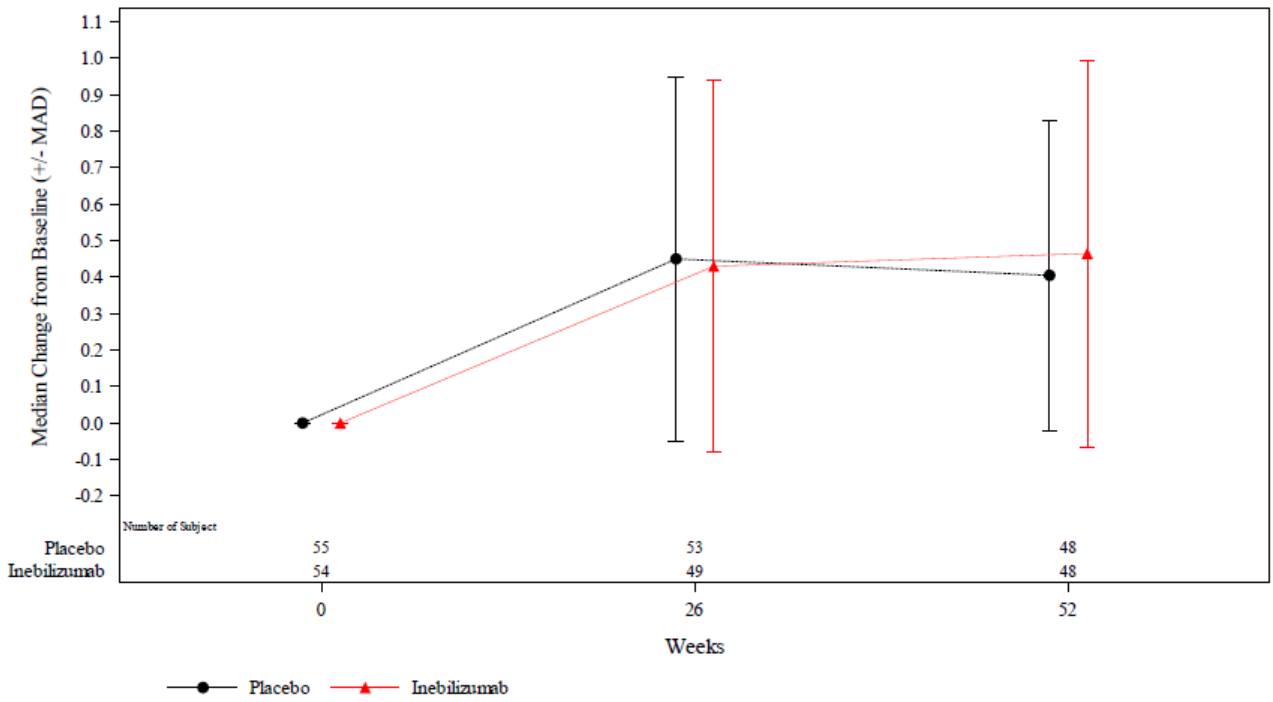
Complement Component C4 Median Change from Baseline

Figure 19 Median Values For Change From Baseline In C4 (g/L) Over Time During Randomized-Controlled Period Full Analysis Set



Enhanced liver fibrosis Median Change from Baseline

Figure 20 Median Values For Change From Baseline In ELF Over Time During Randomized-Controlled Period Full Analysis Set



Ancillary analyses

Additional Analyses of Efficacy from the Open-label Period (OLP)

During the OLP, lower annualized flare rates were observed for both treatment groups. As of the cut-off date for the OLP (09 February 2024), no new treated and AC-determined flares had occurred in the inebilizumab/inebilizumab group during the OLP and 3 had occurred in the placebo/inebilizumab group. The annualized flare rate (95% CI) was 0.00 in the inebilizumab/inebilizumab group and 0.07 (0.02, 0.24) in the placebo/inebilizumab group, which is lower than the annualized flare rate for the placebo group in the RCP.

As of the cut-off date for the OLP, 23 subjects in the inebilizumab/inebilizumab had completed the OLP week 52 visit or discontinued before the visit. Of these, 13 subjects (56.5%) had achieved flare-free, treatment-free complete remission at OLP week 52. Thirteen subjects (56.5%) in the inebilizumab/inebilizumab group had also achieved flare-free, corticosteroid-free complete remission at OLP week 52. These remission rates are similar to those observed in the inebilizumab group at week 52 of the RCP (57.4% for flare-free, treatment-free complete remission and 58.8% for flare-free, corticosteroid-free complete remission.

The proportion of subjects achieving flare-free treatment-free Complete Remission by OLP Week 52 is provided in Table 33.

Table 33 Proportion Of Subjects Achieving Flare-Free Treatment-free Complete Remission by OLP Week 52 (Open-Label Period) Open-Label Analysis Set

	Placebo/ Inebilizumab N=44	Inebilizumab/ Inebilizumab N=46
Number of subjects complete the visit or discontinued before the visit	21	23
The Proportion Of Subjects Achieving Flare-Free Treatment-free Complete Remission	7 (33.3%)	13 (56.5%)
The Proportion Of Subjects Achieving Flare-Free Corticosteroid-free Complete Remission	7 (33.3%)	13 (56.5%)

The proportion of subjects maintaining flare-free Complete Remission by OLP Week 52 is provided in Table 33.

Table 34 Proportion Of Subjects Maintained Flare-Free Complete Remission by OLP Week 52 (Open-Label Period) Open-Label Analysis Set

	Placebo/ Inebilizumab N=44	Inebilizumab/ Inebilizumab N=46
Number of subjects complete the visit or discontinued before OLP WK52 and achieved Flare-Free Treatment-free Complete Remission at RCP WK52	5	11
The Proportion Of Subjects Maintained Flare-Free Treatment-free Complete Remission at OLP WK52	3 (60.0%)	11 (100.0%)
Number of subjects complete the visit or discontinued before OLP WK52 and achieved Flare-Free Corticosteroid-free Complete Remission at RCP WK52	5	11
The Proportion Of Subjects Maintained Flare-Free Corticosteroid-free Complete Remission at OLP WK52	3 (60.0%)	11 (100.0%)

During the OLP, the mean (SD) total GC use for IgG4-RD disease control per subject was 5.33 (36.12) mg prednisone equivalent in the inebilizumab/inebilizumab group and 183.55 (374.94) mg prednisone equivalent in the placebo/inebilizumab group.

One subject (2.2%) in the inebilizumab/inebilizumab group and 18 subjects (40.9%) in the placebo/inebilizumab group used GCs for disease control during the OLP. Among these subjects, the mean (SD) total dose of GC use per subject was 245.00 (not applicable) mg in the inebilizumab/inebilizumab group and 448.68 (479.19) mg in the placebo/inebilizumab group. For both treatment groups, mean total GC use per subject was lower in the OLP compared either group in the RCP.

Subgroup analyses/clinical studies in special populations

Pre-defined and ad hoc important subgroup analyses

The consistency of treatment effect was investigated for the primary and 3 key secondary endpoints in the following subgroups:

- Age (< 65 vs ≥ 65 years)
- Sex (male vs female)
- Region (US vs non-US; EU vs non-EU; and Asia vs non-Asia)
- Serum IgG4 concentrations at baseline (< median vs ≥ median)
- ELF score at baseline (< median vs ≥ median)
- First or subsequent IgG4-RD manifestation (ie, newly diagnosed vs recurrent)
- ADA status at any time during RCP including baseline (positive vs negative) if data allows

The results of the primary analysis were generally consistent across subgroups. The only exceptions were for the US region and positive ADA status at any time during the RCP. A small number of subjects in these 2 subgroups may limit the interpretation of results.

Inebilizumab demonstrated directionally consistent efficacy for the primary endpoint across subgroups. The HR for treated and AC-determined IgG4-RD flare was <1 in each subgroup.

Inebilizumab also showed a directionally consistent efficacy compared with placebo for the key secondary endpoint of annualized flare rate of treated and AC-determined IgG4-RD flares across all subgroups; the rate ratio for was <1 in each subgroup.

The odds ratio for proportion of subjects achieving flare-free treatment-free complete remission and flare-free corticosteroid-free complete remission at week 52 of the RCP was >1 for most subgroups, indicating and increased probability of achieving complete remission for inebilizumab.

Additional analyses provided during the procedure upon the CHMP's request:

To support evidence of efficacy of inebilizumab independent of the number of organs affected at baseline or historically, the MAH provided the following analyses:

- Post hoc analysis demonstrated the benefit of inebilizumab versus placebo in participants with only a single organ involved at baseline. Four participants in the inebilizumab group and 5 participants in the placebo group had only 1 organ involved in the recent flare that qualified them for the study. None of these participants in the inebilizumab group experienced a treated and Adjudication Committee (AC)-determined flare in the randomized-controlled period (RCP), compared to 4/5 (80%) participants in the placebo group. Mean annualized flare rates per participant were 0 and 0.73 in the inebilizumab and placebo groups, respectively.

- Post hoc analysis by number of organs actively involved at study baseline demonstrated that inebilizumab reduced the risk of treated and AC-determined IgG4-RD flares in participants with either ≤ 3 organs actively involved at baseline (HR 0.17 [95% CI: 0.06, 0.45]; p = 0.0004) or > 3 organs actively involved at baseline (HR 0.07 [95% CI: 0.02, 0.32]; p = 0.005).

- Post hoc analysis by number of organs ever involved in the participants' history demonstrated benefit of inebilizumab on the primary endpoint and all key secondary endpoints for participants with ≤ 4 or > 5 organs historically affected by IgG4-RD

To support evidence of inebilizumab efficacy in participants without recent flare, the MAH provided the following post hoc analyses conducted on the 41 participants who received placebo in the RCP and had not experienced a flare within the 60 days prior to entering the OLP:

- Of these 41 participants, only 2 (4.9%) had a treated and AC-determined IgG4-RD flare during the OLP, with a mean (SD) annualized flare rate of 0.06 (0.29). For comparison, in this same set of 41 participants, 20 (48.8%) experienced a flare while on placebo in the RCP, with a mean (SD) annualized flare rate of 0.48 (0.52) during the RCP.

- Sixteen of the 41 participants (39.0%) used GCs for disease control during the OLP and mean daily dose of GC per participant was 0.601 mg prednisone equivalent. For comparison, 22 of these participants (53.7%) used GCs for disease control while on placebo during the RCP, with a mean daily dose of GC per participant of 3.489 mg prednisone equivalent.

To explore the efficacy of inebilizumab in patients with IgG4-RD with fibrotic disease, post hoc analyses on the subset of Study MITIGATE participants who had involvement of organs at baseline considered to be characteristic of fibrotic IgG4-RD were submitted during the procedure. The organs considered to be characteristic of fibrotic IgG4-RD are namely the retroperitoneum, mediastinum, abdominal mesentery (sclerosing mesenteritis), thyroid, or meninges (Lanzillotta et al, 2024[33]). There were 18 Study MITIGATE participants with baseline involvement of 1 of these organs: 8 in the placebo group and 10 in the inebilizumab group. No participant in the inebilizumab group experienced a flare during the RCP (and therefore the annualized flare rate was 0). In comparison, 3 of 8 (37.5%) participants in the placebo group experience a flare during the RCP, with a mean annualized flare rate of 0.5.

An overview of the change from baseline on the Responder Index score is provided in Table 35:

Table 35 Change From Baseline in Responder Index by Visit (Randomized-control Period) (Full Analysis Set)

RI Score Visit Summary	Placebo N = 67	Inebilizumab N = 68
IgG4-RD Responder Index Score		
Baseline[a]		
n	67	68
Mean	5.9	5.4
SD	4.0	4.0

[33] Lanzillotta, Marco, et al. "Fibrotic phenotype of IgG4-related disease." *The Lancet Rheumatology* 6.7 (2024): e469-e480.

Median	5.0	5.0
(Q1, Q3)	(3.0, 8.0)	(2.0, 8.0)
(Min, Max)	(0, 16)	(0, 19)
Week 26		
n	63	63
Mean	3.7	2.0
SD	3.0	2.4
Median	4.0	1.0
(Q1, Q3)	(1.0, 6.0)	(0.0, 3.0)
(Min, Max)	(0, 13)	(0, 10)
Change from Baseline		
n	63	63
Mean	-2.1	-3.5
SD	4.3	3.4
Median	-2.0	-4.0
(Q1, Q3)	(-4.0, 0.0)	(-5.0, 0.0)
(Min, Max)	(-15, 10)	(-14, 2)
Week 52		
n	64	66
Mean	2.7	1.9
SD	2.9	2.5
Median	2.0	1.0
(Q1, Q3)	(0.0, 4.5)	(0.0, 3.0)
(Min, Max)	(0, 13)	(0, 10)
Change from Baseline		
n	64	66
Mean	-3.1	-3.6
SD	4.3	4.0
Median	-2.0	-3.0
(Q1, Q3)	(-6.0, 0.0)	(-6.0, -1.0)
(Min, Max)	(-16, 7)	(-14, 9)

[a] Baseline indicates last non-missing valid assessment prior to first dose.

The MAH provided the following rationale to support the initiation of inebilizumab treatment in the absence of a concurrent steroid regimen:

- Data from the MITIGATE OLP provides evidence for efficacy of inebilizumab initiated in the absence of GC treatment. There was no steroid taper in the OLP, and analysis of OLP efficacy measures for those participants who received placebo in the RCP and initiated inebilizumab treatment in the OLP (without an accompanying GC regimen) suggests benefit of inebilizumab without concomitant GCs. The MAH has therefore not included language in the SmPC (indication and posology) requiring concomitant GC use at treatment initiation.

- In total, 44 participants from the placebo group in the RCP entered the OLP and received inebilizumab, with a median inebilizumab exposure of 279.0 days. In these participants, the annualized flare rate was 0.07 (95% CI: 0.02, 0.24) during the OLP, compared with an annualized flare rate of 0.71 (95% CI:0.53, 0.94) in the placebo group during the RCP. Furthermore, analysis of the rates of flare-free complete remission during year 1 of the OLP demonstrate that 33.3% of placebo/inebilizumab participants achieved treatment-free flare-free complete remission or corticosteroid-free flare-free complete remission, compared with 22.4% of placebo participants in the RCP. Finally, mean total GC use for disease control in the placebo/inebilizumab group during the OLP was 183.55 mg prednisone equivalent, compared with 1384.53 mg prednisone equivalent in the placebo group in the RCP

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36 Summary of Efficacy for trial MITIGATE

Title: A Phase 3, Randomized, Double-blind, Multicenter, Placebo-Controlled Study of Inebilizumab Efficacy and Safety in IgG4 Related Disease		
Study identifier	Protocol number: VIB0551.P3.S2 (MITIGATE; Amgen reference:20230068) EudraCT: 2020-000417-33 ClinicalTrials.gov: NCT04540497	
Design	Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inebilizumab for treatment of IgG4-RD in adults with active disease and who are at risk of recurrent flare.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52-week RCP with an optional 3-year OLP not applicable 2-year safety follow-up period
Hypothesis	Superiority	
Treatments groups	RCP phase: Inebilizumab	68 (out of 135) subjects were randomized (1:1 ratio) to the inebilizumab group (intravenous (IV) inebilizumab 300 mg on day 1, day 15, and week 26 of the 52-week RCP
	RCP phase: Placebo	67 (out of 135) subjects were randomized (1:1 ratio) to the placebo group intravenous (IV) placebo on day 1, day 15, and week 26 of the 52-week RCP
	OLP phase: Inebilizumab	300 mg inebilizumab IV on day 1, blinded 300 mg inebilizumab or placebo on day 15, then inebilizumab 300 mg IV every 6 months thereafter

Endpoints and definitions	Primary endpoint	Time to the first treated and AC-determined IgG4-RD flare	Time to disease flare, defined as the time in days from day 1 (dosing) to the date of the first treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week randomized controlled period (RCP). The date of disease flare is defined as the date of initiation of any flare treatment (new or increased glucocorticoids [GC] treatment, other immunotherapy, or interventional procedure) deemed necessary by the investigator for the flare
	Key Secondary endpoint	Annualised flare rate for treated and AC-determined IgG4-RD flares	Annualized flare rate for treated and AC-determined flares during the RCP
	Key Secondary endpoint	Proportion of subjects achieving treatment-free, flare-free complete remission at week 52	The proportion of subjects achieving flare-free, treatment-free complete remission at week 52, defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no treatment for flare or IgG4-RD disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence
	Key Secondary endpoint	Proportion of subjects achieving corticosteroid-free, flare-free complete remission at week 52	The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52, defined as the lack of evident disease activity at week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence
Database lock	Study is still ongoing. Data cutoff date for the primary analysis: 09 April 2024 for the RCP and 09 February 2024 for the OLP		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Overall, 127 subjects (94.1%) completed the RCP: 64 (94.1%) subjects in the inebilizumab group and 63 (94.0%) in the placebo group. Among the 135 subjects randomized and treated in the RCP, 102 subjects (75.6%) entered the OLP, including 53 subjects (77.9%) from the inebilizumab group and 49 subjects (73.1%) from the placebo group. Baseline Demographics: -Sex: 65.2% men, 34.8% women - Age: mean (SD) age at baseline was 58.2 (11.8) years - Race: Asian (46.7%), White (39.3%), American Indian or Native Alaskan (1.5%), Black (0.7%), Native Hawaiian or other Pacific Islander (0.7%), Not Reported (7.4%), Other (3.0%), or Unknown (0.7%) - Ethnicity: 11.9% Hispanic/Latino Time point description and assessments: per protocol: -RCP: at weeks 0-2-4-8-12-16-20-26-30-34-38-42-46-52 or EDV (early discontinuation visit) -OLP: at weeks 0-2-4, 8-12-16, 20-26-30, 34-38-42, 46-52-61, 87, 113, 139-78, 104, 130-156 or EDV		
Descriptive statistics and estimate variability	Treatment group	Placebo *{as per above terminology}*	Inebilizumab *{as per above terminology}*
	Number of subject	67	68
	Time to the first treated and AC-determined IgG4-RD flare		
	Number of subjects with a IgG4-RD flare	40 (59.7%)	7 (10.3%)
	(Median time to flare (days))	246.0	NA
	95% CI	(191.0, NA)	(371.0, NA)
	Annualised flare rate for treated and AC-determined IgG4-RD flares	0.71	0.10
	95% CI of annualized flare rate	(0.53, 0.94)	(0.05, 0.21)

	Proportion of subjects achieving treatment-free, flare-free complete remission at week 52 Flare-free, treatment-free complete remission at week 52	15 (22.4%)	39 (57.4%)
	Proportion of subjects achieving corticosteroid-free, flare-free complete remission at week 52 Flare-free, corticosteroid-free, complete remission at Week 52	15 (22.4%)	40 (58.8%)
	Total glucocorticoid use (mg) for IgG4-RD flare or maintenance per subject Mean (SD)	1384.53 (1723.26)	118.25 (438.97)

Effect estimate per comparison	Time to the first treated and AC-determined IgG4-RD flare	Comparison groups	Inebilizumab vs. Placebo
		Hazard Ratio	0.13
		95% Confidence interval	(0.06, 0.28)
		P-value	< 0.0001
	Annualized flare rate for treated and AC-determined flares during the RCP	Comparison groups	Inebilizumab vs. Placebo
		Rate ratio	0.14
		95% Confidence interval	(0.06, 0.31)
		P-value	<.0001

	The Proportion Of Subjects Achieving Flare-Free, Treatment-free Complete Remission At Week 52	Comparison groups	Inebilizumab vs. Placebo
		Odds ratio	4.68
		95% Confidence interval	(2.21, 9.91)
		P-value	<.0001
	The Proportion Of Subjects Achieving Flare-Free, Corticosteroid-free Complete Remission At Week 52	Comparison groups	Inebilizumab vs. Placebo
		Odds ratio	4.96
		95% Confidence interval	(2.34, 10.52)
		P-value	<.0001
	Total glucocorticoid use (mg) for IgG4-RD flare or maintenance per subject	Comparison groups	Inebilizumab vs. Placebo
		LSMEAN difference (SE)	-1264.16 (214.86)
		95% Confidence interval	(-1689.16, -839.15)
		Nominal P-value	<.0001
Notes	The time to the first treated and AC determined IgG4-RD flare was longer in the inebilizumab group, compared with the placebo group. Inebilizumab statistically significantly reduced the risk of treated and AC-determined IgG4-RD flare by 87%, compared with placebo (hazard ratio: 0.13; p < 0.0001). In addition, all three key secondary endpoints were met with statistical significance. The mean (SD) total GC use for IgG4-RD disease control per patient was lower in the inebilizumab group compared with the placebo group, with a mean (SD) of 118.25 (438.97) mg prednisone equivalent versus 1384.53 (1723.26) mg prednisone equivalent, respectively (nominal p < 0.0001) during the RCP. In the OLP, no new treated and AC-determined flares occurred in the patients originally randomised to inebilizumab who reminded in the study. Of the 4 subjects (5.9%) in the inebilizumab group who did not complete the RCP, 2 discontinued due to adverse events (AE)s. Two subjects withdrew consent. Eleven subjects discontinued study drug during the OLP; 8 subjects (7.8%) discontinued due an AE and 2 subjects withdrew consent. As of the data cutoff, no subjects have completed the study.		

2.4.3. Discussion on clinical efficacy

The MAH sought initially the following indication: "*treatment of adult patients with IgG4-RD*".

Design and conduct of clinical studies

Efficacy of inebilizumab for IgG4-RD was studied in a single pivotal study (MITIGATE), a randomized, double blind, placebo-controlled, multi-centre, international study. Data cut-off date for the RCT part of MITIGATE was 09 April 2024.

Study participants were adult patients with active disease, defined by clinical, imaging, laboratory or bio biopsy features, and requiring treatment in the judgement of the physician. Eligible patients had newly diagnosed or recurrent IgG4-RD that required glucocorticoid (GC) treatment at screening, had a confirmed history of organ involvement at any time in the course of the disease, and met the 2019 ACR/EULAR classification criteria.

In August 2021 with protocol amendment 7 of the MITIGATE study, the inclusion/exclusion criteria were revised to add that total duration of GC treatment must be at least 3 weeks and not exceed 8 weeks before randomisation, delete the requirement to have B cell counts ≥lower limit of normal (LLN) in subjects who received a B cell-depleting agent in the period 6 - 12 months before screening and exclude subjects with CD19+ B cells at screen <40 cells/L.

The CHMP noted that the changes introduced with this protocol amendment could change the time since last flare and therefore the risk of flare after baseline. Further, these changes were considered to possibly affect the number of participants with induced remission or the number of patients who recently failed a B-cell depleting therapy. However, these changes would be random over treatment groups and both may have diluted a treatment effect rather than exaggerated it. Hence, the consequences of protocol amendment 7 were acceptable to the CHMP.

To better understand the characteristics of the MITIGATE population, the MAH presented baseline disease characteristics which showed that the number of organs affected and the list of organs most commonly affected were similar to several published IgG4-RD cohorts and generally balanced between the inebilizumab group and the placebo group. Also, at baseline, there were both patients with and without involvement of organs which were associated with a particular fibrotic phenotype.

In the absence of approved therapies with established efficacy for the treatment of IgG4-RD, the study was designed with a placebo control, which was considered appropriate to the CHMP. Risks to patients were mitigated by allowing GC treatment for disease flares that occurred during the study and an independent safety data monitoring committee was used. The investigator determined whether protocol-defined flare criteria were met, decided whether flare treatment was warranted, and if so, initiated treatment.

At the time of randomisation, patients were at a uniform dose of GCs (equivalent to 20 mg prednisone per day) and then began a prespecified taper of 5 mg per day every 2 weeks to discontinuation at the end of 8 weeks. The use of GCs during the study was permitted for treatment of IgG4-RD flares, and for other purposes including premedication for investigational treatment, oral GC treatment up to 2 weeks, or at a dose of up to 2.5 mg per day of prednisone or equivalent for treatment of adrenal insufficiency. The concomitant use of biologic and non-biologic immunosuppressive agents was prohibited during the study. Patients who completed the RCP had the option to enrol in an OLP and initiate or continue treatment with inebilizumab. This was endorsed by the CHMP.

Premedication with corticosteroids, antihistamine and an antipyretic was required to avoid infusion-related reactions. Upon the CHMP' request, the MAH provided an overview of the number of incomplete or missed premedication procedures. A total of 9 participants in the Safety Analysis Set (4 in the inebilizumab group and 5 in the placebo group) experienced incomplete or missed premedication procedures during the RCP. The rates of IRRs were low in both treatment groups (7.4% in the inebilizumab group compared with 14.9% in the placebo group). One subject in the inebilizumab group experienced a serious adverse event of anaphylaxis at the first infusion of study drug during the RCP but, according to sensitivity analysis in which this subject was censored at the time of investigational product discontinuation, this event had no impact on the overall efficacy findings. Hence, the CHMP agreed that the incomplete or missed premedication procedures had no impact on the study blinding or reliability of the results.

The primary endpoint was *time to disease flare* in IgG4-RD during 52-weeks. Flare events were adjudicated by an Adjudication Committee according to a predefined charter. Disease flare was defined as new/worsening signs or symptoms that were positively adjudicated and warranted treatment by the investigator. Absence of alternative diagnoses was required.

The key secondary endpoints were:

1) Annualized flare rate for treated and AC-determined flares during the RCP;

2) The proportion of subjects achieving flare-free, treatment-free complete remission at week 52;

3) The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52.

Complete remission was defined as the lack of evident disease activity (either IgG4-RD RI score of 0, or determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence).

The CHMP requested the MAH to justify the choice between RI score and time to flare as the primary endpoint of MITIGATE study. The MAH clarified that the use of time to flare as primary endpoint was endorsed at time of scientific advice. The CHMP agreed that this is a clinical meaningful endpoint. The CHMP acknowledged that, based on the MITIGATE study protocol and the Sample Case Report Form (CRF), the flare criteria are clear. Further, the IgG4-RD RI score was an essential component of the two key secondary endpoints on complete remission.

The CHMP questioned the quality of data related to the assessment of lack of evident disease activity as it is not a validated method. The MAH clarified that lack of evident disease activity was defined as either an IgG4-RD RI score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence. Further, both investigators and sub-investigators were sufficiently trained to record patients IgG4-RD activity. The published instructions were used for RI scoring and data were entered to an electronic data capture system. The primary objective of study MITIGATE was to evaluate the efficacy of inebilizumab in reducing the risk of a disease flare, and during the study conduct, all investigational sites were reminded to focus on the "activity" component of the RI and not the "damage" component. The focus of study MITIGATE was "disease activity", and the entity "Lack of evident disease activity" was implemented as a composite endpoint to overcome specific challenges related to the RI scoring principles. The CHMP concluded that adequate measures were implemented to ensure sufficient data quality.

Exploratory endpoints:

The CHMP noted the exploratory endpoints presented e.g. Enhanced Liver Fibrosis score, the Physician Global Assessment of Disease Activity (PAG), Ig-levels, complement components levels, and Quality of Life (SF-36).

Efficacy data and additional analyses

Primary endpoint:

Inebilizumab demonstrated a significantly longer time to first treated and AC-determined IgG4-RD flare and statistically significantly reduced the risk of treated and AC-determined IgG4-RD flare during the RCP compared with placebo (HR 0.13 [95% CI: 0.06, 0.28; $p < 0.0001$]). The median time to flare was 246 days in the placebo group and could not be estimated in the inebilizumab group due to the low flare rate in this treatment group. A total of 7 subjects (10.3%) in the inebilizumab group and 40 subjects (59.7%) in the placebo group had at least 1 treated and AC-determined IgG4-RD flare during the RCP.

The MAH initially applied for an indication of treatment of adult patients with IgG4-RD. Considering the eligibility criteria, the natural course of disease and response to GC treatment of flares, the CHMP requested initially to limit the indication to adults with a clinical diagnosis of IgG4-RD who have had recent active disease and are at high risk of recurrent flare. In addition, the CHMP raised concerns regarding uncertainties with respect to an effect on the fibrotic part of the disease. In order to address these issues, the MAH submitted additional post hoc analyses during the procedure:

- With regard to the number of organs involved, post hoc analyses of data from the RCP supported benefits of inebilizumab versus placebo both in patients with a single organ involved at baseline, more organs involved at baseline, and in patients with few or with many (≤ 4 or > 5) organs ever involved.
- There were 18 patients with baseline involvement of 1 of organs considered to be characteristic for a fibrotic phenotype of IgG4-RD, 8 in the placebo group and 10 in the inebilizumab group. These organs were retroperitoneum, mediastinum, abdominal mesentery (sclerosing mesenteritis), thyroid, or meninges (Lanzillotta et al, 2024[33]). None of these patients in the inebilizumab group experienced flare during the RCP whereas 3 of 8 (37.5%) patients in the placebo group experienced a flare during the RCP. This was in support of an effect of inebilizumab on the annualized flare rate in patients with IgG4-RD who are at high risk of having a fibrotic phenotype.
- The MAH submitted a post-hoc analysis for patients who had not experienced a flare within 60 days prior to entering the OLP (n=41). This analysis supported a reduced annualised flare rate and a reduced use of GC after initiation of open label inebilizumab treatment compared to placebo during the RCP.

The CHMP considered that the additional analyses supported efficacy in patients with a high and a low number of organs involved, both in patients with and without involvement of organs which are associated with a particular fibrotic phenotype and that IgG4-RD treatment with inebilizumab should not be limited to patient with documented high risk of recurrent flares. Further, considering the pathophysiology of IgG4-RD, the CHMP requested to limit the indication to "active IgG4-RD", to which the MAH agreed. In addition, the definition of active IgG-RD was included in section 5.1 of the SmPC.

Secondary endpoints:

After multiplicity adjustment, all three key secondary endpoints met statistical significance. The annualized flare rate for treated and AC-determined IgG4 RD flares during the RCP was 0.71 in the placebo group and 0.1 in the inebilizumab group (Rate ratio 0.14 [95% CI of ratio: 0.06, 0.31; $p < 0.0001$]).

A greater proportion of subjects in the inebilizumab group achieved flare-free, treatment-free complete remission (Odds ratio 4.68 [95% CI of ratio: 2.21, 9.91; $p < 0.0001$]) and flare-free, corticosteroid-free complete remission (Odds ratio 4.96 [95% CI of ratio: 2.34, 10.52; $p < 0.0001$]) at week 52 compared with placebo.

A clinically relevant effect on flares was shown in MITIGATE study**.**

All patients had recent or ongoing flare requiring glucocorticoid at the time of randomization. The GC use per subject for IgG4-RD disease control was significantly lower in the inebilizumab group compared with the placebo group.

In general, the series of clinically relevant endpoints designated as "exploratory" suggested no treatment effect of inebilizumab vs placebo on IgG4-RD. Neither of these endpoints were specific to occurrence of flare and included Ig-levels, se-complement components C3 and C4 levels, the Enhanced Liver Fibrosis (ELF) score, PROs and the PAG. The PAG was used for validation of the Responder Index.

The study MITIGATE did not provide sufficient data supporting a treatment effect on the fibrotic component of IgG4-RD.

The mean (SD) IgG4-RD RI score at baseline was included in the SmPC section 5.1., but due to limitations including minimal clinically meaningful change, pre-baseline GC effects on the RI-score, risk of increasing RI-score over time due to "lack of imaging" without disease activity, the RI score was not included as a discrete endpoint in study MITIGATE and change from baseline of the RI score was not included in the SmPC.

The OLP cut-off date was 09 February 2024. Compared to the RCT, the OLP data supported maintenance of reduced flare rate in both treatment groups and reduced use of GC during this period. After the RCT, all eligible patients could participate in the 3-year OLP. A 2-year safety follow-up was in place for subjects who did not enter the OLP or who discontinued investigational product during the OLP. Only limited data was available for treatment beyond 1 year, this was adequately reflected in the SmPC section 4.2 where it is stated that *"Based upon the chronic nature of IgG4-RD, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice".*

The CHMP agreed that the results of the single pivotal MITIGATE study were sufficiently compelling to support the extension of indication in patients with active IgG4-related disease, taking into account the points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99).

2.4.4. Conclusions on the clinical efficacy

Efficacy of inebilizumab for IgG4-RD was shown in patients who had a recent or ongoing flare requiring glucocorticoid at the time of randomization. Data support a treatment effect of inebilizumab versus placebo irrespective of the number of organs involved and both in patients who does/does not present characteristics of a fibrotic IgG4-RD phenotype. The agreed indication is *"Uplizna is indicated for the treatment of adult patients with active IgG4-RD (see section 5.1)."*

2.5. Clinical safety

Introduction

This application focused primarily on the safety data from the pivotal Study MITIGATE, a phase 3, randomized, double-blind, placebo-controlled study of inebilizumab in adults with IgG4 RD.

The safety data of inebilizumab in subjects with NMOSD were described in the initial MAA. Due to differences in patient populations, safety data are not pooled with the NMOSD patient population in this application. Differences in the safety profile observed in subjects with IgG4-RD compared to the safety profile in NMOSD patients were discussed.

Patient exposure

This application provided safety data from the primary analysis of Study MITIGATE. This included data from all subjects who completed the 52-week RCP or discontinued prematurely (data cut-off date 09 April 2024). In addition, safety data were provided up to the data cut-off date of 09 February 2024 for the 90 subjects who were included in the OLP analysis set. The safety endpoints are summarized separately for the RCP, OLP, and the combined RCP and OLP.

During the procedure, the MAH provided a safety update with a data cutoff date of 15 August 2024 and included additional safety data since the data cutoff of the original variation application. These results are summarised at the end of the Section 2.5. *Updated analysis of safety data*.

Safety analyses for the RCP are based on the Safety Analysis Set, which includes all subjects who received any dose of investigational product during the RCP.

During the RCP, there were 3 planned doses of investigational product: 300 mg on day 1, day 15, and week 26 (Table 37).

Overall, across the RCP and the OLP, 112 subjects received 1 or more doses of inebilizumab. Nineteen subjects (17%) in the Any Inebilizumab population received inebilizumab for > 730 days (approximately 2 years), and 63 subjects (56.3%) received inebilizumab for at least 1 year.

Table 37 Exposure to investigational product randomized-controlled period safety analysis set

	Placebo N = 67	Inebilizumab N = 68
Number of doses received		
1	0 (0%)	4 (5.9%)
2	15 (22.4%)	6 (8.8%)
3	52 (77.6%)	58 (85.3%)
Duration of the exposure (days)[a]		
n	67	68
Mean	235.6	250.4
SD	71.6	64.9
Median	272.0	272.0
(Q1, Q3)	(267.0, 272.0)	(270.0, 274.5)
(Min, Max)	(103, 333)	(90, 350)
Total dose administered (mg)[b]		
n	67	68
Mean	0.00	834.18
SD	0.00	176.73
Median	0.00	900.00
(Q1, Q3)	(0.00, 0.00)	(900.00, 900.00)
(Min, Max)	(0.0, 0.0)	(24.0, 900.0)

a Duration of exposure for inebilizumab is defined as last dose date - first dose date + 90.
b Total dose was estimated based on actual volume administered. If dose was not fully administered, the dose administered = 300 mg x x actual volume received/planned volume.

Table 38 Exposure to investigational product open-label period and any inebilizumab population

	Open-label Analysis Set		Any Inebilizumab Analysis Set
	Placebo/ Inebilizumab N = 44	Inebilizumab/ Inebilizumab N = 46	Inebilizumab N = 112
Number of inebilizumab doses received[a]			
1	1 (2.3%)	1 (2.2%)	4 (3.6%)
2	8 (18.2%)	11 (23.9%)	13 (11.6%)
3	18 (40.9%)	16 (34.8%)	33 (29.5%)
4	13 (29.5%)	13 (28.3%)	24 (21.4%)
5	4 (9.1%)	5 (10.9%)	21 (18.8%)
6	0	0	13 (11.6%)
7	0	0	4 (3.6%)
Duration of the exposure (days)[b]			
n	44	46	112
Mean	325.5	320.9	461.9
SD	161.7	173.7	261.3
Median	279.0	273.0	455.0
(Q1, Q3)	(265.0, 455.0)	(152.0, 454.0)	(271.5, 657.0)
(Min, Max)	(90, 650)	(90, 688)	(90, 1063)

min = minimum
[a] Excluding placebo dose at open-label period day 15.
[b] Duration of the exposure is defined as the last inebilizumab dose date -first inebilizumab dose date + 90.

Adverse events

Overall summaries of the subject incidence of adverse events in the RCP and the OLP and Any Inebilizumab Analysis Set are provided below in Table 39 and Table 40.

Table 39 Overall summary of treatment-emergent adverse events randomized-controlled period, safety analysis set

Subjects[a] with	Placebo N=67	Inebilizumab N=68
At least one event	66 (98.5%)	66 (97.1%)
At least one investigational product related event	16 (23.9%)	28 (41.2%)
At least one event of ≥ grade 3 severity[b]	8 (11.9%)	12 (17.6%)
Death (grade 5 severity[b])	0	0
At least one serious[c] event	6 (9.0%)	12 (17.6%)
At least one serious[c] and/or ≥ grade 3 severity[b] event	10 (14.9%)	17 (25.0%)
At least one investigational product related serious[c] event	0	2 (2.9%)
At least one event leading to discontinuation of investigational product	3 (4.5%)	6 (8.8%)
At least one event leading to dose interruption	1 (1.5%)	4 (5.9%)
At least one event of special interest	15 (22.4%)	23 (33.8%)

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

Table 40 Overall summary of treatment-emergent adverse events open-label period and any inebilizumab population

	Open-label Analysis Set			Any Inebilizumab Analysis Set
Subjects[a] with	Placebo/ Inebilizumab N = 44	Inebilizumab/ Inebilizumab N = 46	Total N = 90	Inebilizumab N = 112
At least one event	41 (93.2%)	35 (76.1%)	76 (84.4%)	107 (95.5%)
At least one investigational product related event	13 (29.5%)	9 (19.6%)	22 (24.4%)	45 (40.2%)
At least one event of ≥ grade 3 severity[b]	6 (13.6%)	5 (10.9%)	11 (12.2%)	23 (20.5%)
Death (grade 5 severity[b])	0	0	0	0
At least one serious[c] event	7 (15.9%)	7 (15.2%)	14 (15.6%)	25 (22.3%)
At least one serious[c] and/or ≥ grade 3 severity[b] event	9 (20.5%)	8 (17.4%)	17 (18.9%)	33 (29.5%)
At least one investigational product related serious[c] event	2 (4.5%)	2 (4.3%)	4 (4.4%)	6 (5.4%)
At least one event leading to discontinuation of investigational product	1 (2.3%)	5 (10.9%)	6 (6.7%)	12 (10.7%)
At least one event leading to dose interruption	0	2 (4.3%)	2 (2.2%)	4 (3.6%)
At least one event of special interest	8 (18.2%)	6 (13.0%)	14 (15.6%)	35 (31.3%)

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

Common adverse event

In the RCP, the 3 most frequently reported adverse events were COVID-19, lymphopenia, and urinary tract infection (Table 41).

Table 41 Treatment-emergent adverse events (≥ 5% in inebilizumab group) by preferred term: randomized-controlled period (safety analysis set)

Preferred Term[a]	Placebo N = 67	Inebilizumab N = 68
Most common AEs (≥ 5% in the inebilizumab group)		
COVID-19	13 (19.4%)	16 (23.5%)
Lymphopenia	6 (9.0%)	11 (16.2%)
Urinary tract infection	4 (6.0%)	8 (11.8%)
Back pain	5 (7.5%)	6 (8.8%)
Headache	7 (10.4%)	6 (8.8%)
Nasopharyngitis	4 (6.0%)	6 (8.8%)
Pyrexia	3 (4.5%)	6 (8.8%)
Fatigue	5 (7.5%)	5 (7.4%)
Abdominal pain	7 (10.4%)	4 (5.9%)
Arthralgia	7 (10.4%)	4 (5.9%)
Gamma-glutamyltransferase increased	3 (4.5%)	4 (5.9%)
Myalgia	0	4 (5.9%)
Neutropenia	3 (4.5%)	4 (5.9%)
Palpitations	1 (1.5%)	4 (5.9%)
Upper respiratory tract infection	8 (11.9%)	4 (5.9%)

AE = adverse event.
[a]Subjects are counted once for each preferred term regardless of the number of events

In the OLP, the 3 most frequently reported adverse events in the inebilizumab/inebilizumab group were COVID-19, upper respiratory tract infection and nasopharyngitis (Table 42).

Table 42 Summary of adverse events during the open-label period by preferred term reported by ≥ 5% of subjects in the inebilizumab/ inebilizumab group (open-label analysis set)

Subjects[a] with	Placebo/ Inebilizumab N = 44	Inebilizumab/ Inebilizumab N = 46	Total N = 90
Most common adverse events (≥ 5% in the inebilizumab group)			
COVID-19	10 (22.7%)	9 (19.6%)	19 (21.1%)
Upper respiratory tract infection	5 (11.4%)	5 (10.9%)	10 (11.1%)
Nasopharyngitis	1 (2.3%)	4 (8.7%)	5 (5.6%)
Back pain	0	3 (6.5%)	3 (3.3%)
Headache	0	3 (6.5%)	3 (3.3%)
Hypertension	3 (6.8%)	3 (6.5%)	6 (6.7%)

[a]Subjects are counted once for each preferred term regardless of the number of events.

In the Any Inebilizumab group, the 3 most frequently reported adverse events by SOC were infections and infestations (70.5%), gastrointestinal disorders (30.4%) and musculoskeletal and connective tissue disorders (30.4%). A summary of Summary of adverse events by preferred term reported by ≥ 5% of subjects in the any inebilizumab group is provided in Table 43.

Table 43 Summary of adverse events by preferred term reported by ≥ 5% of subjects in the any inebilizumab group (any inebilizumab analysis set)

Subjects[a] with	Any Inebilizumab N = 112
Most common adverse events (≥ 5% in the inebilizumab group)	
COVID-19	32 (28.6%)
Lymphopenia	12 (10.7%)
Upper respiratory tract infection	12 (10.7%)
Nasopharyngitis	11 (9.8%)
Urinary tract infection	10 (8.9%)
Back pain	9 (8.0%)
Fatigue	9 (8.0%)
Pyrexia	9 (8.0%)
Headache	8 (7.1%)
Abdominal pain	7 (6.3%)
Arthralgia	7 (6.3%)
Hypertension	7 (6.3%)
Influenza	7 (6.3%)
Myalgia	7 (6.3%)
Cough	6 (5.4%)
Neutropenia	6 (5.4%)
Urticaria	6 (5.4%)

[a]Subjects are counted once for each preferred term regardless of the number of events.

Adverse Events by Severity

Across both treatment periods, the highest severity adverse event experienced by most subjects was mild (grade 1) or moderate (grade 2).

During the RCP, the percentages of subjects with mild (27.9% inebilizumab, 31.3% placebo), moderate (51.5% inebilizumab, 55.2% placebo), and severe (grade 3) (14.7% inebilizumab,10.4% placebo) events were generally similar between the inebilizumab and placebo groups. Two subjects (2.9%) in the inebilizumab group experienced a life-threatening (grade 4) event. Of these 2 subjects, 1 subject experienced anal cancer and 1 subject experienced a pulmonary embolism and deep vein thrombosis. Both events were not related to the study drug assessed by the investigator. One subject (1.5%) in the placebo group experienced life-threatening (grade 4) events of blood creatinine increased and blood potassium increased, both of which were not related to the study drug assessed by the investigator.

During the OLP, the proportion of subjects with mild (30.4% inebilizumab/inebilizumab, 31.8% placebo/inebilizumab), moderate (34.8% inebilizumab/inebilizumab, 47.7% placebo/inebilizumab) and severe (grade 3) (10.9% inebilizumab/inebilizumab, 11.4% placebo/inebilizumab) events was reported for the inebilizumab and placebo groups. One subject (2.3%) in the placebo/inebilizumab group experienced a life threatening (grade 4) IRR, which was related to the study drug as assessed by the investigator. No subjects in the inebilizumab/inebilizumab group experienced a life threatening (grade 4) event.

As of the data cutoff, no subjects have experienced fatal (grade 5) events.

Serious adverse event/deaths/other significant events

Serious Adverse Events

During the RCP, serious adverse events were reported for 12 (17.6%) subjects in the inebilizumab group and 6 (9.0%) subjects in the placebo group. No serious adverse event occurred in more than 1 subject in either group (Table 44). Serious infections and infestations were reported for 4 subjects (5.9%) in the inebilizumab group.

Table 44 Treatment-emergent serious adverse events by System Organ Class and Preferred Term during the randomized-controlled period (safety analysis set)

Subjects[a] with	Placebo N = 67	Inebilizumab N = 68
Subjects with at least 1 event	6 (9.0%)	12 (17.6%)
Cardiac disorders	1 (1.5%)	0
Coronary artery stenosis	1 (1.5%)	0
Hepatobiliary disorders	1 (1.5%)	0
Hepatic function abnormal	1 (1.5%)	0
Immune system disorders	0	1 (1.5%)
Anaphylactic reaction	0	1 (1.5%)
Infections and infestations	0	4 (5.9%)
Appendicitis	0	1 (1.5%)
COVID-19	0	1 (1.5%)
COVID-19 pneumonia	0	1 (1.5%)
Diverticulitis	0	1 (1.5%)
Injury, poisoning and procedural complications	0	1 (1.5%)
Femoral neck fracture	0	1 (1.5%)
Metabolism and nutrition disorders	1 (1.5%)	2 (2.9%)
Diabetes mellitus	1 (1.5%)	0
Gout	0	1 (1.5%)
Hyponatraemia	0	1 (1.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (2.9%)
Anal cancer	0	1 (1.5%)
Fibroadenomatoid mastopathy	0	1 (1.5%)
Renal and urinary disorders	1 (1.5%)	0
Acute kidney injury	1 (1.5%)	0
Respiratory, thoracic and mediastinal disorders	2 (3.0%)	2 (2.9%)
Epistaxis	1 (1.5%)	0
Pulmonary atypical adenomatous hyperplasia	0	1 (1.5%)
Pulmonary embolism	0	1 (1.5%)
Sinus disorder	1 (1.5%)	0
Vascular disorders	0	1 (1.5%)
Deep vein thrombosis	0	1 (1.5%)

[a]Subjects are counted once for each serious adverse event criterion regardless of the number of events the subject had with that criterion. Subject may be counted under multiple criteria.

During the OLP, serious adverse events occurred in 7 (15.2%) subjects in the inebilizumab/inebilizumab group and 7 (15.9%) subjects in the placebo/inebilizumab group. The only serious adverse event that occurred in > 1 subject was pneumonia (2 subjects) in the inebilizumab/inebilizumab group. All other serious adverse events occurred in 1 subject each.

Serious adverse events occurred in 25 subjects (22.3%) in the Any Inebilizumab group. Serious adverse events that occurred in > 1 subject were COVID-19 pneumonia and pneumonia (2 subjects each). All other serious adverse events occurred in 1 subject each.

Deaths

As of the data cutoff for the primary analysis, no deaths have been reported in the study.

Adverse Events of Special Interest

Anaphylaxis and Serious Hypersensitivity Reactions

During the RCP, 1 subject (1.5%) in the inebilizumab group had a grade 3, serious anaphylactic reaction (Table 45). Symptoms of anaphylactic reaction started approximately 13 minutes into the first inebilizumab infusion, including nausea, burning sensation, hypotension, bradycardia, and decreased blood oxygen saturation. All symptoms resolved after treatment with intravenous saline, hydrocortisone and mask oxygenation. Inebilizumab was permanently discontinued. The event was assessed as related to study drug by the investigator. Of note, the subject did not receive the full dose of protocol defined prophylactic treatment of corticosteroids, i.e. 100 mg hydrocortisone instead of 100 mg methylprednisolone.

No other cases of anaphylaxis were reported in the Any Inebilizumab group (Table 46).

Infusion-related Reactions (IRR)

During the RCP, the percentage of subjects that experienced IRR was higher in the placebo group compared with the inebilizumab group, and all IRRs were non-serious and grade 1 (mild) or grade 2 (moderate) in severity. Infusion-related reactions were reported for a total of 5 subjects (7.4%) in the inebilizumab group and 10 subjects (14.9%) in the placebo group (Table 45). Of the 15 subjects that reported IRR, 2 subjects (2.9%) in the inebilizumab group reported palpitations and 2 subjects (3.0%) in the placebo group reported diarrhea. All other IRR symptoms occurred in only a single subject. The majority of the IRR (8 of 11) occurred during the first or second infusion, 1 at the third infusion, 2 at the fourth infusion, and 1 at the fifth infusion. All IRR cases were compliant with the protocol required treatments, including steroids. No IRR resulted in discontinuation of study treatment in RCP.

There was 1 grade 4 (life-threatening) IRR reported during the OLP. Symptoms of the serious IRR occurred at the end of the first inebilizumab infusion during the OLP, including bronchospasm, bradycardia, and decreased blood oxygen saturation. The subject was hospitalized and received treatment of hydrocortisone, chlorphenamine, and methylprednisolone. The IRR resolved and inebilizumab was permanently discontinued. The event was assessed as related to study drug by the investigator.

In the Any Inebilizumab group, IRR was reported for 11 subjects (9.8%) (Table 46). Of the subjects that reported IRR, 3 subjects (2.7%) reported IRR and 2 subjects (1.8%) reported palpitations. All other IRR related AESI events occurred in 1 subject each.

Cytopenia

During the RCP, cytopenia was reported for 17 subjects (25.0%) in the inebilizumab group and 11 subjects (16.4%) in the placebo group (Table 45). The most frequently reported cytopenia was lymphopenia (all events were non-serious and resolved without a dose change) (11 subjects [16.2%] in the inebilizumab group, 6 subjects [9.0%] in the placebo group), followed by neutropenia (all events were non-serious and resolved without a dose change) (4 subjects [5.9%] in the inebilizumab group, 3 subjects [4.5%] in the placebo group). There was no association seen between lymphopenia and/or neutropenia and serious infections based on case reviews.

In the Any Inebilizumab group, cytopenia was reported for 21 subjects (18.8%) (Table 10). The most common subtype of cytopenia was lymphopenia (12 subjects, 10.7%), followed by neutropenia (6

subjects, 5.4%). The majority of cytopenia events were mild or moderate in severity and no serious cytopenia was reported.

Serious and/or Opportunistic Infections

During the RCP, opportunistic infections were reported for 2 subjects (2.9%) in the inebilizumab group and 1 subject (1.5%) in the placebo group; serious infections were reported for 4 subjects (5.9%) in the inebilizumab group and no subjects in the placebo group (Table 45). All reported opportunistic infections were non-serious, grade 1 (mild) or grade 2 (moderate) herpes zoster (2 subjects [2.9%] in the inebilizumab group, 1 subject [1.5%] in the placebo group).

In the Any Inebilizumab group, opportunistic infections were reported for 3 subjects (2.7%) and serious infections were reported for 9 subjects (8.0%) (Table 46). All 3 opportunistic infections were non-serious herpes zoster infections. All events were grade 1 (mild) or grade 2 (moderate) in severity. One grade 1 herpes zoster resulted in permanent discontinuation of study treatment. All serious infections were reported by single subject except for COVID-19 pneumonia and pneumonia, which were reported by 2 subjects each. All serious infections resolved/recovered, and all serious infections were not related to study drug except for 1 COVID-19, which was assessed related to study drug by the investigator. One COVID-19 pneumonia and dengue fever resulted in permanent discontinuation of study treatment. No subject reported progressive multifocal leukoencephalopathy (PML).

Table 45 Sponsor defined adverse events of special interest by category in the randomized-controlled period (safety analysis set)

Catergory[a]	Placebo N = 67	Inebilizumab N = 68
Subjects with at least 1 event	19 (28.4%)	26 (38.2%)
Anaphylaxis	0	1 (1.5%)
Cytopenia	11 (16.4%)	17 (25.0%)
Infusion related reaction	10 (14.9%)	5 (7.4%)
Opportunistic infections	1 (1.5%)	2 (2.9%)
Serious infections	0	4 (5.9%)

[a] Subjects are counted once for each category regardless of the number of events.

Table 46 Sponsor defined adverse events of special interest by category after first inebilizumab exposure (any inebilizumab analysis set)

Catergory[a]	Any Inebilizumab N = 112
Subjects with at least 1 event	41 (36.6%)
Anaphylaxis	1 (0.9%)
Cytopenia	21 (18.8%)
Infusion related reaction	11 (9.8%)
Opportunistic infections	3 (2.7%)
Serious infections	9 (8.0%)

[a] Subjects are counted once for each category regardless of the number of events.

Laboratory findings

Haematology

During the RCP at Week 2, lymphocyte count had increased on average by 20.56% in the placebo group and was 9.63% lower than baseline in the inebilizumab group. During the RCP overall, lymphocyte counts were lower in the inebilizumab group than the placebo group. At week 52, lymphocyte count had increased by 13.82% in the inebilizumab group and 22.12% in the placebo group since baseline. A total of 41.8% of subjects in the inebilizumab group and 35.8% of subjects in the placebo group had at least 1 post-baseline lymphocyte value below the lower limit of normal (LLN). A total of 9.0% of subjects in the inebilizumab group and 20.9% of subjects in the placebo group had at least one post-baseline lymphocyte value above the upper limit of normal (ULN). Lymphocyte counts grade 2 were observed in 26.9% of both inebilizumab-treated and placebo-treated patients.. A total of 10.4% of subjects in the inebilizumab group and 3.0% of subjects in the placebo group had grade ≥ 3 lymphocyte count decrease. A total of 3.0% of subjects in the inebilizumab group and 11.9% of subjects in the placebo group had grade ≥2 lymphocyte count increases, and no subjects had grade ≥ 3 lymphocyte count increases.

Monocyte levels were elevated in both treatment groups in the RCP through week 52. A total of 4.5% of subjects in the placebo group and 1.5% in the inebilizumab group had at least 1 post-baseline monocyte value below LLN. A total of 6.0% of subjects in the placebo group and 9.0% of subjects in the inebilizumab group had at least one post-baseline monocyte value above ULN.

Neutrophil levels were elevated in both treatment groups in the RCP at week 2. Neutrophil levels started decreasing from baseline at week 8. Mean percent change reduction from baseline at week 52 in neutrophil levels was similar between the treatment groups (35.26% for inebilizumab, 28.23% placebo). A total of 16.4% of subjects in the placebo group and 22.4% in the inebilizumab group had at least 1 post baseline neutrophil value below LLN. A total of 59.7% of subjects in the placebo group and 52.2% of subjects in the inebilizumab group had at least 1 post-baseline neutrophil value above ULN. Neutrophil counts grade 2 were observed in 7.5% of inebilizumab-treated patients versus 3% of placebo-treated patients. Neutrophil counts grade ≥ 3 were observed in 0% of inebilizumab-treated patients versus 1.5% of placebo-treated patients.

During the OLP, there was no trend for neutrophil counts. A total of 7.5% of subjects in the inebilizumab group and 4.5% of subjects in the placebo group had grade ≥2 neutrophil count decrease. No subjects in the inebilizumab group and 1.5% of subjects in the placebo group had grade ≥3 neutrophil count decrease.

During the RCP, a higher proportion of subjects in the inebilizumab group had at least a 2-grade worsening from baseline compared with the placebo group in the following laboratory parameters:

- Lymphocytes (decreased): inebilizumab 23.9% versus placebo 16.4%.
- Neutrophils (decreased): inebilizumab 7.5% versus placebo 4.5%.

No clinically meaningful trends were identified in the average changes from baseline in hemoglobin, hematocrit, eosinophils, leukocytes, eosinophils/leukocytes (%), basophils, basophils/leukocytes (%), erythrocytes, mean corpuscular volume, and platelets.

Chemistry

No clinically meaningful trends were identified in change from baseline, post-baseline by worst Common Terminology Criteria for Adverse Events (CTCAE) grade, and post baseline shift by 2 or more grades for any serum chemistry parameters during the RCP or OLP.

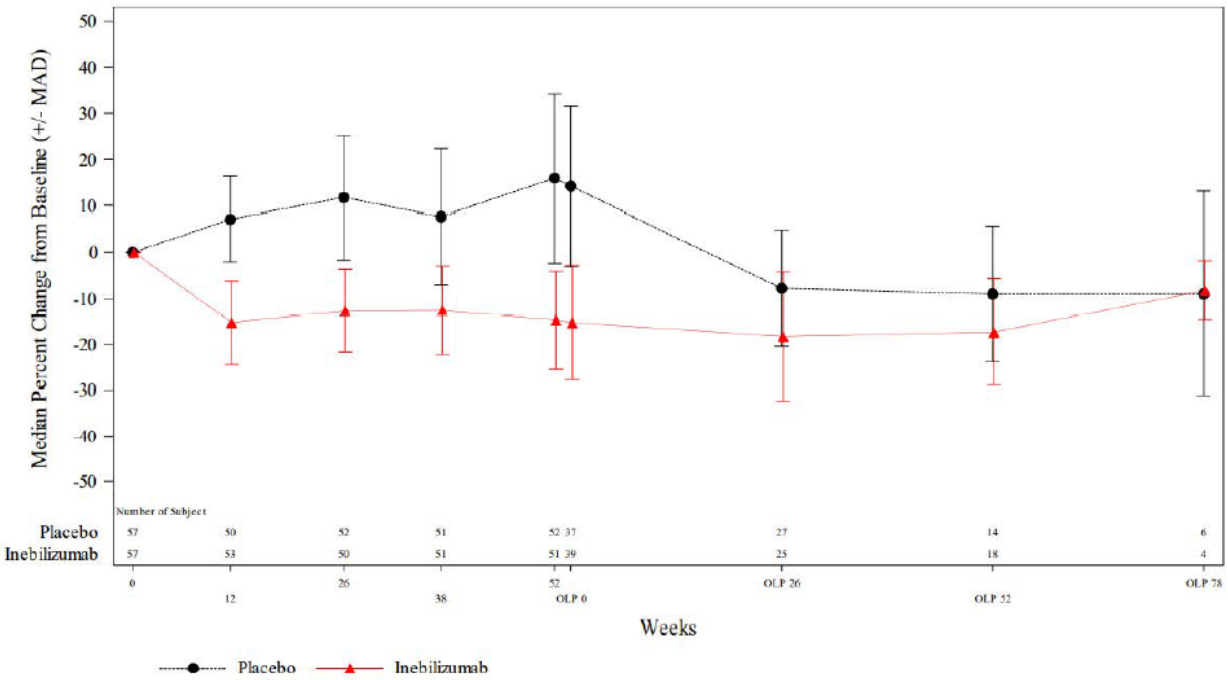
Immunoglobulins

Immunoglobulin (Ig) levels decreased with inebilizumab use.

Median percentage change from baseline to end of the RCP:

- for total Ig, it was -14.7% for the inebilizumab group and +15.9% for the placebo group; mean percent change from baseline was -11.99 for inebilizumab group and +21.05% for the placebo group

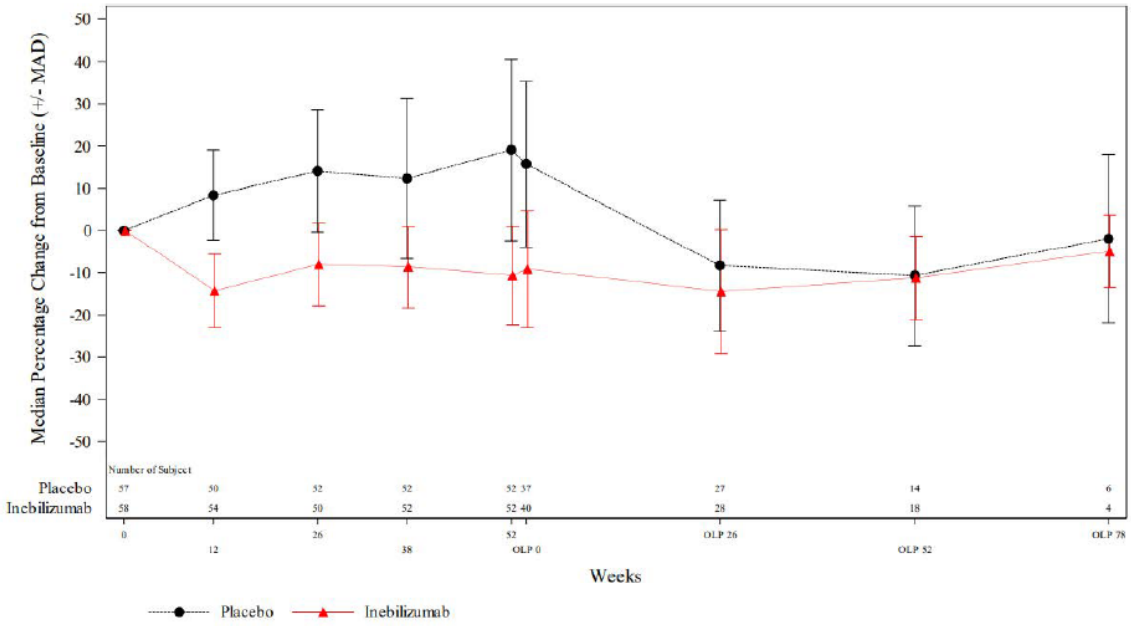
Figure 21 Median values for total Immunoglobulin as a percentage of Baseline over time (full analysis set)



MAD = Median Absolute Deviation; OLP = open-label period; RCP = randomized controlled period.
Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

- for IgG, it was -10.7% for the inebilizumab group and +19.1% for the placebo group; mean percent change from baseline was -8.59 for inebilizumab group and +25.60% for the placebo group

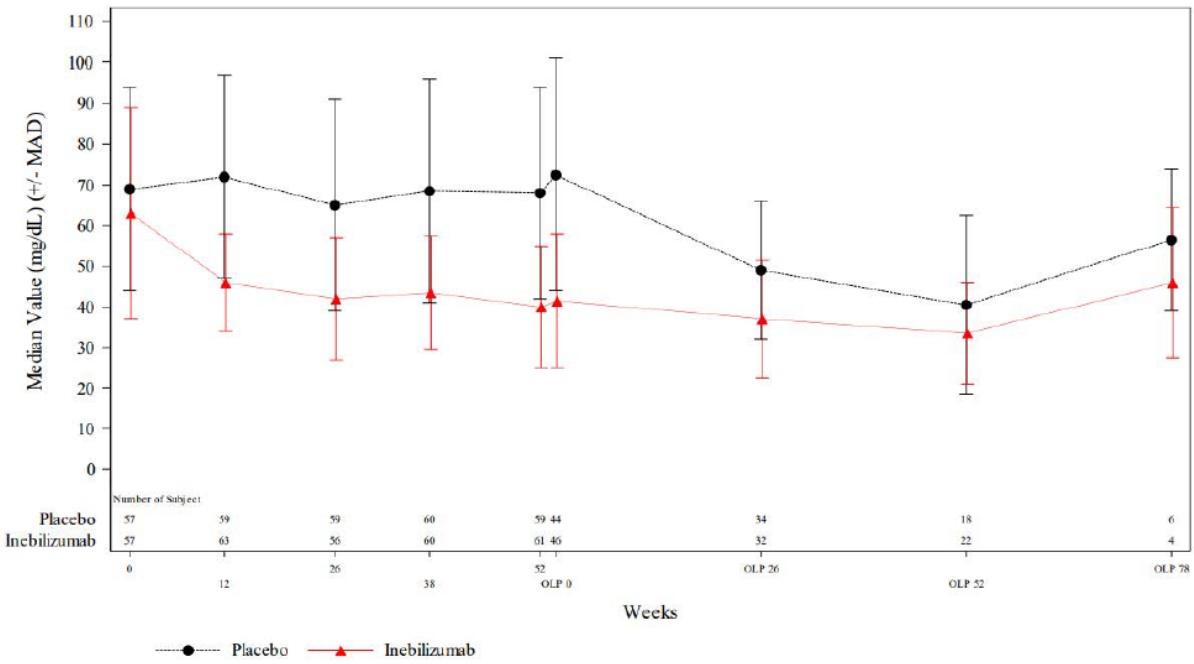
Figure 22 Median values for Immunoglobulin G as a percentage of Baseline over time (full analysis set)



MAD = Median Absolute Deviation; RCP = randomized controlled period.
Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

- for IgM, it was -30.2% for the inebilizumab group and +0.8% for the placebo group; mean percent change from baseline was -31.53 for inebilizumab group and +2.91% for the placebo group

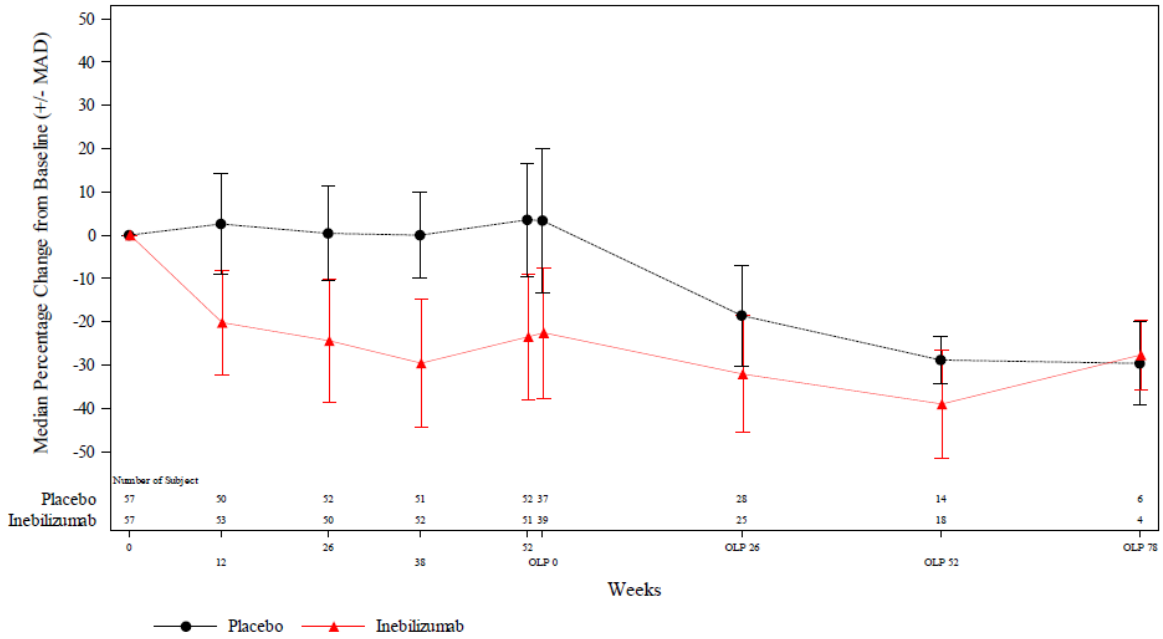
Figure 23 Median values for Immunoglobulin M as a percentage of Baseline over time (full analysis set)



MAD = Median Absolute Deviation; OLP = open-label period; RCP = randomized controlled period.
Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

- for IgA, it was -23.5% for the inebilizumab group and +3.5% for the placebo group.

Figure 24 Median values for Immunoglobulin A as a percentage of Baseline over time (full analysis set)



MAD = Median Absolute Deviation; OLP = open-label period; RCP = randomized controlled period.
Error bars represent MAD. The baseline is the last valid observation before the first dose in RCP.

These reductions of Ig levels were not associated with serious infections.

Of note, in the subjects receiving inebilizumab from the start of the RCP:

- The median percentage change from baseline in total Ig levels was -15% at RCP Week 12, keeping relatively stable throughout the RCP and OLP
- IgG, IgM and IgA followed the same overall decreasing trend as the total Ig levels.

During the OLP, placebo/inebilizumab subjects had similar decreases over time in Ig levels as inebilizumab/inebilizumab subjects in the RCP.

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically significant changes in vital signs in either treatment group during the study.

Electrocardiograms

During the RCP, no abnormal electrocardiogram results were clinically significant at baseline through week 52. The proportions of subjects in the RCP at Week 52 with abnormal, potentially clinically significant electrocardiogram readings were the same (1.9%) for both the placebo and inebilizumab groups.

Physical Findings

There were no trends in body weight or BMI changes in either the inebilizumab group or the placebo group.

Safety in special populations

Intrinsic Factors

The effects of intrinsic factors on the adverse event profile of inebilizumab were assessed by subgroup analyses of adverse events reported during the RCP in Study MITIGATE.

Age (< 65 years vs ≥ 65 years):

Table 47 Overall summary of treatment emergent adverse events (randomized-controlled period) by subgroup, safety analysis set

Subgroup	Subject[a] With	Placebo N=67	Inebilizumab N=68	Risk Difference (95% CI)[d]
Age				
< 65		46	47	NA
	At least one event	45 (97.8%)	46 (97.9%)	0.0% (-9.2%, 9.4%)
	At least one investigational product related event	10 (21.7%)	20 (42.6%)	20.8% (1.8%, 38.5%)
	At least one event of ≥ grade 3 severity[b]	6 (13.0%)	5 (10.6%)	-2.4% (-16.7%, 11.6%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	4 (8.7%)	4 (8.5%)	-0.2% (-13.1%, 12.6%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	6 (13.0%)	7 (14.9%)	1.9% (-13.0%, 16.7%)
	At least one investigational product related serious[c] event	0	0	NA
	At least one event leading to discontinuation of investigational product	2 (4.3%)	2 (4.3%)	-0.1% (-10.9%, 10.5%)
	At least one event leading to dose interruption	0	2 (4.3%)	4.3% (-3.6%, 14.2%)
	At least one event of special interest	8 (17.4%)	12 (25.5%)	8.1% (-8.8%, 24.8%)
>= 65		21	21	NA
	At least one event	21 (100%)	20 (95.2%)	-4.8% (-22.7%, 11.1%)
	At least one investigational product related event	6 (28.6%)	8 (38.1%)	9.5% (-18.8%, 36.5%)
	At least one event of ≥ grade 3 severity[b]	2 (9.5%)	7 (33.3%)	23.8% (-1.1%, 47.3%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	2 (9.5%)	8 (38.1%)	28.6% (3.0%, 51.9%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	4 (19.0%)	10 (47.6%)	28.6% (0.1%, 53.1%)
	At least one investigational product related serious[c] event	0	2 (9.5%)	9.5% (-6.7%, 28.9%)
	At least one event leading to discontinuation of investigational product	1 (4.8%)	4 (19.0%)	14.3% (-6.6%, 36.2%)
	At least one event leading to dose interruption	1 (4.8%)	2 (9.5%)	4.8% (-14.6%, 25.0%)
	At least one event of special interest	7 (33.3%)	11 (52.4%)	19.0% (-10.7%, 45.7%)

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] The 95% CI of the percentage difference based on the Miettinen and Nurminen's score method.

Sex (male vs female):

Table 48 Overall summary of treatment emergent adverse events (randomized-controlled period) by subgroup, safety analysis set

Subgroup	Subject[a] With	Placebo N=67	Inebilizumab N=68	Risk Difference (95% CI)[d]
Sex				
Female		18	29	NA
	At least one event	18 (100%)	28 (96.6%)	-3.4% (-17.2%, 14.4%)
	At least one investigational product related event	3 (16.7%)	11 (37.9%)	21.3% (-6.1%, 43.7%)
	At least one event of ≥ grade 3 severity[b]	2 (11.1%)	3 (10.3%)	-0.8% (-23.9%, 17.7%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	2 (11.1%)	6 (20.7%)	9.6% (-14.9%, 30.0%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	2 (11.1%)	6 (20.7%)	9.6% (-14.9%, 30.0%)
	At least one investigational product related serious[c] event	0	1 (3.4%)	3.4% (-14.4%, 17.2%)
	At least one event leading to discontinuation of investigational product	1 (5.6%)	2 (6.9%)	1.3% (-19.7%, 17.5%)
	At least one event leading to dose interruption	0	0	NA
	At least one event of special interest	3 (16.7%)	7 (24.1%)	7.5% (-18.5%, 29.5%)
Male		49	39	NA
	At least one event	48 (98.0%)	38 (97.4%)	-0.5% (-11.4%, 8.4%)
	At least one investigational product related event	13 (26.5%)	17 (43.6%)	17.1% (-2.9%, 36.2%)
	At least one event of ≥ grade 3 severity[b]	6 (12.2%)	9 (23.1%)	10.8% (-5.1%, 27.9%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	4 (8.2%)	6 (15.4%)	7.2% (-6.5%, 22.7%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	8 (16.3%)	11 (28.2%)	11.9% (-5.4%, 29.8%)
	At least one investigational product related serious[c] event	0	1 (2.6%)	2.6% (-4.8%, 13.2%)
	At least one event leading to discontinuation of investigational product	2 (4.1%)	4 (10.3%)	6.2% (-5.1%, 20.1%)
	At least one event leading to dose interruption	1 (2.0%)	4 (10.3%)	8.2% (-1.9%, 21.8%)
	At least one event of special interest	12 (24.5%)	16 (41.0%)	16.5% (-3.0%, 35.6%)

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] The 95% CI of the percentage difference based on the Miettinen and Nurminen's score method.

Anti-drug antibody status at any time during RCP including baseline (positive vs negative):

Table 49 Overall summary of treatment emergent adverse events (randomized-controlled period) by subgroup, safety analysis set

Subgroup	Subject[a] With	Placebo N=67	Inebilizumab N=68	Risk Difference (95% CI)[d]
ADA status at any time during RCP				
Positive		7	16	NA
	At least one event	6 (85.7%)	16 (100%)	14.3% (-7.0%, 51.3%)
	At least one investigational product related event	0	6 (37.5%)	37.5% (-2.1%, 61.4%)
	At least one event of ≥ grade 3 severity[b]	0	4 (25.0%)	25.0% (-13.5%, 49.5%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	1 (14.3%)	6 (37.5%)	23.2% (-19.6%, 52.4%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	1 (14.3%)	7 (43.8%)	29.5% (-13.9%, 58.1%)
	At least one investigational product related serious[c] event	0	1 (6.3%)	6.3% (-30.0%, 28.3%)
	At least one event leading to discontinuation of investigational product	0	3 (18.8%)	18.8% (-19.1%, 43.0%)
	At least one event leading to dose interruption	0	1 (6.3%)	6.3% (-30.0%, 28.3%)
	At least one event of special interest	1 (14.3%)	6 (37.5%)	23.2% (-19.6%, 52.4%)
Negative		60	52	NA
	At least one event	60 (100%)	50 (96.2%)	-3.8% (-13.0%, 2.3%)
	At least one investigational product related event	16 (26.7%)	22 (42.3%)	15.6% (-1.9%, 32.6%)
	At least one event of ≥ grade 3 severity[b]	8 (13.3%)	8 (15.4%)	2.1% (-11.2%, 16.0%)
	Death (grade 5 severity[b])	0	0	NA
	At least one serious[c] event	5 (8.3%)	6 (11.5%)	3.2% (-8.4%, 15.8%)
	At least one serious[c] and/or ≥ grade 3 severity[b] event	9 (15.0%)	10 (19.2%)	4.2% (-9.9%, 18.9%)
	At least one investigational product related serious[c] event	0	1 (1.9%)	1.9% (-4.2%, 10.1%)
	At least one event leading to discontinuation of investigational product	3 (5.0%)	3 (5.8%)	0.8% (-8.8%, 11.3%)
	At least one event leading to dose interruption	1 (1.7%)	3 (5.8%)	4.1% (-3.8%, 14.2%)
	At least one event of special interest	14 (23.3%)	17 (32.7%)	9.4% (-7.2%, 25.9%)

[a] Subjects are counted once for each category regardless of the number of events.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).
[d] The 95% CI of the percentage difference based on the Miettinen and Nurminen's score method.

Further, there were no differences in safety profiles based on ADA status, based on a summary of TEAEs by system organ class and preferred term during the RCP based on ADA positive or ADA negative participants. Additionally, summaries of immunoglobulins (a safety marker) by ADA status in the RCP showed no differences.

No formal clinical studies have been conducted to investigate the effect of renal or hepatic impairment on inebilizumab. Subjects with mild to moderate decrease in glomerular filtration rate and mild to moderate hepatic impairment were included in inebilizumab clinical studies. Based on population pharmacokinetic analysis, inebilizumab clearance was comparable in IgG4-RD subjects with normal and mild/moderate impaired hepatic function and subjects with normal and mild/moderate impaired renal function.

Extrinsic Factors

The effect of region (US vs non-US; EU vs non-EU; Japan vs non-Japan; and Asia vs non-Asia) on the adverse event profile of inebilizumab was assessed by subgroup analyses of adverse events reported during the RCP in Study MITIGATE. No notable differences in adverse event profile were observed by region; small sample sizes in some subgroups (US [n= 7 in inebilizumab] vs non-US [n = 61 in inebilizumab]) limit the ability to draw definitive conclusions.

Use in Pregnancy and Lactation

Cumulatively through 10 June 2024, from all sources, there were 21 pregnancies reported in which patients were exposed to inebilizumab prior to or during pregnancy. These included a total of 6 pregnancies from study sources and 15 pregnancies from non-study sources. Cumulatively through 10 June 2024, there were no reports of infants receiving breast milk from mothers being treated with inebilizumab. Specifically, for Study MITIGATE, there were 2 reports of paternal drug exposure. The

female partner of a male subject became pregnant during the subject's treatment period. No adverse events were reported and the outcome of the pregnancy was unknown. The other subject was also a male whose female partner became pregnant. No adverse events were reported and the outcome of the pregnancy was also unknown. The subject's partner was lost to follow-up. There were no reports of female subjects exposed to inebilizumab prior to or during pregnancy in Study MITIGATE.

Inebilizumab is a humanized IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with the use of inebilizumab in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B cell depleting antibodies during pregnancy (Klink et al, 2008[34]). B-cell levels in infants following maternal exposure to inebilizumab have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown. Women of childbearing potential should use contraception while receiving inebilizumab and for 6 months after the last infusion of inebilizumab. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity: however, they have shown a B-cell depletion in the foetal livers of progeny.

Regarding use in lactation, there are no data on the presence of inebilizumab in human milk, the effects on a breastfed infant, or the effects on milk production. Human IgG is excreted in human milk, and the potential for absorption of inebilizumab to lead to B cell depletion in the breastfed infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for inebilizumab and any potential adverse effects on the breastfed infant from inebilizumab or from the underlying maternal condition.

Safety related to drug-drug interactions and other interactions

Formal drug-drug interaction studies have not been conducted for inebilizumab.

Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of inebilizumab, a humanized IgG1κ monoclonal antibody. The primary elimination pathway for inebilizumab is clearance by the reticuloendothelial system in the same way as that for an endogenous IgG. Therefore, the potential risk of pharmacokinetic interactions between inebilizumab and other drugs is low. Based on population analysis, commonly used small molecule drugs by subjects with IgG4-RD (prednisolone and methylprednisolone) had no effect on inebilizumab pharmacokinetics.

As with other B-cell depleting drugs, concomitant usage of inebilizumab and other immunosuppressant drugs may increase the risk of infection.

Discontinuation due to adverse events

During the RCP, 6 subjects (8.8%) in the inebilizumab group and 3 subjects (4.5%) in the placebo group experienced at least 1 event resulting in discontinuation. In the inebilizumab group, all events were reported for 1 subject (1.5%) each and included anaphylactic reaction, COVID-19 pneumonia, herpes zoster, anal cancer, malignant melanoma, pulmonary embolism, and deep vein thrombosis. In the placebo group, all events were reported for 1 subject (1.5%) each and included abdominal pain, swelling, and varicella zoster virus infection.

During the OLP, 5 subjects (10.9%) in the inebilizumab/inebilizumab group and 1 subject (2.3%) in the placebo/inebilizumab group experienced at least 1 event resulting in discontinuation. In the

[34] Klink, D. T., Van Elburg, R. M., Schreurs, M. W. J., & Van Well, G. T. J. (2008). Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. *Journal of Immunology Research*, *2008*(1), 271363.

inebilizumab/inebilizumab group, all events were reported for 1 subject (2.2%) each and included hypoglobulinaemia, drug induced liver injury, Dengue fever, prostate cancer, and organizing pneumonia. In the placebo/inebilizumab group, an IRR was reported for 1 subject (2.3%).

In the Any Inebilizumab group, 12 subjects (10.7%) experienced at least 1 event resulting in discontinuation. All events leading to withdrawal occurred in 1 subject each.

Post marketing experience

The first approval for marketing worldwide for inebilizumab was in the United States on 11 June 2020 for the indication of NMOSD. As of 10 June 2024, 38 countries have granted marketing approval for inebilizumab for NMOSD. Post marketing patient exposure estimates are based on unit sales data and converted to patient-time estimates. The estimated cumulative number of patient-years of exposure to inebilizumab for the sponsor regions (US, EU/European Economic Area, Switzerland, Canada and Brazil) was 2045 patient-years. The estimated cumulative number of patient-years of exposure to inebilizumab through 10 June 2024 for Japan, South Korea, and Taiwan was 464 patient years. The estimated cumulative number of patient-years of exposure to inebilizumab through 30 June 2024 for Hansoh territories (China) was 1931 patient years.

A cumulative summary of post-marketing adverse reactions that have been reported for inebilizumab up to 10 June 2024 was presented in the PBRER/PSUR covering the reporting period 11 December 2023 to 10 June 2024. These adverse reactions include serious and nonserious reactions from spontaneous sources (reports from health care professionals, consumers, scientific literature, and regulatory authorities) as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources. As of 10 June 2024, the MAH received cumulatively a total of 449 adverse drug reactions from medically confirmed and unconfirmed spontaneous sources of which 88 were serious adverse drug reactions and 361 were nonserious adverse drug reactions. During that same time frame, a total of 476 serious adverse reactions were received from noninterventional post-marketing sources. A review of the post-marketing data concluded that the overall benefit-risk balance of inebilizumab for its approved indication remains favourable.

Updated analysis of safety data provided during the procedure (data cutoff date of 15 August 2024)

In the Any Inebilizumab population, 119 subjects received 1 or more doses of inebilizumab. Exposure of inebilizumab ranged from 90 to 1393 days, with a mean duration of exposure of 581.4 days. A total of 107 subjects enrolled in the OLP phase of the study.

During the OLP, adverse events were reported in 48 subjects (85.7%) in the inebilizumab/inebilizumab group and 49 subjects (96.1%) in the placebo/inebilizumab group. Grade ≥ 3 adverse events were reported for 8 subjects (14.3%) in the inebilizumab/inebilizumab group and 7 subjects (13.7%) in the placebo/inebilizumab group. Serious adverse events were reported for 9 subjects (16.1%) in the inebilizumab/inebilizumab group and 10 subjects (19.6%) in the placebo/inebilizumab group. All of the serious adverse events in the OLP occurred in 1 subject each (1.8%) in the inebilizumab/inebilizumab group. No deaths were reported. In the inebilizumab/inebilizumab group, 7 subjects (12.5%) had at least 1 adverse event resulting in discontinuation of investigational product and 3 subjects (5.4%) had at least 1 adverse event leading to dose interruption. In the placebo/inebilizumab group, 4 subjects (7.8%) had at least 1 adverse event resulting in discontinuation of the investigational product, and 2 subjects (3.9%) had at least 1 adverse event leading to dose interruption.

In the OLP, the 3 most frequently reported adverse events by preferred term for the inebilizumab/inebilizumab treatment group and placebo/inebilizumab treatment group were

coronavirus disease 2019 (COVID-19) (16.1% and 19.6%, respectively), upper respiratory tract infection (12.5% and 15.7%, respectively), and influenza (5.4% and 9.8%, respectively).

No new cases of anaphylaxis were reported during the OLP.Additional IRRs were reported during the OLP for 4 subjects, including 1 grade 2 serious IRR.

- Serious adverse events of IRR and pulmonary embolism were reported in one subject on the same day of the fifth infusion of the investigational product in the OLP. The IRR occurred after 50 minutes of investigational product infusion, with sudden onset symptoms of wheezing, dyspnea with cough, oropharyngeal discomfort, and transient face erythema. On the same day, the subject was diagnosed with pulmonary embolism. The event outcome was reported as resolved for IRR and not resolved for pulmonary embolism. Investigational product infusion was permanently discontinued due to the IRR. Per investigators' assessment, IRR was grade 2 in severity and related to study investigational product; pulmonary embolism was grade 3 in severity and not related to study investigational product.

Two (2) additional subjects reported neutropenia and 1 additional subject reported lymphopenia.

Two (2) additional subjects reported opportunistic infections (herpes zoster and varicella zoster virus infection) and 3 additional subjects reported serious infections (haemophilus infection, pneumonia viral, pneumonia, and sepsis).

No clinically meaningful trends were identified in the average changes from baseline in haemoglobin, haematocrit, eosinophils, leukocytes, eosinophils/leukocytes (%), basophils, basophils/leukocytes (%), erythrocytes, mean corpuscular volume, and platelets.

No clinically meaningful trends were identified in change from baseline, post-baseline by worst CTCAE grade, and post-baseline shift by 2 or more grades for any serum chemistry parameters during the OLP.

No clinically meaningful trends were identified during the OLP in change from baseline for any urinalysis parameters and for immunoglobulins.

There were no clinically significant changes in vital signs in either treatment group during the study.

There were no new pregnancy exposure cases reported.

2.5.1. Discussion on clinical safety

The safety of inebilizumab is well known for the approved use for the treatment of NMOSD. In this submission, the patient population differed from the initial MAA and therefore, this assessment focused on the clinically significant differences in safety for patients with IgG4-RD compared to the known safety profile of inebilizumab in NMOSD patients.

Safety data

The safety assessment of inebilizumab in this submission was based on data from the RCT and the OLP of Study MITIGATE (data cut-off date 09 April 2024 for RCT and data cut-off date of 09 February 2024 for OLP). Overall, across the RCP and the OLP, 112 subjects received 1 or more doses of inebilizumab. The median duration of inebilizumab in the Any Inebilizumab population was 455.0 days and the median number of doses received was 4.0 doses. Nineteen subjects (17%) in the Any Inebilizumab population received inebilizumab for more than 2 years, and 63 subjects (56.3%) received inebilizumab for at least 1 year.

Despite the low prevalence of the disease (approximately 5.3 per 100 000), the safety database was considered small and did not fulfil the recommendations according to the Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95). Upon the CHMP's request, the MAH provided an updated interim analysis of available safety data with a data cutoff date of 15 August 2024. Overall, across the RCP and the OLP, 119 subjects received 1 or more doses of inebilizumab. The median duration of inebilizumab in the Any Inebilizumab population was 621.0 days and 35 subjects in the Any Inebilizumab population received inebilizumab for more than 2 years and 88 subjects received inebilizumab for at least 1 year. The safety profile of inebilizumab in the updated interim analysis provided during the procedure was consistent with the known safety profile of inebilizumab. The CHMP noted that further safety data for the treatment of IgG4 RD will be collected by the ongoing study MITIGATE until completion of the study.

Further, the Category 3 PASS Study 20230063, which is an ongoing real-world observational study of outcomes for patients with treated with inebilizumab in Europe will also include patients with IgG4 RD. The MAH committed to amend the protocol of the PASS Study 20230063 within 4 months from the CHMP opinion of the present variation application to include both NMOSD and IgG4-RD patients. The due date for completion of the study was extended to 2030 in the agreed RMP. In addition, post-marking safety data and routine pharmacovigilance activities were considered sufficient to further characterise the long-term safety profile of inebilizumab in patients with IgG4 RD.

Adverse events

The frequencies of the different categories of AEs (e.g. AEs, SAEs, Grade ≥3 AEs) in the study MITIGATE were similar to the observed frequencies in the initial MAA. However, AEs leading to discontinuations were reported more frequent in study MITIGATE. Discontinuations were assessed further below.

Common adverse events

The most common AEs were consistent with the known safety profile of inebilizumab. However, COVID-19 (23.5% for inebilizumab vs. 19.4% for placebo), pyrexia (8.8% for inebilizumab vs. 4.5% for placebo), myalgia (5.9% for inebilizumab vs. 0 for placebo), palpitations (5.9% for inebilizumab vs. 1.5% for placebo), dermatitis (4.4% for inebilizumab vs. 0 for placebo) and hypoaesthesia (4.4% for inebilizumab vs. 0 for placebo) were reported more frequently in the RCT in the inebilizumab group compared to placebo.

Pyrexia (frequency: common) and myalgia (frequency: common) have been added to the adverse reactions in the SmPC section 4.8 and palpitations were added to the description of infusion related reactions in the SmPC sections 4.4. and 4.8. This was endorsed by the CHMP.

The high frequency of COVID-19, reflected that the RCT were conducted during the global COVID-19 pandemic, hence, no product information update was made.

With regard to dermatitis, 3 cases were reported in inebilizumab-treated patients. All cases were assessed as not related by the investigator, had varying time to onset and non-specific nature. Therefore, dermatitis was not considered an adverse drug reaction.

Hypoaesthesia was reported in 3 inebilizumab-treated patients. One of the events occurred on Day 2, following the Day 1 dose of inebilizumab, and was assessed by the investigator as related to inebilizumab. Given the short time to onset and the causality assessment, this event could represent an infusion-related reaction to inebilizumab. The two other events were assessed as not related by the Investigator and both events had alternative etiologies. Based on the provided data, hypoaesthesia was not considered an adverse drug reaction.

Adverse Events by Severity

The percentages of participants with mild, moderate and severe events were overall similar between the inebilizumab and placebo groups. Two participants in the inebilizumab group experienced a life-threatening event (anal cancer in one participant and pulmonary embolism and deep vein thrombosis in another participant). Both events were considered not related to inebilizumab assessed by the investigator. This was agreed by the CHMP, due to relevant comorbidities.

During the OLP, the proportion of participants with mild and severe AEs were overall similar between the groups. Moderate AEs were more frequent in the placebo/inebilizumab group compared to the inebilizumab/inebilizumab group (34.8% vs. 47.7%), reflecting the change from placebo to inebilizumab. One participant in the placebo/inebilizumab group experienced a life-threatening IRR, which was related to the study drug as assessed by the investigator. This event was assessed under *Adverse Events of Special Interest*.

Serious Adverse Events

Serious adverse events were reported for 17.6% of participants in the inebilizumab group and 9.0% of participants in the placebo group during the RCP. No serious adverse event occurred in more than 1 participant. Serious infections and infestations were reported for 4 participants in the inebilizumab group and were assessed under *Adverse Events of Special Interest*.

During the OLP, serious adverse events occurred in 15.2% of participants in the inebilizumab/inebilizumab group and 15.9% of participants in the placebo/inebilizumab group.

Serious adverse events occurred in 22.3% of participants in the Any Inebilizumab group. Serious adverse events that occurred in > 1 participant were COVID-19 pneumonia and pneumonia (2 participants each). All other serious adverse events occurred in 1 participant.

No deaths were reported during the study.

Overall, the SAEs reported did not raise new safety concerns.

Adverse Events of Special Interest

Anaphylaxis and Serious Hypersensitivity Reactions

One serious anaphylactic reaction was reported during the RCT in the inebilizumab group. Since the participant did not receive the full dose of prophylactic treatment of corticosteroids, no update of the product information on anaphylactic reactions was needed.

Infusion-related Reactions (IRRs)

During the RCP, IRR were reported in 5 participants (7.4%) in the inebilizumab group and 10 participants (14.9%) in the placebo group. 2 participants (2.9%) in the inebilizumab group reported palpitations. As stated above, palpitations have been included in the description of Infusion-related reactions in the SmPC sections 4.4 and 4.8. This was endorsed by the CHMP.

There was one grade 4 (life-threatening) IRR reported during the OLP. Symptoms of the serious IRR occurred at the end of the first inebilizumab infusion during the OLP, including bronchospasm, bradycardia, and decreased blood oxygen saturation. The subject was hospitalized and received treatment of hydrocortisone, chlorphenamine, and methylprednisolone. The IRR resolved and inebilizumab was permanently discontinued. The event was assessed as related to study drug by the investigator. Information about pre-medication and serious infusion reactions is already included in the SmPC sections 4.2 and 4.4. and infusion reactions was already an important identified risk in the RMP. No further measures were deemed necessary to further mitigate this risk. In order to align with the

preferred term of Infusion-related reaction, the important identified *risk infusion reaction* was renamed to *infusion-related reactions* in the agreed RMP.

Cytopenia

During the RCP, cytopenia was reported for 25.0% of participants in the inebilizumab group and 16.4% of participants in the placebo group. In the Any Inebilizumab group, cytopenia was reported for 18.8% of participants. The most frequently reported cytopenia was lymphopenia, followed by neutropenia. The majority of cytopenia events were mild or moderate in severity and no serious cytopenia was reported and no association was seen between lymphopenia and/or neutropenia and serious infections based on case reviews.

The reported frequencies for lymphopenia and neutropenia in Study MITIGATE was higher than the frequencies in NMOSD participants. This difference could be attributed to high background corticosteroid use and COVID-19 infections. Neutropenia was adequately described in the SmPC section 4.8. The frequency of the adverse reaction lymphopenia was updated from common to very common in SmPC Section 4.8.

Serious and/or Opportunistic Infections

Common infections were similar in both studies, but serious infections were reported at a higher frequency in Study MITIGATE compared to the study in NMOSD patients. The difference could be attributed to COVID-19.

Opportunistic infections were reported for 2 participants (2.9%) in the inebilizumab group and 1 participant (1.5%) in the placebo group during the RCP. Serious infections were reported for 4 participants (5.9%) in the inebilizumab group and no participants in the placebo group. All reported opportunistic infections were non-serious herpes zoster infections. Opportunistic infections were balanced between inebilizumab and placebo groups of Study MITIGATE, no opportunistic infections were reported in the study with NMOSD patients. Herpes zoster is already listed as an adverse reaction in the SmPC section 4.8.

In the Any Inebilizumab group, opportunistic infections were reported for 3 participants (2.7%) and serious infections were reported for 9 participants (8.0%). All 3 opportunistic infections were grade 1 or grade 2 non-serious herpes zoster infections. All serious infections were reported by single participants except for COVID-19 pneumonia and pneumonia, which were reported by 2 participants each. One COVID-19 pneumonia and dengue fever resulted in permanent discontinuation of study treatment.

The important potential risk of Serious infections, viral reactivation, and opportunistic infections was therefore updated in the agreed RMP, as follows:

- Infections, including serious infections was listed as an important identified risk.
- Viral reactivation and opportunistic infections remained an important potential risk.

Furthermore, neutropenia, previously identified as an important identified risk, was removed from the list of safety concerns in the RMP since it was included within the risk of infections now classified as an important identified risk. The risk of neutropenia will be followed in the PSURs.

No subject reported PML.

Overall, no new safety concerns further to the palpitations related to IRRs were found based on the AESI evaluation.

Immune complex disease was also an AESI in the study. No events related to immune complex disease were identified or reported during the study.

Laboratory findings

Hematology

Overall, lymphocyte counts were lower in the inebilizumab group than the placebo group during the RCP, which is consistent with the mechanism of action of the drug. With longer-term exposure at week 52 in the RCT and during the OLP, the lymphocyte levels trended back to the baseline level.

Neutrophil levels were elevated in both treatment groups at Weeks 2, likely reflecting an effect from corticosteroids. Neutrophil levels started decreasing at week 8. Mean percent change reduction from baseline at week 52 in neutrophil levels was similar between the treatment groups. During the OLP, there was no trend for neutrophil counts.

The increased risk of infections associated with neutropenia and lymphopenia was already reflected in the SmPC sections 4.4 and 4.8.

Immunoglobulins

In the study in IgG4 RD patients, immunoglobulin levels decreased with inebilizumab use. A greater reduction from baseline was seen compared to the reduction seen in NMOSD patients. This observation was probably due to the longer duration of the study in IgG4 RD patients. The decrease in serum immunoglobins was a concern at the time of the initial MAA, as it may over time lead to increased risk of serious and/or opportunistic infections. As a consequence, warnings on the risk of infections relating to decreased levels of immunoglobulins were included in section 4.4 of the SmPC, and monitoring of quantitative serum immunoglobulins is also detailed in section 4.2 of the SmPC and are also adequate to the IgG4 RD indication.

Overall, the observed laboratory parameters, vital sign and ECG abnormalities did not raise any new safety concerns.

Safety in special populations

Subgroup analyses did not show any clinically relevant difference in AE incidence by age, sex, anti-drug antibody status or geographic region, except for more severe and serious events in patients ≥65 (33.3% and 38.1%) compared to patients <65 (10.6% and 8.5%). However, the small numbers of subjects within certain subgroups limit interpretation of the comparisons. Safety in patients >65 years was already listed as missing information in the RMP.

Renal and hepatic impairment has not been formally studied for inebilizumab. However, dose adjustment based on renal or hepatic function was not warranted because Ig G monoclonal antibodies are not primarily cleared via renal or hepatic pathways.

In the RMP, the rewording of the current missing information "Use in pregnancy and lactation" as "Use in pregnancy and breastfeeding" was agreed.

Drug-drug interactions

Concomitant usage of inebilizumab and other immunosuppressant drugs may increase the risk of infections. Patients concomitantly receiving other immunosuppressive agents was already included as missing information in the safety concerns in the RMP.

Discontinuations due to adverse events

AEs for which the treatment were discontinued (8.8% in the inebilizumab group) were reported more frequently in study MITIGATE during the RCP compared to the study in NMOSD patients (1.1% in the inebilizumab group).

During the OLP, 5 participants (10.9%) in the inebilizumab/inebilizumab group and 1 participant (2.3%) in the placebo/inebilizumab group experienced AEs resulting in discontinuation. All events were reported for one participant each. Hence, no concern was raised.

Post marketing experience

The post-marketing safety data were in line with the known safety profile. No conclusions could be drawn on the serious adverse events due to the limited data. No new safety concerns were raised.

2.5.2. Conclusions on clinical safety

The available safety data from the study MITIGATE in patients with IgG4 RD was consistent with the known safety profile for inebilizumab in NMOSD patients. Pyrexia (frequency: common) and myalgia (frequency: common) were added as adverse reactions in the SmPC section 4.8. Serious infections were reported at a higher frequency in Study MITGATE compared to the study in NMOSD patients. Therefore, infections, including serious infections was listed as an important identified risk in the RMP. Viral reactivation and opportunistic infections remained an important potential risk in the RMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 is acceptable.

Safety concerns

Important identified risks	• Infusion-related reactions • Infections, including serious infections
Important potential risks	• Viral reactivation and opportunistic infections • Progressive multifocal leukoencephalopathy (PML) • Malignancy • Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women
Missing information	• Safety in patients ≥ 65 years • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20230064 (Previously VIB0551.P4.S4) An Observational Pregnancy Safety Study in Women with NMOSD Exposed to UPLIZNA (NMOSD Indication) Ongoing	The registry is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The specific objectives are: • To assess pregnancy and birth outcomes in female patients with neuromyelitis optica spectrum disorder (NMOSD), exposed to inebilizumab commercial product (UPLIZNA) during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception • To describe major congenital malformations, minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA	• Use in pregnancy and breastfeeding • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Protocol submission Interim study report Final report	October 2021 July 2026 July 2033
Study 20257092 (Previously VB-4149) CorEvitas SPHERES (Synergy of Prospective Health & Experimental Research for Emerging Solutions) Registry for Neuromyelitis	To prospectively study the natural history of NMOSD and the comparative effectiveness and comparative safety of approved and off-label medications used in the treatment of NMOSD, as well as to systematically evaluate the burden for patients with this disease and to describe treatment utilization patterns. Adverse events of special interest (Targeted Events) including the important risks and missing information such	• Infusion-related reactions • Infections, including serious infections • Viral reactivation and opportunistic infections • PML • Malignancy • Blood disorders particularly decrease in B-cell levels in fetal and newborns exposed	First Patient In Final study report	June 2021 December 2028

Optica Spectrum Disorder (NMOSD) (NMOSD Indication) Ongoing	as serious infections, malignancies, severe hypersensitivity reactions/anaphylaxis, and pregnancy will be evaluated	to inebilizumab in pregnant women • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years		
Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study of Outcomes for Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) and IgG4-related Disease (IgG4-RD) Treated With inebilizumab in Europe (NMOSD and IgG4-RD Indications) Ongoing	• Describe the characteristics (including demographics, disease burden, selected comorbidities and concomitant medication use) of patients with NMOSD and IgG4-RD who initiate treatment with inebilizumab • To assess treatment and drug utilization patterns of patients with NMOSD and IgG4-RD who initiate treatment with inebilizumab • Observe clinical and treatment outcomes by estimating the occurrence of events of interest including infusion related reactions, serious infections including PML, and malignancy	• Infusion-related reactions • Infections, including serious infections • Viral reactivation and opportunistic infections • PML • Malignancy • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	Protocol submission Final study report	March 2022 December 2030

Study 20230115 (Previously HZNP-UPL-401) A safety study of NMOSD patients receiving inebilizumab following closure of the open-label period N-MOMENTUM Study (NMOSD Indication) Ongoing	• To understand the long-term effects of inebilizumab • To assess specific safety, laboratory, and other measures in patients with NMOSD, during long-term treatment with inebilizumab and following its discontinuation	• Infusion-related reactions • Infections, including serious infections • Viral reactivation, and opportunistic infections • PML • Malignancy • Use in pregnancy and breastfeeding • Patients concomitantly receiving other immunosuppressive agents • Safety in patients ≥ 65 years	Protocol submission Final study report	March 2022 August 2028

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Infusion-related reactions	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.8, Section 5.1. • PL Section 2 and Section 4. • Recommendation to receive treatment under the supervision of a physician experienced with NMOSD or IgG4-RD and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions is provided in SmPC Section 4.2 • Recommendations to use prophylaxis medications (corticosteroid, antihistamine, and antipyretic) prior to each inebilizumab infusion is provided in SmPC Section 4.2 and 4.4. • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. • Legal status: prescription only. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Infections, including serious infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8. • PL Section 2 and Section 4. • Recommendation to obtain a recent (ie, within 6 months) complete blood count including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment is provided in SmPC Section 4.2 and Section 4.4. • Recommendations for treatment discontinuation in the case of serious infections and recurrent infections are included in SmPC Section 4.4. Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Important Potential Risks		

Viral reactivation and opportunistic infections	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, and 4.8. • PL Section 2 and Section 4. • Recommendation to obtain a recent (ie, within 6 months) complete blood count including differentials and immunoglobulins before initiation of inebilizumab and periodically during treatment and after discontinuation until B-cell repletion and to determine if there is a clinically significant infection prior to treatment is provided in SmPC Section 4.2 and Section 4.4. • Recommendations for HBV screening and evaluation for active tuberculosis and test for latent infection before administration of inebilizumab are included in SmPC Section 4.2. • Recommendations for treatment discontinuation in the case of serious opportunistic infection are included in SmPC Section 4.4. • Clinical setting: IV product that can only be administered in an infusion centre or hospital setting. • Legal status: prescription only. Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Progressive Multifocal Leukoencephalopathy	Routine risk minimization measures: • SmPC Section 4.3 and 4.4 • PL Sections 2, and 4 • Recommendations to evaluate further at the first sign or symptom suggestive of PML, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JCV DNA, with repeat neurological assessments to be considered are included in SmPC Section 4.4. • Recommendations for treatment suspension if signs and symptoms of PML should occur and to discontinue treatment if PML is confirmed are included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting. • Legal status: prescription only. Additional risk minimization measures: • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Malignancy	Routine risk minimization measures: • SmPC Sections 4.3 and 4.4 • PL Section 2 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Blood disorders, particularly decrease in B-cell levels in fetal and newborns exposed to inebilizumab in pregnant women	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • Recommendations on monitoring newborns for B-cell depletion and to not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant are included in SmPC Section 4.4 and Section 4.6 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Recommendation to consider consulting with a qualified specialist to assess whether a protective immune response has been mounted is included in SmPC Section 4.4 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD indication)

Missing information		
Safety in patients ≥ 65 years	Routine risk minimization measures: • SmPC Sections 4.2 and 5.2 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)
Use in pregnancy and breastfeeding	Routine risk minimization measures: • SmPC Sections 4.4 and 4.6 • PL Section 2 • Recommendations that women of childbearing potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving inebilizumab during treatment and for 6 months after the last dose of treatment are included in SmPC Section 4.4 and Section 4.6 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • Study 20230064 (Previously VIB0551.P4.S4) Pregnancy Registry (NMOSD indication) • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

Patients concomitantly receiving other immunosuppressive agents	Routine risk minimization measures: • SmPC Sections 4.4 and 4.5 • PL Section 2 • Recommendations to consider the potential for increased immunosuppressive effects in the presence of concomitant immunosuppressive therapy are included in SmPC Section 4.4 and Section 4.5 • Clinical setting: IV product that can only be administered in an infusion centre or a hospital setting • Legal status: prescription only. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20257092 (Previously VB-4149) CorEvitas SPHERES (NMOSD indication) • Study 20230063 (Previously HZNP-UPL-402) Real-World Observational Study (NMOSD and IgG4-RD Indications) • Study 20230115 (Previously HZNP-UPL-401) Post-Authorization Safety Study (NMOSD indication)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Iceland.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The previously submitted report for user testing study conducted in NMOSD patients as adequate and applicable to support this new IgG4-RD indication, for bridging purposes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Immunoglobulin G4-related disease (IgG4-RD) is a rare, systemic, chronic immune-mediated relapsing disorder that can cause fibrosing inflammatory lesions in nearly any organ (Kamisawa, 2022[35]; Maehara et al, 2020[36]; Perugino and Stone, 2020[37]; Zhang and Stone, 2019[38]; Stone et al, 2012[39]).

3.1.2. Available therapies and unmet medical need

Patients with IgG4-RD are generally treated with immunosuppressive agents, in particular, GCs are considered the first line treatment for IgG4-RD.

Certain immunomodulatory agents have been used for steroid-sparing maintenance therapy in IgG4-RD. These include azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, tacrolimus, and cyclophosphamide (Khosroshahi et al, 2015[40]; reviewed in Lanzillotta et al, 2020[41]). However, the efficacy of these agents has not been rigorously evaluated in a double-blind, randomized, controlled study, and most studies have examined immunomodulatory agents in addition to GCs rather than as monotherapy (Omar et al, 2020[42]).

Surgery is also used, particularly in organs amenable to excision such as the pancreas, aorta, biliary ducts, and thyroid (Lee et al, 2019[21]), and some patients, particularly those with pancreatobiliary or renal disease, may require stenting for mechanical obstruction.

In conclusion, there is a high unmet medical need in IgG4-RD for steroid-sparing treatments for which clinically meaningful benefit and safety have been unambiguously demonstrated in randomized, controlled, double-blind studies.

3.1.3. Main clinical studies

Inebilizumab was evaluated in a single pivotal study, MITIGATE, a randomized, prospective, double blind, placebo-controlled, multi-centre, international study in patients with IgG4-RD. The study was ongoing at the time of submission. Data cut-off date for the RCT part of MITIGATE study was 09 April 2024; DLP for the OLP was 09 February 2024.

[35] Kamisawa, T. (2022). Immunoglobulin G4-related disease: a new systemic disease emerging in Japan. *JMA journal*, *5*(1), 23-35.
[36] Maehara, T., Moriyama, M., & Nakamura, S. (2020). Review of a novel disease entity, immunoglobulin G4-related disease. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, *46*(1), 3-11.
[37] Perugino, C. A., & Stone, J. H. (2020). IgG4-related disease: an update on pathophysiology and implications for clinical care. *Nature Reviews Rheumatology*, *16*(12), 702-714.
[38] Zhang, W., & Stone, J. H. (2019). Management of IgG4-related disease. *The Lancet Rheumatology*, *1*(1), e55-e65.
[39] Stone, J. H. (2012, November). IgG4-related disease: nomenclature, clinical features, and treatment. In *Seminars in diagnostic pathology* (Vol. 29, No. 4, pp. 177-190). WB Saunders.
[40] Khosroshahi, A., Wallace, Z. S., Crowe, J. L., Akamizu, T., Azumi, A., Carruthers, M. N., ... & Stone, J. H. (2015). International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis & rheumatology*, *67*(7), 1688-1699.
[41] Lanzillotta, M., Mancuso, G., & Della-Torre, E. (2020). Advances in the diagnosis and management of IgG4 related disease. *Bmj*, *369*.
[42] Omar, D., Chen, Y., Cong, Y., & Dong, L. (2020). Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta-analysis. *Rheumatology*, *59*(4), 718-726.

During the RCP, patients received either 300 mg inebilizumab or placebo IV on day 1, day 15, and week 26. A total of 135 patients were randomized (68 to inebilizumab and 67 to placebo).

During the OLP, patients received 300 mg inebilizumab IV on day 1, blinded 300 mg inebilizumab or placebo on day 15, then inebilizumab 300 mg IV every 6 months thereafter. With regards to inclusion/exclusion criteria, only adult patients with a clinical diagnosis of IgG4-RD according to the 2019 ACR/EULAR classification criteria were eligible. Also, the subjects were to be newly diagnosed or have had recent flare which require treatment. They should have been at high risk of recurrent flare and their IgG4-RD should have affected at least 2 organs/sites at any time in the course of IgG4-RD.

The primary endpoint was time to disease flare in IgG4-RD during 52-weeks.

The key secondary endpoints were:

1) Annualized flare rate for treated and AC-determined flares during the RCP

2) The proportion of subjects achieving flare-free, treatment-free complete remission at week 52

3) The proportion of subjects achieving flare-free, corticosteroid-free complete remission at week 52.

Complete remission was defined as either an IgG4-RD Responder Index (Wallace et al, 2018[43]) score of 0, **or** a determination by the investigator that no disease activity is present based on physical, laboratory, pathology, or other evidence.

3.2. Favourable effects

Inebilizumab demonstrated a significantly longer time to first treated and AC determined IgG4-RD flare. The median time to flare was 246 days in the placebo group and could not be estimated in the inebilizumab group due to the low flare rate in this treatment group during the RCT period of 52 weeks.

Also, inebilizumab statistically significantly reduced the risk of treated and AC-determined IgG4 RD flare during the RCP compared with placebo (HR 0.13 [95% CI: 0.06, 0.28; $p < 0.0001$]). A total of 7 subjects (10.3%) in the inebilizumab group and 40 subjects (59.7%) in the placebo group had at least 1 treated and AC determined IgG4-RD flare during the RCP.

After multiplicity adjustment, all three key secondary endpoints met statistical significance. The annualized flare rate for treated and AC-determined IgG4 RD flares during the RCP was 0.71 in the placebo group and 0.1 in the inebilizumab group (Rate ratio 0.14 [95% CI of ratio: 0.06, 0.31; $p < 0.0001$]). A greater proportion of subjects in the inebilizumab group achieved flare-free, treatment-free complete remission (Odds ratio 4.68 [95% CI of ratio: 2.21, 9.91; $p < 0.0001$]) and flare-free, corticosteroid-free complete remission (Odds ratio 4.96 [95% CI of ratio: 2.34, 10.52; $p < 0.0001$]) at week 52 compared with placebo.

The MAH sought initially the following indication: *treatment of adult patients with IgG4-RD*. At the time of randomisation, all patients had recent or ongoing flare requiring glucocorticoid treatment. Hence, the therapeutic indication was revised in line with the studied population of *adult patients with active IgG4-RD.*

The mean (SD) total GC use per subject for IgG4-RD disease control was significantly lower in the inebilizumab group compared with the placebo group.

[43] Wallace, Z. S., Khosroshahi, A., Carruthers, M. D., Perugino, C. A., Choi, H., Campochiaro, C., ... & Stone, J. H. (2018). An international multispecialty validation study of the IgG4-related disease responder index. *Arthritis care & research*, *70*(11), 1671-1678.

The OLP data supported a reduced risk of flares and GC-sparing effect of inebilizumab in the MITIGATE study population.

3.3. Uncertainties and limitations about favourable effects

Efficacy of inebilizumab for IgG4-RD was studied in one pivotal study (MITIGATE). However, the CHMP agreed that the results of the MITIGATE study were sufficiently compelling to support the extension of indication in patients with active IgG4-related disease, taking into account the points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99).

In general, the series of endpoints designated as "exploratory" (Ig-levels, ELF score, PROs, PAG) suggested no treatment effect of inebilizumab vs placebo on IgG4-RD. *Post hoc* analyses supported the efficacy of inebilizumab in IgG4-RD both in patients with a high and a low number of organs involved and both in patients with and without involvement of organs which are associated with a particular fibrotic phenotype. The study MITIGATE did not provide sufficient data supporting a treatment effect on the fibrotic component of IgG4-RD. SmPC section 5.1 was updated in accordance with the indicated population of patients with active IgG4-RD.

Data available for treatment beyond 1 year were limited. This was adequately reflected in the SmPC section 4.2 so that treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

3.4. Unfavourable effects

The profile of inebilizumab was consistent with its mechanism of action (anti-CD19 monoclonal antibody leading to B-cell depletion) with reported cases of infusion-related reactions, infections, neutropenia, lymphopenia and decreases in immunoglobulins.

The most common AEs were consistent with the known safety profile of inebilizumab. However, COVID-19, pyrexia, myalgia, palpitations, dermatitis and hypoaesthesia were reported more frequent in the RCT in the inebilizumab group compared to placebo. Pyrexia (frequency common) and myalgia (frequency common) were added to the adverse reactions in the SmPC section 4.8 and palpitations added to the description of infusion related reactions in the SmPC sections 4.4. and 4.8. The high frequency of COVID-19, reflect that the RCT were conducted during the global COVID-19 pandemic, hence no product information update was needed.

Two participants (2.9%) in the inebilizumab group experienced a life-threatening event (anal cancer in one participant and pulmonary embolism and deep vein thrombosis in another participant).

Serious adverse events were reported for 17.6% of participants in the inebilizumab group and 9.0% of participants in the placebo group during the RCP. No serious adverse event occurred in more than 1 participant.

No deaths were reported during the study.

Opportunistic infections were reported for 2 participants (2.9%) in the inebilizumab group and 1 participant (1.5%) in the placebo group during the RCP. Serious infections were reported for 4 participants (5.9%) in the inebilizumab group and no participants in the placebo group. All reported opportunistic infections were non-serious, grade 1 or grade 2 herpes zoster.

Since inebilizumab is intended for chronic administration and considering that neutropenia, lymphopenia and decreases in immunoglobulin (consistent with the mechanism of action of inebilizumab) were common during the study and previous study in NMODS, a risk of infections

(including opportunistic infections) cannot be excluded for patients receiving long-term treatment. A section is included in SmPC section 4.4 about infections. Serious infections were reported at a higher frequency in Study MITIGATE compared to the study in NMOSD patients. Therefore, infections, including serious infections was listed as an important identified risk in the RMP. Viral reactivation and opportunistic infections remained an important potential risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

The main safety database consisted of a total of 112 subjects receiving 1 or more doses of inebilizumab, 19 subjects received inebilizumab for more than 2 years and 63 subjects received inebilizumab for at least 1 year. This was not considered sufficient since inebilizumab is intended to be used as a chronic therapy for IgG4 RD. Upon the CHMP's request, an updated interim analysis was provided during the procedure, the safety profile was consistent with the known safety profile of inebilizumab. The CHMP noted that safety data for the treatment of IgG4 RD will be collected by the ongoing study MITIGATE until completion of the study. Further, the Category 3 PASS Study 20230063, which is an ongoing real-world observational study of outcomes for patients with treated with inebilizumab in Europe will also include patients with IgG4 RD. Finally, the CHMP concluded that post-marking safety data and routine pharmacovigilance activities would be sufficient to further characterise the long-term safety profile of inebilizumab in patients with IgG4 RD.

Due to a death of probable PML in the previous NMODS study, the SmPC includes a section for PML in SmPC section 4.4. and PML was already included in the RMP as an important potential risk. There were no reports of PML in study MITIGATE.

Given the limited long-term safety data at current stage, the potential impact of treatment with inebilizumab on the development of malignancies is unknown. A section is already included in SmPC section 4.4 and malignancy was already included as an important potential risk in the RMP.

Subgroup analyses showed differences in the incidence of severe and serious events in patients ≥65 (33.3% and 38.1%) compared to patients <65 (10.6% and 8.5%). However, the small numbers of subjects limited interpretation of the comparisons. Safety in patients >65 years was already listed as missing information in the RMP.

There was missing information regarding the safety in patients concomitantly receiving other immunosuppressive medications and in pregnant or lactating women. Specific sections are already included in the SmPC section 4.4. and 4.5. and these groups were already included as missing information in the RMP.

3.6. Effects Table

Table 50 Effects Table for Uplizna for IgG4-RD (Study is still ongoing). Data cutoff date for the primary analysis: 09 April 2024 for the RCP and 09 February 2024 for the OLP

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			Inebilizumab (n=68)	Placebo (n=67)		
IgG4—RD flare	Time to first treated and AC-confirmed IgG4-RD flare	n (%)	7 (10.3%)	40 (59.7%)	**SoE**: Flares are adjudicated, Sens. Analyses consistent.	Study MITIGATE RCP

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	(PEP)				**Unc**: Impact on long-term outcome, i.e. both the inflammatory and the fibrotic component of the disease.	
	Hazard ratio (95% CI); p-value		0.13 (0.06;0.28); p<0.0001			
Complete remission	Proportion Of patients flare free and treatment free at W52	N (%)	40 (58.8%)	15 (22.4%)	**SoE**: hierarchy tested **Unc**: Whether the Complete Remission effect-size is a clinically important difference when the RI criteria is optional. Ref. definition in the study protocol.	
Unfavourable Effects						
Infections	-	%	75.0	53.7	Important identified risk	Study MITIGATE RCP
Serious infections	-	%	5.9	0	Important identified risk	
Opportunistic infections	-	%	2.9	1.5	Important potential risk due to neutropenia, lymphopenia and immunoglobulin decrease	
Infusion related reaction	-	%	7.4	14.9	Important identified risk	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

IgG4-RD is a fibroinflammatory disease associated with an increased risk of death. Nearly any organ can be affected by IgG4-RD. The goal of treatment in IgG4-RD is to reduce disease activity and prevent irreversible damage. There are currently no approved medicinal products for the treatment of IgG4-RD.

The single pivotal study in adult patients with active IgG4-RD who are diagnosed in accordance with the 2019 ACR/EULAR classification criteria, showed that inebilizumab is glucocorticoid-sparing and reduces the risk of flares.

The safety profile of inebilizumab in patients with IgG4-RD was consistent with its mechanism of action (anti-CD19 monoclonal antibody leading to B-cell depletion) with reported cases of infusion-related reactions, infections, neutropenia, lymphopenia and decreases in immunoglobulins. The CHMP noted the limited safety database, however, post-marking safety data and routine pharmacovigilance activities were considered sufficient to further characterise the long-term safety profile of inebilizumab in patients with IgG4 RD. There are important identified risks (Infusion-related reactions and infections, including serious infections) and important potential risks (viral reactivation and opportunistic infections, PML and malignancy) with inebilizumab therapy which are considered sufficiently minimised with the information include in the SmPC and package leaflet, the educational programme and the patient card. Further, these risks will be further characterised via routine and additional pharmacovigilance activities. The ongoing Category 3 PASS, which is a real-world observational study of outcomes for patients with treated with inebilizumab in Europe will also include patients with IgG4 RD.

3.7.2. Balance of benefits and risks

A benefit of inebilizumab for the treatment of IgG4-RD flare was shown in adult patients with active IgG4-RD. Inebilizumab was glucocorticoid-sparing and reduced the risk of flares. Efficacy was shown in patients with defined by clinical, imaging, laboratory or biopsy features, and requiring treatment in the judgement of the physician. These patients had newly diagnosed or recurrent IgG4-RD that required GC treatment at screening, had a confirmed history of organ involvement at any time in the course of the disease, and met the 2019 ACR/EULAR classification criteria. The study MITIGATE did not provide sufficient data supporting a treatment effect on the fibrotic component of IgG4-RD. The safety profile of inebilizumab was consistent with its mechanism of action and the known safety profile in NMODS patients. The important identified and potential risks are considered manageable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Uplizna is positive for the treatment of adult patients with active IgG4-RD.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with active Immunoglobulin G4-Related

Disease (IgG4-RD) for Uplizna, based on the results from study MITIGATE. This is a pivotal phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab in adult subjects with IgG4-RD. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 2.2 of the RMP is agreed. In addition, the MAH took the opportunity to introduce editorial changes to the PI. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Iceland.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Uplizna-H-C-5818-II-0012'