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PLATFORM

Clinical Trial Protocol CCFZ533H12201BC

A randomized, subject and investigator blinded, placebo-controlled and multi-center platform study, to assess efficacy and safety of different investigational drugs in patients with moderate to severe hidradenitis suppurativa

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

A	Abscesses
AD	atopic dermatitis
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIH	autoimmune hepatitis
ALOX5/5-LO	Arachidonate 5-lipoxygenase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN	Abscess and inflammatory nodule counts
aPTT	activated Partial Thromboplastin Time
AST	aspartate aminotransferase
AxMP	Auxiliary Medicinal Product
BAFF(-R)	B cell activating factor (receptor)
BCRP	Breast cancer resistance protein (also known as ABCG2) drug transporter
BDR	Bioanalytical Data Report
b.i.d.	twice a day
BMX	Bone Marrow kinase gene on the X chromosome
BTK(i)	Bruton's tyrosine kinase (inhibitor)
BUN	blood urea nitrogen
CD40 (L)	Cluster of differentiation 40 (ligand)
CDC	complement dependent cytotoxicity
CFR	U.S. Code of Federal Regulation
CL	Clearance
cm	Centimeter
CMV	Cytomegalovirus
CNS	central nervous system
COVID-19	Corona virus disease 2019
(e)CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CS	Corticosteroid
CSF	cerebro-spinal fluid
CSU	Chronic Spontaneous Urticaria
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CXCL	Chemokine (C-X-C motif) ligand
DAMPs	Damage Associated Molecular Patterns
DDE	Direct Digital Entry
dL	Deciliter
CCI	[redacted]

DMC	Data Monitoring Committee
DNA	Deoxy-ribonucleic acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
ePPND	enhanced pre-and postnatal development
eSource	Electronic Source
ESSDAI	EULAR Sjögren's syndrome disease activity index
EU CTR	European Union Clinical Trial Regulation 536/2014
F	Draining fistulae
Fc	Fragment crystallizable
FcεR1	Fc epsilon receptor 1, high-affinity receptor for the Fc region of immunoglobulin E
FcγR	Fc gamma receptor, receptor for the FC portion of Immunoglobulin G
FDA	Food and Drug Administration
FiH	First in human
GCP	Good Clinical Practice
(e)GFR	(estimated) Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GROα	Growth regulated oncogen alpha
h	Hour
HbcAb	Hepatitis B core Antibody
HbsAg	Hepatitis B surface antigen
HDL	High Density Lipoprotein
HHV-6	Human Herpes Virus-6
HiSCR	Hidradenitis suppurativa clinical response
HIV	human immunodeficiency virus
HS	Hidradenitis suppurativa
hsCRP	High sensitivity C-reactive protein
CCI	[redacted]
HV	Healthy volunteers
Kg	Kilogram
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization (of Technical Requirements for Registration for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
IG	Immunogenicity
IgG(1)	immunoglobulin G (1)
IgM	Immunoglobulin M

CCI	[redacted]
IL-1ß/IL-1beta	Interleukin 1 beta
IL-18	Interleukin-18
IL-18BP	Interleukin-18 binding protein
INR	International Normalized Ratio
IP-10	Interferon-gamma inducible Protein-10
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITK	IL2-inducible T-cell kinase
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	Intravenous
L	Liter
LDL	Low Density Lipoprotein
LFT	Liver function test
LIVI	Liquid in Vial
LLOQ	lower limit of quantification
LTA4H	leukotriene A4 hydrolase
LTB4	Leukotriene B4
LXA4	Lipoxin A4
m^2	meters squared
mAb	monoclonal antibody
MCH	Mean Corpuscular Hemoglobin
MCII	minimal clinically important change
MCP-Mod	Dose-response modelling
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
µg	microgram(s)
mg	milligram(s)
min	Minute
mL	milliliter(s)
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
N	Inflammatory nodules
ng	nanogram(s)
nM	nanoMolar
NN	Non-inflammatory Nodules
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NRS	Numerical Rating Scale

NRS30	At least 30% reduction and at least 1 unit reduction from baseline in Skin Pain NRS
PAMP	Pathogen Associated Molecular Patterns
PCOS	Polycystic ovary syndrome
PD	pharmacodynamic(s)
CCI	[redacted]
PK	pharmacokinetic(s)
CCI	CCI [redacted]
PML	progressive multifocal leukoencephalopathy
p.o.	Oral
PoC	proof of concept
PRO	Patient Reported Outcome
pSS	primary Sjögren's Syndrome
PT	prothrombin time
CCI [redacted]	
RA	Rheumatoid arthritis
RCT	Randomized Clinical Trial
RNA	Ribonucleic Acid
s.c.	Subcutaneous
SAE	serious adverse event
CCI	[redacted]
sCr	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sHISCR	Simplified Hidradenitis Suppurativa Clinical Response
sIL2R	Serum soluble Interleukin-2 Receptor
SLE	Systemic lupus erythematosus
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TBNK	T and B Lymphocyte and Natural Killer
TEC	Tyrosine kinase Expressed in hepatocellular Carcinoma
TNFα	Tumor Necrosis Factor alpha
TXK	T and X cell expressed Kinase
UAS7	weekly urticaria activity score
ULN	upper limit of normal
WHO	World Health Organization

WoC	Withdrawal of Consent
WoCBP	women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Auxiliary medicinal product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess end-points in the clinical trial). Concomitant therapy is not considered as AxMP.
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. CCI once a day, CCI twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Flare	An exacerbation of a chronic disease. Sometimes referred to as a flare-up, a flare occurs when symptoms of a disease that has been present for a time suddenly worsen. A flare is a transient worsening in severity of a disease or condition that eventually subsides or lessens.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.

Amendment 10 (May 2024)

Amendment rationale

As of the 23 May 2024, this study has enrolled 229 patients, of which 45 were assigned to Cohort A, 40 to Cohort B, 43 to Cohort C, 77 to Cohort D and 24 to Cohort E. Last Patient Last Visit was achieved for Cohort A, B, C and D.

The main purpose of this amendment is to introduce the Auxiliary Medicinal Products (AxMP) definition and related safety reporting rules, to comply with EU Clinical Trial Regulation 536/2014 (EU CTR). In addition, clarifications on CCI sampling process and AE causality assessment were added.

Editorial changes have been made throughout the protocol for increased clarity and consistency.

Changes to the protocol

The following sections in the protocol were updated:

- Section 6.1.2, Additional Treatments: AxMP details Table 6-2 was added for predniso(lo)ne or equivalent
- Section 8, Visit Schedule and Assessments
  - Table 8-2, Table 8-3, Table 8-4, Table 8-5 and Table 8-6, Cohorts A to E, Schedule of Activities:
    - Inclusion/Exclusion Criteria documentation was clarified as recorded in the source (not eCRF)
  - Section 8.5.3.7, Exploratory CCI the site of collection and few more details were described more in details
- Section 10.1.1 Adverse Events: causality assessment was clarified and AE reporting was updated to include AxMP related text
- Section 10.1.3.2 Serious Adverse Events: SAE reporting requirements were updated to include AxMP related text

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IRBs/IECs

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

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

The changes herein do not affect the Informed Consent.

Amendment 9 (November 2023)

Amendment rationale

As of the 20 November 2023, this study has enrolled 205 patients, of which 45 were assigned to Cohort A, 40 to Cohort B, 43 to Cohort C and 77 to Cohort D. Last Patient Last Visit was achieved for Cohort A, B, C and D.

The main purpose of this amendment is to revise the exclusion criteria no. 30, specific to Cohort E. In error, the wash-out period was missing in exclusion criterion no. 30. This criterion has been deleted and content incorporated into exclusion criterion no. 2a. Additionally, further clarifications were added to exclusion criteria no. 2a and 3.

Other updates include revisions to align with the latest version of Investigator Brochure with a cut-off date of 24-Sep-2023. The number of patients exposed to ianalumab, the number of clinical trials conducted with ianalumab and the number of Covid-19 cases were updated. In addition, a summary statement on no observation of opportunistic infections was included.

The US FDA recommendations for expedited reporting of potential Hy's Law cases were also included in this amendment.

Editorial changes have been made throughout the protocol for increased clarity and consistency.

Changes to the protocol

The following sections in the protocol were updated:

- Protocol summary: skin tape stripes assessment in Cohort E was deleted for consistency with the other sections of the protocol.
- Section 1.1.7 Ianalumab summary: the number of subjects that have been exposed to ianalumab and number of clinical studies with ianalumab were updated.
- Table 2-1 Objectives and related endpoints: CCI endpoint was added for Cohort E for consistency with the other sections of the protocol.
- Section 4.5.5.2 Potential risks associated with exposure to ianalumab: the information on number of Covid-19 cases was updated and a summary statement on no observation of opportunistic infections was included.
- Section 5.2 Exclusion criteria has been updated by deleting the exclusion criteria no. 30 and inserting its content into exclusion criteria no. 2a. Additionally, further clarifications were added to exclusion criteria no. 2a and 3.
- Table 8-6 Assessment Schedule, Cohort E: Ianalumab Treatment and Mandatory Follow-up periods was updated by adding a foot note to clarify that PK sample on Day 88 should be taken 3 days +/- 1 day after the dose on Day 85.
- Section 10.1.2 Serious adverse events and Table 16-2 were updated to comply with FDA requirement for expedited reporting of potential Hy's Law cases.
- Table 16-2 was updated with regards to appropriate CRFs to be used for recording of liver events.

Minor typographical errors have been corrected.

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IRBs/IECs

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The changes herein do not affect the Informed Consent.

Amendment 8 (July 2023)

Amendment rationale

As of the 12 June 2023, this study has enrolled 205 patients, of which 45 were assigned to Cohort A, 40 to Cohort B, 43 to Cohort C and 77 to Cohort D. Last Patient Last Visit was achieved for Cohort A, B, C and D.

The main purpose of this amendment is to update the dosage form for Cohort E (ianalumab) from pre-filled syringe to liquid in vials.

Other updates include revisions to update the number of patients exposed to ianalumab and the associated risks, additions to the eligibility criteria to further align with other ianalumab trials and an update to the statistics section reflecting that Cohort E will be the only ongoing cohort.

Changes to the protocol

Changes made to the protocol relating to change of drug supply for Cohort E (ianalumab):

- Protocol summary has been updated.
- Section 1.1.7 ianalumab summary has been updated.
- Section 4.5.5.2.1 and Section 4.5.5.2.2 has been updated to reflect the latest potential risks associated with exposure to ianalumab.
- Section 4.5.6.2: blood sample volume for cohort E has been updated.
- Section 5.2 has been updated to further align with other ianalumab protocols.
- Section 6.1.1 and Table 6.1 has been updated to reflect the dosage form that will be used.
- Table 6-2 has been updated to include iscalimab in the prohibited medications list for Cohort E.
- Table 8-10 laboratory assessments have been updated.
- Section 8.5.3.6 title updated.
- Section 9.1.1 has been updated to include a statement regarding patients that discontinue treatment should continue with follow up visits.
- Section 9.2 has been updated to clarify the wording regarding B cell recovery and study completion/post study treatment.
- Figure 12-1 updated for iscalimab and LYS006 cohorts.
- Section 13.4 Update of retention period.
- Section 16.2 Appendix 2: Renal event follow up and actions have been updated to align with the current Novartis template.

Minor typographical errors have been corrected.

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IRBs/IECs

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

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

Amendment 7 (March 2023)

Amendment rationale

As of the 8 February 2023, this study has enrolled 205 patients, of which 45 were assigned to Cohort A, 40 to Cohort B, 43 to Cohort C and 77 to Cohort D. Last Patient Last Visit was achieved for Cohort A, B and C and recruitment into Cohort D has now been completed.

The main purpose of this amendment is to introduce an additional cohort (Cohort E) into this platform study. Ianalumab (VAY736) is a human IgG1/κ mAb which targets the B cell activating factor BAFF receptor, (BAFF-R), expressed on the surface of immature and mature B cells up to the lymphoblast stage. Ianalumab has dual mechanisms of action: i) enhanced antibody dependent cellular cytotoxicity (ADCC) mediated B cell depletion and ii) blocking BAFF-mediated activation through the BAFF-R thereby inhibiting B cell activation, proliferation, maturation and survival.

The rationale for targeting BAFF-R in HS is based on the emerging role for both B cells and plasma cells both present in HS lesions and autoantibodies correlating with disease severity and duration. Little is known about the survival factors supporting the persistence of immune cells in HS but increased BAFF expression correlating with lesional B cell and plasma cell presence has recently been demonstrated.

CCI have been removed from the protocol due to limited uptake by sites (only a single site taking part) and subject interest of this optional assessment (zero out of five patients consented to this optional assessment). As there are fewer subjects required in Cohort E, it is unlikely that having this assessment in the protocol will yield any significant data.

Changes to the protocol

Changes made to the protocol relating to the addition of Cohort E (Ianalumab):

- Protocol summary has been updated.
- Updates have been made to Platform study design in Section 1.1.2
- Section 1.1.7 Ianalumab summary section has been created
- Updates have been made to the purpose in Section 1.2
- Objectives have been updated in Table 2-1 to include Cohort E
- Updated text and new study design Figure 3-3 for Cohort E have been added in Section 3
- Section 3.5 has been created for Cohort E describing the specifics of the cohort such as number of patients and dose levels used.
- Section 4.1 has been updated for Cohort E with respect to the clinical endpoints being evaluated
- Section 4.2.5 has been created describing the rationale for the dose/regimen and duration of treatment for Cohort E.
- Section 4.4 has been updated

- Section 4.5.5 and subsections Section 4.5.5.1 and Section 4.5.5.2 have been added to describe the risk and benefits of ianalumab
- Section 4.5.6.2 on Blood sample volume was updated for Cohort E
- Updates have been made to Section 5 incorporating Cohort E into the description of the population of the study
- Eligibility criteria have been updated for Cohort E in Section 5.1 and Section 5.2
- Section 6.1 and sub-sections Section 6.1.1, Section 6.1.2 and Section 6.1.3 have been updated to include Cohort E study treatment information.
- Update to Section 6.2 and sub-sections to link information about vaccinations to an early section in the protocol and state concomitant and prohibited medications.
- Cohort E has been added to the treatment assignment and randomization information in Section 6.3.2
- Treatment blinding information for Cohort E has been added to Section 6.4
- Treatment compliance information for Cohort E have been added Section 6.6.1
- Recommended treatment of adverse events for Cohort E have been added with the creation of Section 6.6.2.6
- Information on preparation and dispensation of ianalumab have been added to Section 6.7
- The assessment schedule for Cohort E (Table 8-1, Table 8-6 and Table 8-7) has been added to Section 8
- Update of Section 8.4.1 and subsection Section 8.4.1.2, together with Table 8-10 that has been updated to include analysis of TBNK panel, CD19 B cell count and B cell subset panel and additional test (IgG, IgM, sBAFF).
- Section 8.4.3 on Pregnancy and assessments of fertility was updated for Cohort E.
- Pharmacokinetic information for Cohort E has been added in Section 8.5.2.5
- Biomarker information has been added for Cohort E in Section 8.5.3 and all corresponding subsections
- Section 8.5.4 on Immunogenicity was updated for Cohort E
- Rules for discontinuation of study treatment has been updated to include Cohort E in Section 9.1.1
- Rules for putting Cohort E on hold have been added to Section 9.1.4
- Additional information regarding study completion and post study treatment has been added to Section 9.2
- Adverse event monitoring timeline has been updated to include Cohort E in Section 10.1.1
- Ianalumab has been added to data analysis and statistical methods in Section 12 and subsections.
- Rationale for pooling placebo data from Cohort E despite the use of prednisone/prednisolone has been added to Section 12.
- Section 12.6.3.5 has been added to include Cohort E PK analysis information

- Section 12.6.4.5 has been added to include Cohort E pharmacodynamic analysis information
- Exploratory biomarker information has been updated in Section 12.6.7 to add information regarding Cohort E
- Section 12.7 on Interim analyses has been updated
- Sample size information for the primary endpoint has been added to Section 12.8.1 for Cohort E

Other changes made to the protocol:

- List of abbreviations has been updated to add new abbreviations
- Removal of 'If additional cohorts are added, the Sponsor will strive to further limit the number of subjects exposed to placebo, based on the learnings from previous cohorts and / or published studies.' paragraph from Section 4.3.
- Clarification regarding AE analysis for infections (all cohorts) vs renal events (LYS006) in Section 12.5.2.1.
- CCI have been removed (previously Section 8.5.4 and Section 12.6.8.2.
- Section 12.7 on Interim analyses has been updated
- Section 15 has been updated to include all new and updated references

Minor typographical errors have been corrected.

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IRBs/IECs

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

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

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

Amendment 6 (June 2022)

Amendment rationale

As of the 03rd May 2022, this study has enrolled 128 patients, of which 45 were assigned to Cohort A, 40 to Cohort B and 43 to Cohort C. Last Patient Last Visit was achieved for Cohort A and B and recruitment into cohort C has now been completed.

The purpose of this amendment is to address comments raised by the Health Authority in Germany (PEI) on the study protocol amendment 5, pertaining to eligibility criteria and stratification planned for Cohort B. It is clarified that the group size of patients with 3-4 lesions is limited to 15 patients and that this stratification only applies for Cohort B. Indeed, the interim analysis showed that in terms of response to placebo, patients with lower severity as compared with higher severity had a similar response in the primary endpoint, the simplified HiSCR or sHiSCR. Thus, no further stratification is deemed needed for cohort D.

It has been re-emphasized that inclusion criterion providing disease severity definition by number of inflammatory lesions is unchanged between Cohort B and D as outlined in chapter 5.1. There is a difference of minimally required lesions counts between oral cohorts (at least 3 abscesses and/or nodules) and injectable biologics cohorts (at least 5 abscesses and / or nodules), that reflect that biologics are usually reserved for more severe patients, but still both populations have been considered as moderate to severe hidradenitis suppurativa (HS) (see Section 4.1. Rationale for study design).

The scientific rationale of the newly proposed cohort has been updated.

Changes to the protocol

- Purpose and rationale have been updated in Protocol summary section
- Section 3 has been modified to clarify overall eligibility criteria
- Section 4.5.4.1 has been modified to clarify and update the potential benefit of treatment with remibrutinib
- Absence of stratification for Cohort D has been clarified in Section 6.3.2
- Section 12.4: Primary objective of the study has been clarified
- References have been added in the references list Section 15

A minor typographical error has been corrected.

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IRBs/IECs

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

The non-substantial changes described in this amended protocol do NOT require IRB/IEC and Health Authority approval.

The changes herein do NOT affect the trial specific model ICF.

Amendment 5 (January 2022)

Amendment rationale

As of the 14th January 2022, this study is registered in 11 countries, ongoing in 10 countries and has enrolled 112 patients, of which 45 were assigned to Cohort A, 40 to Cohort B and 27 to Cohort C. Recruitment into both cohorts A and B have now been completed.

The purpose of this amendment is to add a blood sample for coagulation parameters to Cohort D, visits 101, 103, 105 and 199 for safety monitoring reasons. In cohort D, remibrutinib, A BTK inhibitor, will be tested and BTK is a signaling molecule in one of several platelet activation pathways. The blood volume is still within the previously communicated volume of approximately 200 mL for Cohort D.

In addition, after comments received from the US FDA, physical treatments, including photodynamic therapy, laser and intense light treatments will be considered prohibited treatment and a with a wash-out period of 4 weeks as part of exclusion criterion 2.6.

Changes to the protocol

- Inconsistency corrected in the protocol summary to ensure the highly effective contraception duration post treatment is consistent with the body of the protocol.
- Reference to prohibited physical treatments for HS added in Section 4.2.
- The title of Section 4.5.4.2.3 has been updated from ‘Bleeding risk’ to ‘Risk for bleeding’ in order to align with the wording in the IB.
- Exclusion criterion 2.6 in Section 5.2 has been updated from ‘Surgical treatment for HS in the last 4 weeks prior to randomization’ to ‘Surgical **and physical** treatment for HS in the last 4 weeks prior to randomization’.
- In Table 6-2 the row ‘Photodynamic therapy or laser therapy’ will be changed to ‘Physical treatment for HS, including laser, intense light and photodynamic therapy’ and will continue to lead to discontinuation of study treatment.
- IgA samples added to Table 8-5 Assessment Schedule, Cohort D: Remibrutinib along with hsCRP to be consistent with the text in the body of the protocol. No additional samples will be added to Cohort C as the enrolment will likely be concluded before this protocol is approved and there will be no baseline data.
- IgE samples will no longer be taken and the reference to this has been removed from the protocol in Table 8-8 Laboratory Assessments.
- Coagulation panel added to Table 8-5 Assessment Schedule, Cohort D: Remibrutinib at visits 101, 103, 105 and 199 (after 4 weeks and 12 weeks of treatment and at the end of the treatment period) for safety monitoring.
- Correction to footnote 5 in Table 8-5 Assessment Schedule, Cohort D: Remibrutinib. Fasting on PK days should be 12 hours as already indicated in Section 6.7.
- Addition of non-draining fistulas in Section 8.3.3.

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IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 4 (December 2021)

Amendment rationale

As of the 27th October 2021, this study is registered in 11 countries, ongoing in 10 countries and has enrolled 92 patients, of which 45 were assigned to Cohort A, 40 to Cohort B and 7 to Cohort C. Recruitment into both cohorts A and B have now been completed.

The main purpose of this amendment is to introduce an additional cohort (Cohort D) into this platform study. LOU064, also called remibrutinib, is an oral covalent binding Bruton's tyrosine kinase (BTK) inhibitor (or BTKi), currently in active clinical development for the treatment of chronic spontaneous urticaria (CSU), primary Sjögren's Syndrome (pSS) and multiple sclerosis (MS). BTK is in the central node in the Fc epsilon receptor 1, high-affinity receptor for the Fc region of immunoglobulin E (FcεR) as well as B cell receptor (BCR) signaling and thus could block B cell driven effects.

Recently B cells and more so, the BTK-pathway activation has been shown to be a central signal transduction network in hidradenitis suppurativa (HS) and thus provides a solid scientific rationale for testing a BTKi such as remibrutinib, in patients with HS (Gudjonsson et al 2020).

30 subjects will receive remibrutinib CCI mg CCI and 10 subjects will receive corresponding placebo in Cohort D, however unlike previous cohorts, an additional dose regimen of remibrutinib (CCI mg CCI.) will be evaluated in a further 30 subjects to explore a dose response relationship in patients with HS. In addition, selected exploratory objectives have been updated as below:

Changes to the protocol

Changes made to the protocol relating to the addition of Cohort D (remibrutinib):

- Updates have been made to Background in Section 1.1.1
- Section 1.1.6 Remibrutinib summary section has been created
- Updates have been made to the purpose in Section 1.2
- Objectives have been updated in Table 2-1 to include Cohort D and the Hidradenitis Suppurativa – CCI
- Updated text and new study design figure for Cohort D have been added in Section 3

- Section 3.4 has been created for Cohort D describing the specifics of the cohort such as number of patients and dose levels used.
- Section 4.1 has been updated with respect to the clinical endpoints being evaluated
- Section 4.2.4 has been created describing the rationale for the dose/regimen
- Additional information relevant to Cohort C has been added to Section 4.3 describing the number of placebo subjects needed for this cohort and the ratio of active to placebo subjects.
- Section 4.5.4 and subsections have been added to describe the risk and benefits of remibrutinib
- Updates have been made to Section 5 incorporating Cohort D into the description of the population of the study
- Eligibility criteria have been updated for Cohort D in Section 5.1 and Section 5.2
- Section 6.1 and sub-sections have been updated to include Cohort D study treatment information.
- Update to Section 6.2 and sub-sections to link information about vaccinations to an early section in the protocol and state concomitant and prohibited medications.
- Cohort D has been added to the treatment assignment and randomization information in Section 6.3.2
- Treatment blinding information for Cohort D has been added to Section 6.4
- Treatment compliance information for Cohort D have been added Section 6.6.1
- Recommended treatment of adverse events for Cohort D have been added with the creation of Section 6.6.2.5
- Information on preparation and dispensation of remibrutinib have been added to Section 6.7
- The assessment schedule for Cohort D (Table 8-5) has been added to Section 8
- Pharmacokinetic information for Cohort D has been added in Section 8.5.2.4
- Biomarker information has been added for Cohort D in Section 8.5.3 and subsections
- Rules for discontinuation of study treatment has been updated to include Cohort D in Section 9.1.1
- Rules for putting Cohort D on hold have been added to Section 9.1.4
- Adverse event monitoring timeline has been updated to include Cohort D in Section 10.1.1
- Remibrutinib has been added to data analysis and statistical methods in Section 12 and subsections.
- Section 12.6.3.4 has been added to include Cohort D PK analysis information
- Section 12.6.4.4 has been added to include Cohort D pharmacodymanic analysis information
- Exploratory biomarker information has been updated in Section 12.6.7 to add information regarding Cohort C

- Sample size information for the primary endpoint has been added to Section 12.8.1 for Cohort D

Other changes made to the protocol:

- List of abbreviations has been updated to add new abbreviations
- Updates have been made to the objectives in Table 2-1 to add additional biomarker objectives and additional objectives for lesion counts relating to abscesses and nodules.
- Section 4.5.4.2 has been deleted as the CCI sub-study has been stopped due to very low enrolment.
- Exclusion criterion 23 has been removed Section 5.2 due to the stopping of the CCI sub-study
- Clarification on how to proceed after a dose interruption has been added to Section 6.5
- Treatment compliance information formatting has been updated in Section 6.6.1
- The CCI assessments have been removed from Table 8-2 (Cohort A), Table 8-3 (Cohort B) and Table 8-4 (Cohort C)
- Additional information has been added to Section 8.3.1 regarding the review of reduction of abscesses and nodules.
- Table 8-8 has been updated to include analysis of IgA.
- Section 8.4.1.2 has been updated to clarify that CCI panel will be carried out on both on-site and at-home urine samples.
- Section 8.5.1.2 has been added to include the CCI into the study.
- Section 8.5.3.5 has been updated to include CCI assessments.
- Section 8.5.4.1 has been removed due to the cessation of the optional CCI assessments.
- Wording has been updated regarding reporting of SAEs in Section 10.1.3.2
- Section 12.6.8.2 has been deleted due to removal of optional CCI sub-study
- References section has been updated to include all new and updated references

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 3 (February 2021)

Amendment rationale

As of 17th February 2021, this study is ongoing in 10 countries and has enrolled 61 patients, of which 32 were assigned to Cohort A and 29 to Cohort B.

The main purpose of this amendment is to introduce an additional cohort (Cohort C) into this platform study, with MAS825, a CCI antibody targeting the key inflammasome effector cytokines interleukin-1 beta (IL-1ß) and interleukin-18 (IL-18). Kelly et al 2015 described that IL-1ß and IL-18 expression was increased in lesional and perilesional hidradenitis suppurativa (HS) skin, suggesting that the upregulation of both cytokines may play a role in the pathogenesis of HS. Tzanetakou et al 2016 has shown efficacy of interleukin-1 (IL-1) blockade in HS patients, as significant differences were noted between anakinra and placebo treated patients in the Hidradenitis suppurativa clinical response (HiSCR) and in HS exacerbations. Thus, MAS825 may show efficacy in HS patients and it is proposed to be added in Cohort C into this protocol.

In Cohort C, 30 subjects will receive MAS825 and 10 subjects placebo, a further reduced proportion of subjects exposed to placebo, as the placebo groups across cohorts will be pooled while maintaining the ability to have the treatments blinded within the same cohort. MAS825 is in early clinical development for the treatment of IL-1ß and IL-18 driven inflammatory diseases. A clinical proof of concept study has started in the treatment of COVID-19.

The protocol was also updated to remove unnecessary text which is detailed in other documents such as the current versions of the Investigator's Brochures (IB).

Inhibitors of BCRP are no longer excluded in Cohort B since no effect on the PK of LYS006 is expected based on new *in vitro* data as per the IB version 6 dated 05-Oct-2020. In addition, some wording has been adapted and/or harmonized between cohorts.

Optional CCI has been reinstated in the protocol (was present in protocol version 00 but removed in protocol version 01). This will be conducted at a limited number of sites only and is an exploratory assessment.

Changes to the protocol

Changes made to the protocol relating to the addition of Cohort C (MAS825):

- Randomization ratio of active to placebo added in Section 1.1.2
- Background added in Section 1.1.5.
- Purpose updated in Section 1.2.
- Objectives updated in Table 2-1 to include Cohort C. Objectives have been moved to group together by type e.g. clinical outcomes, PK and immunogenicity etc. but no objectives have been deleted. Exploratory objective added for CCI CCI for all cohorts.
- Figure 3-1 study design graphic updated to include the new cohort.
- Updates made to the study design in Section 3 and Section 3.3.

- Updates made to the rationale in Section 4.1, the rationale for does/regimen and duration of treatment in Section 4.2.3 and information about placebo in Section 4.3.
- Benefit and risk information for MAS825 has been added in Section 4.5.3.
- Approximate blood volume has been added in Section 4.5.4.3
- Cohort C information has been added in Section 5 and eligibility criteria updated to include Cohort C (Section 5.1 and Section 5.2)
- Various updates made to study treatment in Section 6.1 and subsections Section 6.1.1, Table 6-1 and Section 6.1.3 incorporating information about MAS825.
- Updated to include Cohort C into prohibited medication in Table 6-2.
- Randomization ratio of active to placebo added in Section 6.3.2.
- Cohort C blinding information added in Section 6.4.
- Cohort C information has been added in Section 6.6.1 regarding treatment compliance.
- A new section on the recommended treatment of adverse events added in Section 6.6.2.4.
- Cohort C information added to preparation and dispensation (Section 6.7).
- Visit and assessment schedule for Cohort C added in Table 8-4.
- Cohort C added to the CCI specimen section regarding central CCI [redacted] panel in Section 8.4.1.2
- Specific information regarding pregnancy testing added in Section 8.4.3.
- Assessments relating to Cohort C added to Section 8.5 and subsections.
- Discontinuation of treatment criteria updated for Cohort C in Section 9.1.1.
- Added text confirming no specific study stopping rules for MAS825 in Section 9.1.4.
- Adverse event monitoring timeline added for MAS825 in Section 10.1.1.
- Reference to MAS825 added in Section 12.3 (Treatments) and the analysis of primary endpoint information in Section 12.4 and subsections of Section 12.4.
- PK analysis section created for Cohort C (Section 12.6.3.3).
- Pharmacodynamic analysis section created for Cohort C (Section 12.6.4.3).
- Cohort C added to the immunogenicity information in Section 12.6.6.
- Cohort C exploratory biomarkers added in Section 12.6.7.
- Updates made in Section 12.8.1 to include the total subjects required in Cohort C and the study as a whole.

Other changes made to the protocol:

- References to patient or subject has been harmonized throughout the protocol. Patient is a term used to refer to a person suffering with HS whereas a subject is a HS patient taking part in the study.
- The List of Abbreviations has been updated to remove abbreviations that were not present in the protocol and add new abbreviations.
- Protocol summary updated to align with changes in the body of the protocol.

- Clarification of the term 'PD' provided in Section 3.1 (Cohort A) and Section 3.2 (Cohort B).
- Information duplicated from the Investigator's Brochure regarding the risks of CFZ533 and LYS006 have been removed from Section 4.5.1.2 and Section 4.5.2.2 respectively. Readers are directed to the current version of the respective IB. Also updated is the information about vaccinations in Section 4.5.1.2.1, Section 4.5.2.2.3.
- New wording added to exclusion criterion 9 regarding SARS-CoV-2 infection, exclusion 10 regarding live/attenuated vaccines and exclusion 16, point 5 regarding haematological abnormalities (Section 5.2).
- Wording to direct readers to vaccination sections added to Section 6.2.1 Concomitant therapy.
- BCRP inhibitors removed from Table 6-2 as this requirement is no longer applicable to LYS006 base on new information in the IB.
- Duplicate information removed from Section 6.2.2 and Table 6-2 revised to aid clarity (no changes other than in the bullet above).
- Reference to IB made in relation to treatment of adverse events in Section 6.2.3.
- The blinding and unblinding plan has been updated to include the scenario when a cohort is complete before the completion of the study in Table 6-3 (Final analysis per cohort). It has also been clarified that appropriate external consultants and DMC members may be unblinded.
- In Section 6.7 (preparation and dispensation), wording has been added to allow outpatient injections for Cohort A and C in the case of a pandemic and if local regulations allow.
- COVID-19 testing added when in line with health and governmental authority guidance to exclusion criterion 9 in Section 5.2.
- Table 8-1 updated to reflect changed made in rest of the protocol.
- Optional CCI [redacted] assessments added back into the assessment schedules for all three cohorts in Table 8-2, Table 8-3 and Table 8-4. Additional information added in Section 8.5.4.2.
- Clarification to CMV testing added in Section 8.4.4.2.
- Clarifications made to the tests laboratory evaluations performed and calculated from those evaluations in Table 8-6.
- Clarification made to the CMV discontinuation criterion in Section 9.1.1.
- Text relating to discontinued subjects deleted from Section 12.4.1 and added to Section 12.4.3.
- Updates made to the sensitivity analysis description in Section 12.4.4.1.
- Updates made to the supportive analyses in Section 12.4.4.2.
- Updates to the analysis of secondary endpoints for ECGs and vital signs in Section 12.5.2.2 and Section 12.5.2.3.
- Section added detailing the analysis of CCI [redacted] in Section 12.6.8.3.

- Clarification made to Section 12.7 regarding the communication of interim results.
- Wording updated in Section 12.8.1 to allow subjects to be replaced if required to preserve the statistical power, unless treatment was stopped for safety reasons.
- References updated in Section 15.

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

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 2 (June 2020)

Amendment rationale

The main purpose of this amendment is to address requests from Health Authorities and Ethics Committees, as well as to correct some inconsistencies in the protocol discovered during implementation.

Eligibility criteria have been updated. In the inclusion criteria the maximum number of fistula have been increased in order to be in line with other clinical studies in HS (such as Kimball et al 2016, Tzanetakou et al 2016), where more fistulae were allowed.

The sponsor has updated the exclusion criteria relating to levels of bilirubin, lipase and amylase. Only values **above** the upper limit of normal will now be exclusionary, instead of values outside normal range, as only abnormal high levels should be avoided. This will not impact on patient safety.

At the request of Health Authorities, we are implementing a precautionary CMV serology test at screening, in particular for patients participating in cohort A (CFZ533). An acute CMV infection will lead to a discontinuation of treatment in patients in Cohort A. For the same purpose, history of antiphospholipid syndrome is now specified and will lead to an exclusion (for patients in cohort A, CFZ533).

One assessment of skin pain was added for cohort A to align with cohort B (V199).

At the time of this amendment, the study has randomized 11 patients in cohort A and 5 in cohort B. 2 patients are currently in treatment period, while 9 have completed the study and 5 have completed the treatment period and are in follow up. There have been no Serious Adverse Events reported. The recruitment of the study is currently halted until the ease of the lock down measures due to COVID-19 permits it to continue but may restart prior to the implementation of this amendment. Additional information has been added regarding handling of missed visits or patients in lockdown but this is not specific to COVID-19. Some patients may discontinue due to the impact of the lockdown measures. To reflect this specific case, the statistical handling has been adapted, as has the analysis of pain in patients with pain medication.

Other changes include clarification of prohibited medication and/or therapies, extending the screening period to 35 days (previously 30) and widening some visit windows to provide more flexibility for patients. This does not impact on patient safety or data integrity but will avoid unnecessary protocol deviations.

The protocol was also updated to correct typographical errors and inconsistencies also incorporating changes requested by IEC/IRBs.

Changes to the protocol

The following sections of the protocol were changed:

- Updates to abbreviation list and protocol summary to reflect changes to the main body of the protocol.
- Section 1.1.4 reference and additional information about metabolites derived from skin lesions added in the LYS006 summary.
- Section 4.5.1.2.2: Updated risk text to include fatal SAE in a different CFZ533 study in a lupus nephritis patient treated with CFZ533.
- Section 4.5.3.3: Blood volumes have been updated (reduced) in line with the actual blood volumes from the central lab for the study.
- Section 5.1 and Section 5.2: Eligibility criteria have been tabulated to add clarity around which criteria apply to which cohort.
- Section 5.1: Inclusion criterion 5 reworded
- Section 5.2: Addition of wording in exclusion criterion 8 for positive IgM for CMV at screening
- Section 5.2: Addition of wording in exclusion criterion 15 for patients with antiphospholipid syndrome.
- Section 5.2: Update to exclusion criterion 16 for lipase, amylase and bilirubin exclusionary values
- Section 6.2 (and sub-sections): Removed duplicative wording, added references to non-drug therapies.
- Section 6.2.2: added list of non-prohibited medications and non-drug therapies, from section 6.2.3
- Table 6-2: Systemic corticosteroids added to the list of prohibited medication.
- Table 6-2: Wording for surgery, photodynamic therapy and laser clarified in list of prohibited medication.
- Table 6-2: Wording for surgery, photodynamic therapy and laser clarified in list of prohibited medication.
- Table 6-2: Consolidated rows for systemic immunosuppressants and immunomodulators
- Table 6-2: Added row for other investigational drugs
- Table 6-2: Clarified wording for use of spironolactone and other anti-androgens
- Table 6-2: Clarified “systemic” antibiotic row
- Table 6-2: Reworded “other systemic treatments for HS” row
- Table 6-2: Live/attenuated vaccines added for Cohort C
- Section 6.2.3: Moved text regarding conservative treatment of skin infections / HS lesion exacerbations with non-prohibited medications from Section 6.2.3 and further clarified.
- Section 6.7: Wording has been added regarding the shipment of IMP to a patient in certain circumstances.

- Section 7: Text regarding informed consent in the case of home nursing has been added.
- Section 8: Guidance text added for how to deal with missed visits and the any potential future issue in which patients would be unable to travel to the site due to local restrictions.
- Table 8-1: Screening period extended to 35 days from 30 days.
- Table 8-2 and Table 8-3: Visit windows updated for both cohorts to avoid unnecessary protocol deviations.
- Table 8-3, footnote 6 updated to allow for central lab CCI analysis where local analysis is not available.
- Table 8-3, footnote 10 updated: CCI collection for PK assessment on the day prior to the visits has been removed for non-treatment visits. The samples can be taken on the day of the visit by the site.
- Section 8.1: Additional wording added that will allow patients that were screen failed due to the temporary halt in enrolment to be screened like a new patient.
- Section 8.4: Text added regarding the use remote communication for safety monitoring in case patients are unable to travel to the site.
- Section 8.3.2 the primary endpoint has been clarified as the HiSCR50. The addition of the HiSCR75 and HiSCR90 has also been included.
- Table 8-6 has been updated to include the assessments done by the laboratory as per the assessment schedule and statement of work.
- Section 8.4.1.2 has been updated to include the assessments done by the laboratory as per the assessment schedule and statement of work.
- Section 8.4.4.2 added to give clarity around CMV and SARS-CoV-2 (COVID-19) assessments.
- Section 8.5.1 added wording regarding completion of PROs in case of epidemic or pandemic.
- Section 8.5.2: additional wording regarding the collection of PK samples in case patient travel is restricted.
- Section 12.3: Addition of analysis to explore pain medication use across cohorts and treatment groups.
- Wording included in Section 12.4.4 stating how surgical incisions/excisions will be handled.
- Section 12.6.1: Addition of details of analysis of exploratory endpoints in relation to the HiSCR 50, 75 and 90.
- Removal of Section 17 (Information on Investigational treatments) as this data is in the IB and will be updated as necessary.

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

Amendment 1 (July 2019)

Amendment rationale

The main purpose of this amendment is to remove the requirement for male contraception in the LYS006 cohort given that completed preclinical safety studies with LYS006 showed there was no teratogenic or genotoxic potential observed with LYS006, reflected in the last update of the investigator's brochure (Ed. 4). However, in order to harmonize eligibility criteria between cohorts, highly effective contraception for women of childbearing potential (WOCBP) will be kept as requirement for both cohorts.

Further, the eGFR exclusion criterion (<80 ml/min/1.73 m^2) is proposed to be updated, as the eGFR assessment is not performed with strict hydration and meat restriction prior to the test, resulting in a frequent underestimation of kidney function. Thus, a minimal threshold of 60 ml/min/1.73 m^2 is proposed to exclude patients with potential moderate or severe kidney damage.

Two additional Hidradenitis Suppurativa (HS) scores have been added:

- CCI an exploratory endpoint derived from the other lesion counts, has been added to the analysis without adding a new clinical assessment.
- Hurley score has been added at Day 1 only to document patient population and disease severity.

This protocol amendment also adds clarifications per recent comments received from HAs and ECs, e.g. the rationale for pooling placebo.

A Data Monitoring Committee (DMC) has been set up and will function independently of the individuals associated with the conduct of this clinical trial.

Additionally, in an effort to reduce site and patient burden, the following updates were made:

- The baseline visit has been removed from the study. However, the term "baseline" is maintained and used throughout the protocol to refer to "prior to study treatment". Eligibility criteria will be confirmed based on the evaluations that take place during the screening visit and at randomization (pre-dose on Day 1).
- LYS006 quantification of CCI has been removed, as this assessment presented a major operational hurdle and sufficient information can be gathered from the other LYS006 CCI assessment.
- CCI (exploratory endpoints) have been removed.
- Some exploratory sample time points have been removed (such as for CCI .

In order to provide more accurate qualitative and quantitative assessment of HS lesions, the CCI .

The protocol was also updated to correct typographical errors and inconsistencies.

Changes to the protocol

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

The following sections of the protocol were changed:

- List of Abbreviations and Glossary updated
- Protocol summary updated
- Section 3 and Figure 3-1 updated to reflect changes in design. Baseline visit was removed.
- Section 4.5.2.2 CCI CCI assessment removed
- Section 4.5.2.2 Teratogenicity data updated with most recent findings from animal studies
- Section 4.5.3.2 CCI added
- Section 5.1 wording of some of the inclusion criteria clarified.
- Section 5.2 wording of some of the exclusion criteria clarified:
  - Criterion #3: Period of using of highly effective methods of contraception for WOCBP in Cohort A changed from 12 subsequent weeks after dosing to 14 weeks subsequent weeks after dosing.
  - Criterion #8: Testing for Hepatitis B and Hepatitis C was specified.
  - Criterion #12 was updated to remove laboratory assays to assess drug abuse since this was inadvertently added in the protocol.
  - Criterion #17: History of hypersensitivity or allergy now specified to any constituent of the investigational compounds.
  - Criterion #19 was removed following LYS006 IB update.
  - Criterion #21: Change of eGFR from 80 ml/min/1.73 m2 to 60 ml/min/1.73 m2.
  - Criterion #23: Hypersensitivity to any constituent of the gadolinium contrast agent was added.
- Section 6.7 study treatment preparation and dispensation updated
- Prior Section 8.1.1 removed
- Section 8.2.1 Added Hurley score
- Section 8.3.6 Added CCI
- Section 8.4.1.1 Blood specimens updated
- Section 8.4.1.2 Urine specimens updated
- Section 8.5.3.5 Exploratory CCI specified for both cohorts
- Section 8.5.4 The administration of a CCI procedure has been added. CCI removed.
- Section 10.1.1 Adverse events reporting updated.
- Section 10.2.3 Added a Data Monitoring Committee.
- Section 12 Added rationale for pooling placebo data.

- Section 12.6 Added an exploratory endpoint, CCI [redacted].
- Section 12.6.8 CCI [redacted] details removed

The following tables were changed:

- Table 2-1 Exploratory objectives and endpoints updated
- Table 6-2 Medications requiring wash out have been removed from the table to remove duplication of information and discrepancy with Exclusion Criteria.
- Table 8-1 Baseline visit removed.
- Table 8-1, Table 8-2, and Table 8-3 CCI [redacted] exploratory endpoints removed. Footnotes updated.
- Table 8-2 CCI [redacted] sampling removed at Day 113.
- Table 8-3 CCI [redacted] assessment removed at EOS.
- Other minor updates were made in the document to align different document sections and to improve readability.

Protocol summary

Protocol number	CCFZ533H12201BC
Full Title	A randomized, subject and investigator-blinded, placebo-controlled and multi-center platform study, to assess efficacy and safety of different investigational drugs in patients with moderate to severe hidradenitis suppurativa
Brief title	Study of efficacy and safety of investigational treatments in patients with moderate to severe hidradenitis suppurativa
Sponsor and Clinical Phase	Novartis II
Investigation type	Drug and Biological
Study type	Interventional
Purpose and rationale	This study is designed to assess the efficacy, safety, tolerability, PK of various selected systemic investigational treatments for 16 weeks in moderate to severe hidradenitis suppurativa (HS) subjects in comparison to placebo. Data from this study will enable determination of whether the clinical profile of these investigational treatments support further clinical development in moderate to severe HS.
Primary Objective(s)	The primary objective of this study is to assess the efficacy of the investigational treatments when compared to placebo, in moderate to severe inflammatory HS patients by comparing the proportion of patients achieving clinical response defined by the simplified Hidradenitis Suppurativa Clinical Response (HiSCR) after 16 weeks of treatment
Secondary Objectives	To assess the safety and tolerability of the investigational treatments in patients with moderate to severe hidradenitis suppurativa (HS) by (i) number and severity of AEs and (ii) physical examination, vital signs, safety laboratory measurements and ECGs at baseline and repeatedly until study completion visit
Study design	This is a non-confirmatory, randomized, subject and investigator-blinded, placebo-controlled, multi-center and parallel-group study to assess efficacy, safety and tolerability of several active investigational drugs, iscalimab, LYS006, MAS825, remibrutinib and ianalumab, in patients with moderate to severe hidradenitis suppurativa. The maximum duration of any subject's participation in a Cohorts A, B and C may not exceed 33 weeks, 25 weeks for Cohort D; remibrutinib, and 121 weeks for Cohort E; ianalumab and will consist of a 35 day screening period, a 16 week treatment period and will be concluded by a 12 week safety follow-up (4 week safety follow up for remibrutinib). For ianalumab there will be a mandatory follow up period of 16 weeks, followed by a conditional follow up period for up to 84 weeks. Subjects will be allocated to either of the cohorts (based on the eligibility criteria for each cohort). Within each cohort, subjects will be randomized 2:1 (Cohort A and B) or 3:1 (Cohort C and E), or 3:3:1 (Cohort D) to either investigational treatment or matching placebo. The study will be set up as a platform study to allow early discontinuation of cohorts and inclusion of new cohorts.
Population	Adult male and female participants, 18 to 65 years of age, presenting with moderate to severe hidradenitis suppurativa, diagnosed with recurrent inflammatory lesions for at least 12 months prior to screening.

Key Inclusion criteria	• Male and female subjects, 18 to 65 years of age (inclusive), with clinically diagnosed HS for at least 12 months prior to screening
	• Patients with moderate to severe HS, as per evaluation at screening and randomization (pre-dose on Day 1):
	  • **For Cohort A, C and E ONLY:**
	  • A total of at least **5 inflammatory lesions**, i.e., abscesses and/or inflammatory nodules, **and**
	  • No more than 15 fistulae, **and**
	  • At least two anatomical areas need to be involved with HS lesions
	  • **For Cohort B and D ONLY:**
	  • A total of at least **3 inflammatory lesions**, i.e., abscesses and/or inflammatory nodules, **and**
	  • No more than 15 fistulae, **and**
	  • At least two anatomical areas need to be involved with HS lesions
	• Minimal body weight of 50 kg (inclusive) at screening
	• Able to communicate well with the investigator and understand and comply with the requirements of the study, and the ability and willingness to conduct study visits as per the study schedule.

Key Exclusion criteria	These criteria are applicable for all subjects across all cohorts. Please also refer to the cohort-specific eligibility criteria for any additional factors to consider. • Use of other investigational drugs at the time of screening, or within 30 days or 5 half-lives of randomization, whichever is longer; or longer if required by local regulations. • WoCBP (defined as all women physiologically capable of becoming pregnant), unless they are using highly effective methods of contraception during dosing and for a minimum of 14 weeks after the last study drug administration for Cohort A (iscalimab) and a minimum of 2 weeks after the last study drug administration for Cohort B (LYS006). In Cohort C (MAS825), WoCBP will be asked to adhere to highly effective contraception from at least 3 months prior to first drug administration and until 5 months after the final dose (Day 225 to Day 253), when a pregnancy test will be conducted. In Cohort D (remibrutinib), WoCBP will be asked to adhere to highly effective contraception while receiving study medication and for 2 weeks after stopping study medication. In Cohort E (ianalumab), WoCBP will be asked to adhere to highly effective contraception while on study treatment and for 6 months after the final dose (Day 253 to Day 281) • Pregnant or nursing (lactating) women at screening or randomization, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • For Cohort D: significant bleeding risk or coagulation disorders e.g.: • History of gastrointestinal bleeding, e.g. in association with use of nonsteroidal anti-inflammatory drugs (NSAID), that was clinically relevant

	• Use of anticoagulant medication [for example, warfarin or Novel Oral Anti-Coagulants (NOAC)] within 2 weeks prior to randomization • International Normalized Ratio (INR) of more than 1.5 at screening • Use of anti-platelet medication [including dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel)] within two weeks prior to randomization. • Note: monotherapy with acetylsalicylic acid (up to 100 mg/day) or clopidogrel is not exclusionary. • Major surgery within 8 weeks prior to screening or planned surgery the during study treatment period. • For Cohort E: Subjects with evidence of existing hematological abnormalities at screening: • Hemoglobin below 8.0 g/dL • White blood cell count: below 2 x 10^9/L • Absolute Neutrophil count: below 1.5 x 10^9/L • Platelets: below 50 x 10^9/L • History of hypersensitivity to drugs of similar chemical classes to ianalumab (e.g. mAb of IgG1 class) or to any of the constituents of the study drug [redacted] • Prior use of any B cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb or anti-CD52 mAb) within 1 year prior to dosing. • History of major organ, hematopoietic stem cell or bone marrow transplantation
Study treatment	• CFZ533 (iscalimab), 600 mg, s.c. or matching placebo as follows: weekly from Day 1 (Week 1) to Day 29 included (Week 5) and then bi-weekly from Day 43 (Week 7) to Day 99 included (Week 15). • LYS006, 20 mg, p.o. or matching placebo as follows: b.i.d. from Day 1 (Week 1) to Day 113 included (Week 17). • MAS825, [redacted] mg, s.c. or matching placebo as follows: [redacted] ([redacted]) from Day 1 (week 1) to Day 29 (Week 5) and then [redacted] ([redacted]) until Day 85 included (Week 13). • LOU064 (remibrutinib), [redacted] mg [redacted]. p.o or [redacted] mg [redacted]. p.o or placebo from Day 1 (Week 1) to Day 113 included (Week 17). • VAY736 (ianalumab), [redacted] mg s.c. or matching placebo: [redacted] ([redacted]) from Day 1 (week 1) until Day 85 included (Week 13)
Key efficacy assessments	• Simplified and original Hidradenitis Suppurativa clinical response (HiSCR) rate • [redacted]

Key safety assessments	• Number and severity of Adverse Events (CTCAE v5.0 grading) • Physical examination, incl. vital signs, safety laboratory measurements, and ECGs
Other assessments	• PK • CCI (optional), skin tape strips (Cohort B and C) • CCI • Patient reported outcomes including Skin Pain Numerical Rating Scale (NRS), CCI For Cohort E: • CCI •
Data analysis	In each treatment group, the primary variable, the proportion of subject with simplified HiSCR after 16 weeks of treatment, will be modeled with a binomial distribution. A neutral non-informative Beta (1/3, 1/3) distribution will be used for the prior for the response rate all treatment groups. Based on the priors and the observed primary outcome, posterior distributions for the response rate in investigational treatment and pooled placebo groups will be computed respectively. The posterior distribution of the difference of response rates, investigational treatment (iscalimab/LYS006/MAS825/each remibrutinib regimen/ianalumab) minus placebo, will be obtained by simulations, i.e. sampling from the posterior distributions of the corresponding treatment groups. The posterior probabilities for the difference of response rates will be assessed according to the dual efficacy criteria as a guide to decision making. Each investigational treatment will be assessed separately in comparison to the pooled placebo group. Subjects who do not complete the 16-week treatment due to lack of efficacy or adverse events due to worsening of disease, or subjects who discontinue before 12 weeks of treatment (if ≤10% of the PD analysis set population) will be considered as non-responders. If subjects who discontinue before 12 weeks of treatment constitute >10% of the PD analysis set population, multiple imputation methods will be used.
Key words	Hidradenitis suppurativa, acne inversa, platform study

1 Introduction

1.1 Background

1.1.1 Hidradenitis suppurativa

Hidradenitis suppurativa (HS), also called "acne inversa" or "maladie de Verneuil", is a chronic, recurrent, and debilitating inflammatory skin condition that typically presents with deep, inflammatory, painful lesions in apocrine gland-bearing parts of the body. The most common areas affected are the axillae, the groin, and the anogenital region (Jemec 2012; Fimmel, Zouboulis 2010).

HS is currently considered to be an inflammatory disease of the pilosebaceous follicle with an underlying immune system imbalance that occurs in genetically predisposed individuals (Sabat 2022, Kelly et al 2014). While it is considered a disease primarily triggered by follicular occlusion, HS is an inflammatory skin disease characterized by large numbers of neutrophils and macrophages in inflammatory lesions (Lima et al 2016, Shah et al 2017). While HS pathophysiology is still largely unknown, the benefit of tumour necrosis factor alpha (TNFα) blockade have been described in larger studies (Kimball et al 2016).

Evidence of the efficacy of anti-Interleukin (IL)1 treatment using the IL-1 receptor blocker anakinra (Tzanetakou et al 2016), or with an antibody against anti-IL-1α bermekimab (Gottlieb et al 2020), or an IL-1ß blocker, CCI [redacted] have been described. Blocking IL-17A (Thorlacius et al 2018, Schuch et al 2018, Giuseppe et al 2018, Jørgensen et al 2018, Reguiaï et al 2020, Casseres et al 2020) or anti IL-23 treatment (Sharon et al 2012, Blok et al 2016) has also been successful in smaller studies and/or in case reports. Interestingly, Blok observed that a low serum LTA4H at baseline and low severity was correlated with efficacy of ustekinumab. More recently, investigational approaches using the oral PDE4 inhibitor apremilast (Weber et al 2017) or an anti-complement 5a compound (Kanni et al 2018; Giamarellos-Bourboulis 2020) have been described. Other innovative approaches to tackle the high medical need in HS include treatment with JAK inhibitors or more specific kinase inhibitors, such as TYK2 or IRAK4 inhibitors.

A more recent study has identified Bruton's tyrosine kinase (BTK) pathway activation as a central signal transduction network in HS (Gudjonsson et al 2020).

The disease starts after puberty and women are more frequently affected than men (3:1). Risk factors include obesity and smoking. Although epidemiological prevalence estimates vary widely (0.03-4.3%; Jemec 2012, Jemec, Kimball 2015), and geographical differences exist, a prevalence of approximately 0.1-1% is accepted by the scientific community (Garg et al 2018).

The clinical manifestations of HS are heterogeneous, but the disease tends to manifest with chronic, relapsing, deep, painful, inflammatory skin lesions, mostly inflammatory nodules and abscesses, leading to possible drainage and suppuration. Inflammatory lesions are complicated during disease progression by sinus tract formation and fistulization, and may lead to hypertrophic scarring with a possible impact on functional use. Generally, the inflammatory burden of HS is considered high (Riis et al 2015) and specifically inflammatory markers such as CRP are increased and correlate with disease severity (Hessam et al 2015, Akdogan et al 2020).

HS is associated with pain, malodorous discharge from the wounds, and scarring, and does frequently have devastating psychosocial effects. HS is a profoundly debilitating disease with a high negative impact on CCI with multiple studies confirming that the impact is greater than that seen with other dermatologic diseases (Deckers, Kimball 2016). Patients with HS also often suffer from depression, social isolation, have impaired sexual health, and may have difficulty performing their work duties (Esmann, Jemec 2011, Fimmel, Zouboulis 2010, Janse et al 2017).

HS is difficult to treat. Official European treatment guidelines were only developed in 2015 and suggest that patients should be provided with adjuvant, medical and surgical therapy (Zouboulis et al 2015).

While topical antibiotics can be used for mild cases, long courses of multiple systemic antimicrobial therapies are preferred for moderate to severe HS, generally with tetracyclines or a combination of clindamycin and rifampicin, which can be followed by maintenance with chronic antibiotic treatment for months or even years (Bettoli et al 2016, Dessinioti et al 2016, Zouboulis et al 2015).

However, it is widely recognized that HS is a chronic inflammatory condition, not an infectious disease (Jemec 2012). Therefore, anti-inflammatory agents are an alternative and probably more appropriate approach than antibiotics. Over time, the consequence of chronic, recurrent, inadequately treated inflammation is irreversible fibrosis, which manifests as scarring and tunnels, or sinus tracts, which often do not respond to medical therapy. Once lasting anatomical changes occur, the only therapeutic option to reduce the volume of fibrotic tissue and improve functionality in the areas of affected skin is surgery (Andersen, Jemec 2017). One of the future treatment goals should be to reduce persistent scarring and to avoid surgery, which may be achieved by prevention of inflammatory lesions or may need a specific treatment.

In 2015, adalimumab (Humira®), a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody to soluble and membrane bound TNF-α, received regulatory approval for the treatment of moderate to severe HS. Efficacy has been seen with adalimumab, with HiSCR (Hidradenitis Suppurativa clinical response) response rates over placebo of approximately 16% (41.8% adalimumab vs 26% placebo) and 31% (58.9% adalimumab vs 27.6% placebo) as reported in PIONEER I and II studies, respectively (Kimball et al 2016). As captured in the adalimumab labels, adalimumab is associated with an increased safety risk for serious infections including tuberculosis, invasive fungal infections and other opportunistic infections. An increased incidence of malignancies has also been reported with adalimumab.

There is, therefore, an unmet need for systemic therapies that effectively reduce inflammation while having a favorable safety profile for patients suffering from moderate to severe HS. No oral drug is currently approved, though oral antibiotics are used.

1.1.2 Platform study design

This study uses a platform study design to investigate multiple targeted investigational treatments in the context of a single disease. An adaptive platform design offers flexible features such as dropping treatment cohorts for futility, declaring one or more investigational treatments superior, or adding new investigational treatments to be tested during the course of a trial.

As a result, platform studies may find beneficial treatments with fewer subjects, fewer subject failures, less time, and with greater probability of success than a traditional two-arm strategy.

In addition, the results are based on very similar conditions and can be compared. This platform design also limits placebo exposure, with an overall 2:1 investigational drug:placebo randomization rate in Cohorts A and B, 3:1 in Cohort C and E, and 3:3:1 Cohort D.

1.1.3 Iscalimab summary

Iscalimab (CFZ533) is a non-agonistic, fully human, Fc-silent, antagonistic IgG1 anti-CD40 antibody that binds to the CD40 ligand (CD40L) binding site on CD40 and prevents the binding of CD40L to CD40. Since it is Fc-silent, iscalimab binding is able to block the CD40/CD40L costimulatory pathway and inhibit cellular proliferation and other effector functions, but does not cause antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Iscalimab inhibits CD40L-induced activation *in vitro* and T cell-dependent antibody formation and germinal center formation *in vivo*. Iscalimab was able to prolong non-human primate renal allograft survival alone or in combination with sub-therapeutic doses of cyclosporine. In addition, iscalimab was able to completely suppress primary and secondary antibody responses to immunization with a T cell-dependent antigen. Iscalimab has been tested in Phase 1 and is currently in Phase 2 trials in various immune-mediated conditions. Based on human data (approximately 295 subjects in the development program to date), iscalimab has shown a favorable safety and tolerability profile. More information can be found in the chapters below dedicated to iscalimab and in the Iscalimab Investigator's Brochure (IB). Overall, these results suggest that inhibition of the CD40/CD40L pathway by iscalimab may represent a safe and efficacious novel therapeutic approach for the treatment of HS.

The presence and upregulation of B cells has been observed previously in HS lesions (Hunger et al 2008, van der Zee et al 2012). B cells and plasma cells were detected in HS lesions and in particular in chronic lesions (as opposed to early-stage) by van der Zee et al 2012, as compared to perilesional and healthy skin. In some samples, lymphoid follicles with CD20+ B cells were detected in chronic lesions. In a recent study CCI involving moderate to severe HS subjects, CCI samples showed a CCI CCI in lesional skin as well as several CCI in the lesional tissue. In the same study, CCI in CCI data from CCI showed not only a clear CCI but also a CCI based on transcriptomics (data on file). In line with these observations, abnormalities and upregulation in CCI CCI in HS patients were observed by CCI).

In addition, and perhaps more importantly, macrophages are abundantly found in chronic HS lesional skin (Shah et al 2017). Recently, these macrophages were identified as potentially M2 CD163+ macrophages (Byrd et al 2018). In the CCI HS samples, CCI was expressed on CCI present in HS lesions and is abundantly expressed in HS lesional CCI while the CCI was expressed by CCI in HS lesional CCI . The CCI confirmed the pathway engagement seen with signatures on the transcriptional level (data on file). Thus, iscalimab could be the first treatment for HS that targets the CCI pathophysiology recently observed in HS.

1.1.4 LYS006 summary

LYS006 is a highly potent and selective oral inhibitor of the enzyme leukotriene A4 Hydrolase (LTA4H). LYS006 inhibits the biosynthesis of pro-inflammatory leukotriene B4 (LTB4) and increases the generation of anti-inflammatory, resolution-enhancing lipoxin A4 (LXA4). Both lipid mediators are known to play an important role in the orchestration of neutrophilic inflammation. LTA4H inhibition therefore represents a relevant mechanism for treatment of neutrophil-driven inflammatory conditions (Zouboulis 2009). LTB4 inhibitors, however, have not been developed for these indications yet, and no LTA4H inhibitor is currently marketed. LYS006 would therefore constitute a new therapeutic approach for this chronic inflammatory skin disease. In preclinical pharmacological models, inhibition of LTB4 generation by LYS006 in peripheral blood correlated well with the anti-inflammatory efficacy of LYS006 observed in inflamed tissues in different mechanistic models. LYS006 inhibited neutrophil influx and swelling in an acute CCI skin inflammation model. The first-in-human study (FiH, CLYS006X2101) showed that LYS006 was well tolerated in healthy volunteers (HV) after a single dose (up to CCI mg CCI administered CCI) and multiple dose for CCI (up to CCI mg CCI). The pre-clinical signal of CCI , observed in dogs and rodents at high doses, was not observed in any of the active treated subjects with ~4 fold higher doses used in the FiH, than proposed in the present study. In the same study, CCI mg CCI had an effect on CCI after CCI stimulation (CCI % suppression at CCI) and the dose of CCI mg CCI exhibited a CCI) throughout the day.

The dose used in this study, CCI mg CCI is 4 times lower than the highest multiple dose tested in controlled conditions over 12 days in HV and was well tolerated. No CCI were observed in any LYS006 treated subject in the FiH study. Laboratory events were without significant findings. However, sporadic, transient and isolated elevations of lipase without clear correlation to the dose or treatment duration have been observed. No signs of pancreatitis were observed and the transient elevations of lipase resolved even with continuation of treatment. More information can be found in the current edition of the LYS006 IB.

As described above, neutrophils and macrophages are involved in HS lesions and are the main producers and target cells of LTB4 and LXA4 (Serhan et al 2008). Relevance of LTB4 was clinically demonstrated in related skin pathology inflammatory acne (Zouboulis et al 2003). As a sign for pathway activation, perinuclear localization of ALOX5 (5-LO) in lesional leukocytes has been previously described (Christmas et al 1999). Penno et al 2020 report that lesional HS skin displays an enrichment of 5-lipoxygenase (5-LO) derived metabolites, in particular leukotriene B4 (LTB4), which is the target of LYS006. Hyper-activation of the 5-LO pathway in lesional macrophages, identified these cells as potential source of LTB4, which may cause neutrophil influx and activation. In addition, LXA4 elevation may have impact on fibrosis in addition to the anti-inflammatory effect of the drug (Börgeson et al 2011).

1.1.5 MAS825 summary

MAS825 is an CCI monoclonal antibody (mAb) containing a CCI part that CCI neutralizes the key inflammasome effector cytokines interleukin-1 beta (IL-1ß) and interleukin-18 (IL-18). MAS825 has CCI affinities to both cytokines and inhibits IL-1β and IL-18 signaling in cellular *in vitro* assays at CCI

concentrations. IL-1β and IL-18 are the two pro-inflammatory cytokines secreted after inflammasome activation in response to the recognition of damage associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs). The combined inhibition of IL-1β and IL-18 is expected to result in a more effective down-modulation of the inflammasome-driven pro-inflammatory responses compared to the inhibition of either cytokine alone.

Kelly et al 2015 pointed out that in HS both cytokines, IL-1ß and IL-18 are upregulated and could thus play a role in its pathogenesis. Witte-Händel et al 2019 has confirmed these findings and showed specifically that IL-1ß signature was present in HS lesions and could be reversed by application of IL-1 receptor antagonist. Tzanetakou et al 2016 in a small proof of concept study was able to show promising clinical efficacy results versus placebo with anakinra, a recombinant IL-1R antagonist, while case reports or series have as well confirmed these findings (Leslie et al 2014, Zarchi et al 2013, André et al 2019). Case reports have shown that CCI using CCI may be of benefit in moderate to severe HS (Houriet et al 2017) or to associated syndromes such as PASH (pyoderma gangraenosum, acne and suppurative hidradenitis (Jaeger et al 2013). However, some observed failures in HS CCI CCI and with anakinra (van der Zee, Prens 2013, Russo, Alikhan 2016) hint possibly to the fact that only subpopulations may be responsive to anti-IL-1 blockade or that this blockade alone may not be sufficient to achieve results in most patients.

By targeting both inflammasome effector cytokines, IL-1ß and IL-18, MAS825 has therefore the potential for superior clinical efficacy in (auto)-inflammatory conditions or where both IL-1β and IL-18 independently contribute to disease pathophysiology, such as HS. MAS825, a CCI anti-IL-1β/18 mAb, is expected to rapidly neutralize all inflammasome dependent as well as inflammasome independent sources of IL-1β and IL-18.

MAS825 was well tolerated when administered to CCI s.c. up to CCI mg/kg, CCI for 26 weeks (No Observed Effect Level (NOEL) CCI mg/kg; Cmax,ss of CCI µg/mL, AUC0-72h,ss of CCI µ·h/mL) and did not show any safety pharmacology (central nervous, cardiovascular and respiratory systems), toxicology (including CCI CCI) or local tolerability effects. No effects were also seen after CCI intravenous (i.v.) dosing at CCI mg/kg for 26-weeks (Cmax,ss of CCI µg/mL, AUC0-72h,ss of CCI µg·h/mL). Furthermore, no treatment-related effects were noted CCI in the peripheral blood as well as on primary and secondary humoral immune responses upon foreign antigen challenge.

A Phase 2 study in adult patients who are hospitalized, and diagnosed with COVID-19 pneumonia, impaired respiratory function and evidence of hyperinflammation (increased CRP and/or Ferritin; CMAS825F12201) has started. In this study, MAS825 is administered as single dose of CCI mg/kg.

1.1.6 Remibrutinib summary

Remibrutinib (LOU064) is a selective, potent, covalent inhibitor of BTK. It has the potential of being one of the first oral treatments approved in HS. BTK is a member of the TEC-family kinases (TEC=Tyrosine protein kinase), such as TEC, Bone Marrow kinase gene on the

X chromosome (BMX), IL2-inducible T-cell kinase (ITK), T and X cell expressed Kinase (TXK). It plays a crucial role in B cell development, as it is downstream from the B cell receptor signaling and also downstream of the Fc gamma receptor, receptor for the FC portion of Immunoglobulin G (FcγR) which can be found on macrophages. BTK is selectively expressed in cells of the adaptive and innate immune system including B cells, macrophages, mast cells, basophils and thrombocytes. BTK is indispensable for signaling through the Fc epsilon receptor (FcεR1 for Immunoglobulin E) and the activating Fc gamma receptors (FcγR for IgG), as well as the B cell antigen receptor (BCR). It is hypothesized that inhibition of BTK may be an attractive therapeutic concept to treat various autoimmune and chronic inflammatory diseases and clinical development programs with various BTK inhibitors have been initiated or are ongoing in, Sjögren´s syndrome, rheumatoid arthritis, asthma, CSU and other immune-mediated diseases (Rip et al 2018).

The scientific rationale of inhibiting BTK to treat HS is based on several observations:

In HS lesional skin, several authors have demonstrated that macrophages, plasma and B cells are present and predominant in HS skin Shah 2017, Altman, Criswell 2021, Gudjonsson et al 2020, Frew et al 2020, Musilova 2020. Recently, Gudjonsson at al 2020 described that B cells and plasma cells are pivotal players in HS pathogenesis and they constitute the predominant infiltrating leucocyte population in HS. While FcεR, FcγR and BCR signaling was detected in HS lesional skin, BTK besides SYK and STAT1 or Jun pathway activation constitute a central signal transduction network (Gudjonsson et al 2020). In addition, BTK pathway activation is shown in HS lesions (Gudjonsson et al 2020, Rumberger 2020).

Remibrutinib has been and is being tested in several indications (Mar 2021): at least 650 subjects (including healthy volunteers (HVs) and patients suffering from atopic dermatitis (AD), chronic spontaneous urticaria (CSU), asthma, and primary Sjögren's Syndrome (pSS) have received remibrutinib in doses between CCI mg and CCI mg or placebo in 10 clinical studies. Pharmacodynamics (PD) of remibrutinib in healthy volunteers (HV) were characterized by assessing target occupancy (i.e.: BTK occupancy), distal pathway inhibition in basophils and B cells, and inhibition of a response to a known allergen in the skin prick test of atopic HV in the first-in-human (FIH) study CLOU064X2101. A single dose of CCI mg remibrutinib results in complete BTK occupancy in blood for >24 h. The B cell activation marker CD69 was inhibited by ≥50% at doses of CCI mg. Consistent with its covalent mode of action, remibrutinib provided prolonged PD effect in targeted cells. In the skin, remibrutinib showed a dose-dependent reduction of the wheal diameter of the allergen induced skin prick test, (for more details please refer to the IB).

In the Phase 1 studies, the frequency and distribution of AEs observed did not appear to be dose dependent, with the majority of AEs occurring as single events. Given the non-serious and generally mild nature of AEs reported, they were not considered as clinically relevant safety concerns and they did not prevent dose escalation. A maximal tolerated dose (MTD) has not been defined. There were no clinically relevant changes in any of the cohorts with regards to ECG, vital signs, coagulation parameters or clinical signs of bleeding, clinical chemistry, hematology, or urinalysis following the administration of remibrutinib. Furthermore, remibrutinib showed encouraging blood and skin pharmacodynamics with a favorable safety profile, fully supporting further development for diseases driven by B cells, mast cells, or basophils (Kaul et al 2021). Beyond that, the Phase 2b CSU clinical trial CLOU064A2201

primary endpoint analysis demonstrated clinical efficacy and a fast onset of action of remibrutinib in the treatment of CSU patients as well as a favorable safety profile with no dose-dependent safety concerns (for detailed information please refer to the IB).

1.1.7 Ianalumab summary

Ianalumab (VAY736) is a human IgG1/κ mAb which targets the *B* cell *A*ctivating *F*actor of the TNF-alpha *F*amily (BAFF) receptor, BAFF-R (Syn:BR3), expressed on the surface of immature and mature B cells up to the lymphoblast stage. BAFF-R is not expressed by precursor B cells in the bone marrow or on long-lived plasma cells therefore there is no risk of inducing hypogammaglobulinemia.

Ianalumab works through two distinct mechanisms.

Enhanced antibody dependent cellular cytotoxicity (ADCC): afucosylation of the ianalumab Fc (fragment cystallizable) part enhances binding to human FcγRIIIa/CD16 resulting in an enhanced ability to mediate CD16-dependent ADCC of BAFF-R+ B cells.

Blocking BAFF-mediated activation of BAFF-R: Through its antigen binding region, ianalumab efficiently competes with BAFF for binding to BAFF-R on B cells, thereby inhibiting BAFF:BAFF-R signaling. BAFF-R signaling is critically involved in activation of B cell effector functions such as antibody production, isotype class switching (Mackay, Schneider 2009) and B cell proliferation, and also for BAFF-mediated B cell maturation of transitional B cells and B cell survival. Provided that ianalumab can access peripheral tissues in the same way as native immunoglobulins and existing therapeutic antibodies, it is expected to block BAFF:BAFF-R-mediated activation and survival of tissue B cells.

The rationale for targeting BAFF-R in HS is based on the emerging role for both B cells and plasma cells both present in HS lesions (Gudjonsson et al 2020) and autoantibodies correlating with disease severity and duration (Macchiarella et al 2022). Little is known about the survival factors supporting the persistence of immune cells in HS but increased BAFF expression correlating with lesional B cell and plasma cell presence has recently been demonstrated (Sabat 2022). As of 24-Sep-2023 an estimated total of 905 subjects have been exposed to ianalumab, at various doses, in 22 clinical studies across multiple indications (rheumatoid arthritis (RA), chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Sjögren's syndrome, multiple sclerosis, pemphigoid vulgaris, idiopathic pulmonary fibrosis (IPF), systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), lupus nephritis (LN). A phase 2b dose-range study in Sjögren's syndrome explored three ianalumab doses (CCI mg, CCI mg and CCI mg) administered CCI compared to placebo at Week 24. CCI [redacted] has an acceptable safety profile with no dose-dependent safety observations other than local injection site reactions (which were mostly mild-to-moderate). For detailed information please refer to the IB.

1.2 Purpose

The purpose of this proof of concept platform study is to determine whether selected systemic investigational treatments, mostly in early stage clinical development, have an adequate clinical profile to support further clinical development in moderate to severe hidradenitis suppurativa (HS). This proof of concept study is designed as a platform study. This platform design allows several investigational drugs to be tested in an adaptive way under the same conditions in one study. This study started initially with two investigational drugs (iscalimab and LYS006), was extended to include a third cohort using MAS825, a fourth cohort using remibrutinib and now a fifth cohort using ianalumab.

Cohorts A, B, C, D and E will assess safety and efficacy of three injectable drugs (iscalimab - Cohort A; MAS825- Cohort C; ianalumab – Cohort E) and two orally administered drugs (LYS006 - Cohort B; remibrutinib – cohort D). No further cohorts, investigating additional drugs, may be included via substantial protocol amendment(s).

2 Objectives and endpoints

NOTE: the term "baseline" is used throughout this protocol to refer to "prior to study treatment".

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of the investigational treatments, compared to placebo in moderate to severe inflammatory HS patients	• Proportion of patients achieving clinical response evaluated by the simplified Hidradenitis Suppurativa Clinical Response (HiSCR) after 16 weeks of treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of the investigational treatments in patients with moderate to severe HS	• Number and severity of AEs • Physical examination, vital signs, safety laboratory measurements, ECGs at baseline and repeatedly until study completion visit
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

Objective(s)	Endpoint(s)
CCI	

Objective(s)	Endpoint(s)
CCI	

3 Study design

Figure 3-1 CCI

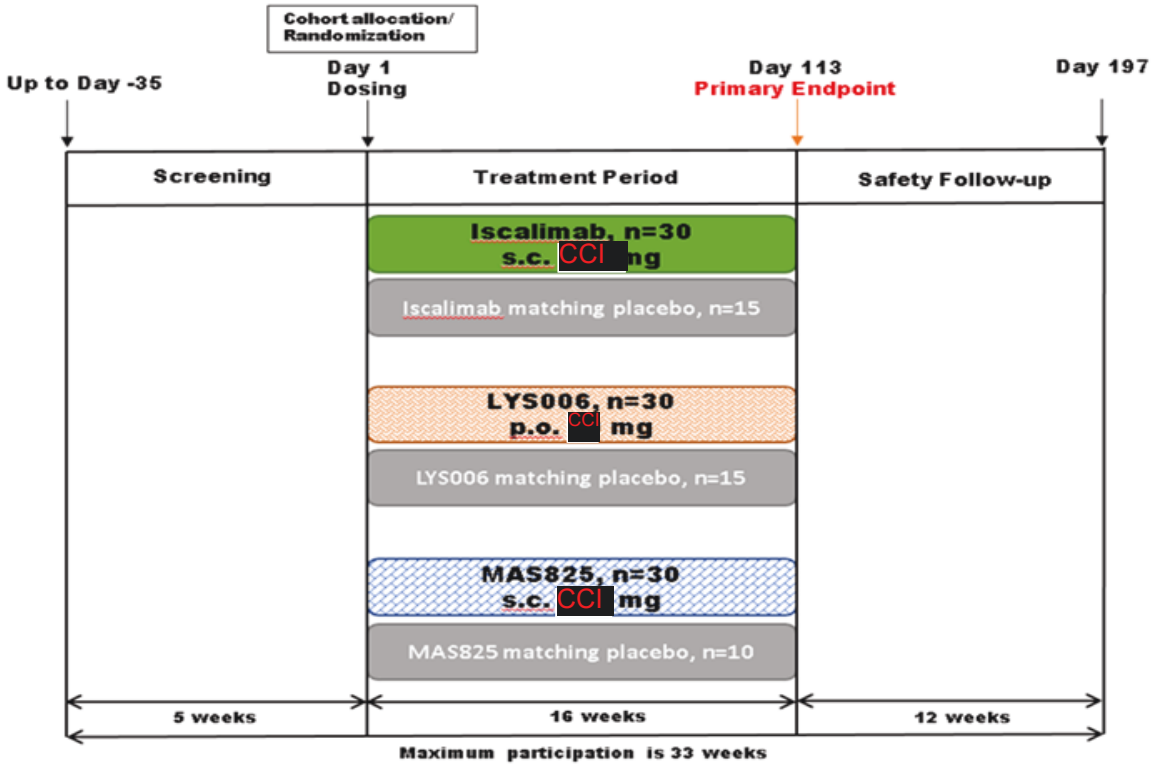


Figure 3-2 Cohort D study design

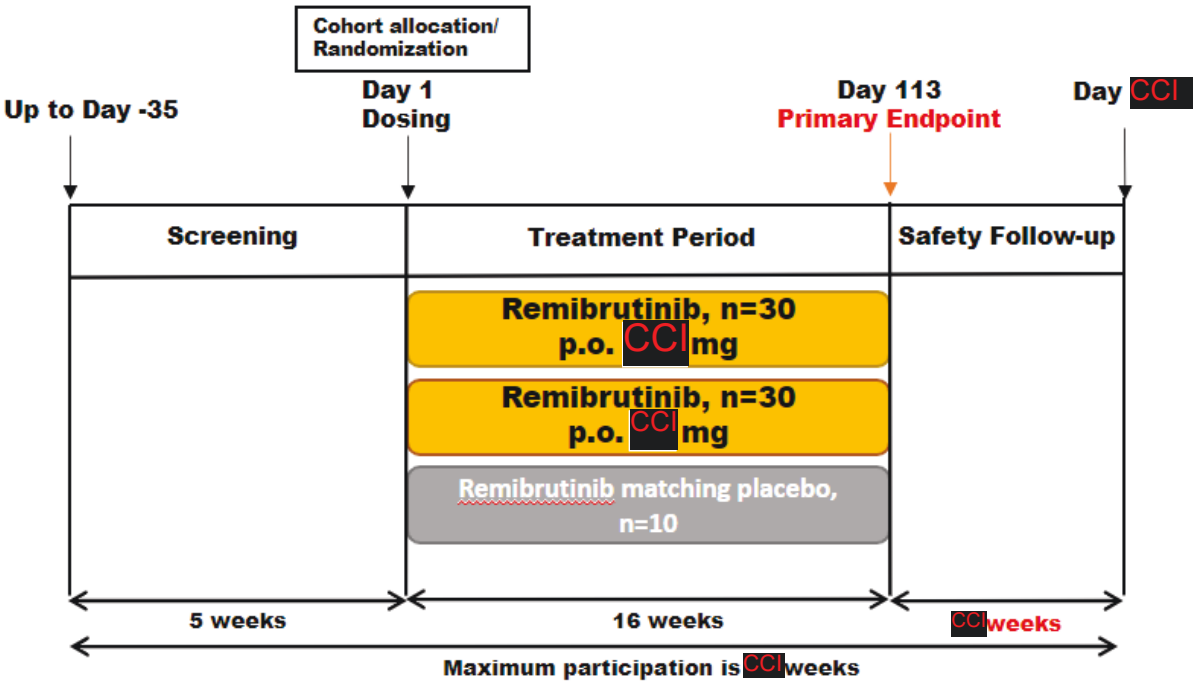
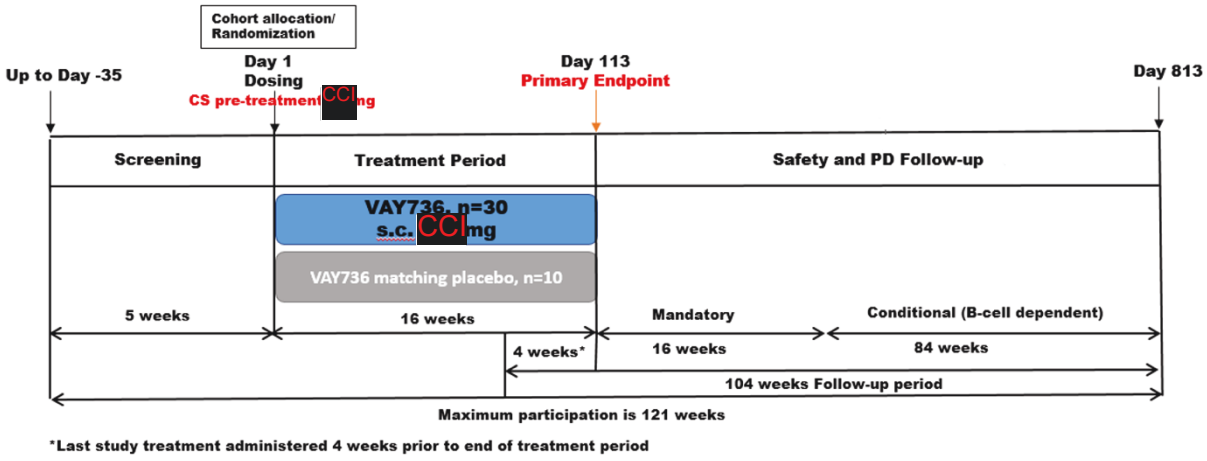


Figure 3-3 Cohort E study design



This is an exploratory, randomized, subject and investigator-blinded, placebo-controlled, multi-center and parallel-group non-confirmatory study to assess the efficacy, safety and tolerability of five investigational drugs, iscalimab, LYS006, MAS825, remibrutinib and ianalumab in subjects with moderate to severe HS. The study will be set up as a platform study to allow early discontinuation of cohorts and inclusion of new cohorts. The study will consist of a screening period of up to 35 days, a treatment period of 16 weeks and a safety follow-up of 12 weeks CCI [redacted] For ianalumab, following the last treatment on Day 85 and the End of treatment visit on Day 113, there will be a mandatory follow up period of 16 weeks, followed by a conditional follow up period for up to 84 weeks.

Eligibility criteria will be confirmed based on the evaluations that take place during the screening visit and at randomization (pre-dose on Day 1), as specified in Section 5. Randomization may be performed only after a subject's study eligibility is confirmed on Day 1. With the exception of the urine pregnancy test, Day 1 laboratory and ECG results are not required to be available prior to randomization.

Subjects will be allocated to either Cohort A, B, C, D or E based on the cohort-specific eligibility criteria. Should a subject be eligible for more than one cohort, they will be randomized to any suitable cohort. HS disease severity at Day 1 will be used to determine cohort eligibility.

Subjects will be allocated to either:

- **Cohort A**: consisting of an investigational treatment arm, iscalimab, 600 mg (2 injections of 2 mL) s.c. weekly for 4 weeks then biweekly, or its corresponding placebo (2 x 2 mL) s.c. weekly for 4 weeks then biweekly

or

- **Cohort B**: consisting of an investigational treatment arm, LYS006, CCI mg CCI or its corresponding placebo b.i.d. p.o.

or

- **Cohort C**: consisting of an investigational treatment arm, MAS825, CCI mg s.c. CCI injections of CCI mL) CCI then CCI or its corresponding placebo s.c. CCI mL) CCI

or

- **Cohort D**: consisting of two investigational treatment arms and placebo CCI. p.o.:
  - CCI mg CCI remibrutinib plus placebo to CCI mg remibrutinib CCI
  - CCI mg CCI. remibrutinib plus placebo to CCI mg remibrutinib CCI
  - Placebo to CCI mg remibrutinib and placebo to CCI mg remibrutinib CCI.

or

- **Cohort E**: consisting of an investigational treatment arm, ianalumab, CCI mg CCI CCI injections of CCI mL) CCI or its corresponding placebo s.c. CCI injections of CCI mL) CCI.

Within each cohort, subjects will be randomized to either the investigational treatment arm or its corresponding placebo in a 2:1 ratio for Cohorts A and B, 3:1 for Cohort C and Cohort E or 3:3:1 for Cohort D. Cohort allocation will be performed by the IRT system. If a subject is only eligible for one open cohort, they will be allocated 100% to that cohort. If the subject is eligible for more than one open cohort, the IRT will randomly allocate the subject to a cohort. The sponsor can set the cohort allocation ratio to favor any of the cohorts but this favoring to any one cohort will not exceed 80%.

In the event that enrolment into any cohort is not possible e.g. due to pending approvals, vendor readiness or study supply availability enrolment may continue into other available cohorts.

This platform study is set up to allow for further addition of cohorts of similar size and population, for other investigational treatments in early clinical phase for subjects with moderate to severe HS. These additional cohorts may include orally administered or injectable compounds. Inclusion of cohorts, to up to 5 in total, will only be proposed via substantial protocol amendments and will depend on the following criteria:

- at least one study cohort still ongoing or communication has been provided to HAs, IRBs/ECs to confirm that further cohorts may be included.
- CCI scientific rationale
- perceived favorable benefit-risk profile
- pre-requisites that allow for at least 12, ideally 16 weeks of treatment duration

It is expected that additional cohorts will be subject and investigator-blinded and include a placebo.

Adult subjects with confirmed HS and with moderate to severe disease severity will be enrolled.

Subjects with a minimum of 5 or more lesions at randomization (pre-dose on Day 1) will be eligible for all cohorts (A, B, C, D and E).

For Cohort B only, a stratification factor will be utilized. Subjects with a minimum of 3 but less than 5 lesions (i.e. 3 - 4 lesions) at randomization (pre-dose on Day 1) will be capped at a maximum number of 15 subjects in Cohort B (up to 15 subjects with 3-4 lesions).

For Cohort D, all subjects must have 3 or more lesions. Interim analysis in Cohort A and Cohort B showed that in terms of response to placebo, patients with lower severity as compared with higher severity had a similar response in the primary endpoint simplified HiSCR. Thus, no further stratification was used for cohort D. Randomization to the cohorts and respective arms will be done using a centralized Interactive Response Technology (IRT) system.

The primary clinical endpoint is the simplified HiSCR (Hidradenitis Suppurativa Clinical Response) after 16 weeks of treatment.

On Day 113 (Week 17), after safety and other assessments have been performed, all subjects will enter the follow-up period and will not receive any further study drug administrations. If medically justified, and if no potential safety concerns have been identified (after discussion with the sponsor), subjects may receive previously prohibited medication during this follow-up period.

Safety and efficacy assessments will be conducted at follow-up visits as specified in the assessment schedule. Pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity (IG; Cohorts A, C and E only) and biomarker samples will also be collected. The end of study (EOS) visit will occur on Day 197 (Week 29) for Cohorts A, B and C, Day 141 (Week 21) for Cohort D and up to Day 813 (Week 121) for Cohort E, and will include study completion evaluations followed by discharge from the study. Blinding will be maintained for the investigator and the subject until the study is completed.

3.1 Cohort A (iscalimab)

This cohort will comprise approximately 45 subjects, 30 will receive the investigational treatment and 15 will receive placebo.

- On Day 1, a dose of 600 mg iscalimab or matching placebo (2 injections of 2 mL) will be administered by subcutaneous injection (s.c.) by trained site personnel.
  Clinical assessments will be performed as well as PK, target engagement, IG, pathway and disease biomarkers and safety assessments. Subjects will be discharged from the site on the same day after completion of all assessments, provided there are no safety concerns. Following the first administration, subjects should be observed for immediate injection site reactions for at least one hour at the site, or longer at the discretion of the Investigator.
- Subjects will return to the study center to receive weekly s.c. doses of either 600 mg iscalimab or matching placebo (same as they have received on Day 1) on Day 8 (Week 2), Day 15 (Week 3), Day 22 (Week 4) and Day 29 (Week 5).
- After Week 5, subjects will receive 600 mg s.c. iscalimab every other week, on Day 43 (Week 7), Day 57 (Week 9), Day 71 (Week 11), Day 85 (Week 13), and Day 99 (Week 15; last dose).

Safety and selected efficacy assessments will be conducted during these visits and PK/target engagement/IG/pathway and disease biomarker samples will be collected.

3.2 Cohort B (LYS006)

This cohort will comprise approximately 40 to 45 subjects, approximately 30 subjects will receive the investigational treatment and approximately 15 subjects will receive matching placebo.

- On Day 1, LYS006 20 mg or its corresponding placebo will be provided to the subjects at the site. The subject will be instructed by the site personnel how to take the drug (b.i.d.), including the need for sufficient fluid intake (preferably water) and to take the drug during or shortly after their morning and evening meal. Clinical assessments will be performed as well as PK, target engagement, pathway and disease biomarkers, and necessary safety assessments. Subjects will be discharged from the site on the same day after completion of all assessments provided there are no safety concerns.
- Subjects will return to the study center on the days specified in the assessment schedule. Safety and selected efficacy assessments will be conducted during these visits and PK/biomarker samples will be collected.

3.3 Cohort C (MAS825)

This cohort will comprise approximately CCI subjects; CCI subjects will receive the investigational treatment and CCI subjects will receive matching placebo.

- On Day 1, MAS825 CCI mg or its corresponding placebo (CCI injections of CCI mL) will be administered by subcutaneous injection (s.c.) by trained site personnel.
  Clinical assessments will be performed as well as PK, target engagement, immunogenicity, pathway and disease biomarkers and safety assessments. Subjects will be discharged from the site on the same day after completion of all assessments, provided

there are no safety concerns. Following the first administration, subjects should be observed at the site for immediate injection site reactions for at least one hour, or longer at the discretion of the Investigator.

- Subjects will return to the study center during the CCI (from Day 1 (Week 1) to Day 29 (Week 5)) to receive MAS825 CCI s.c. (CCI; 3 doses).
- Then during the maintenance phase of the study (from Day 29 (Week 5) to Day 85 (Week 13)) MAS825 will be administered at CCI mg s.c. CCI (CCI doses).

Safety and selected efficacy assessments will be conducted during these visits and PK, target engagement, immunogenicity and pathway/disease biomarker samples will be collected.

3.4 Cohort D (Remibrutinib)

This cohort will comprise approximately CCI subjects. Approximately CCI subjects will receive the investigational treatment: CCI will receive CCI mg CCI, 30 will receive CCI mg CCI., approximately CCI subjects will receive matching placebos.

- On Day 1, remibrutinib CCI mg, CCI mg or their corresponding placebo will be provided to the subjects at the site. The study medication may be taken with or without a meal on non-PK assessment days, but subjects should adhere to their choice throughout the study. If taken without food, the study medication should be taken with a glass of water (250 mL) at least 2 hours after the last meal and 1 hour before the next meal. Clinical assessments will be performed as well as PK, target engagement, pathway and disease biomarkers, and necessary safety assessments. Subjects will be discharged from the site on the same day after completion of all assessments provided there are no safety concerns.
- Subjects will return to the study center on the days specified in the assessment schedule. Safety and selected efficacy assessments will be conducted during these visits and PK/biomarker samples will be collected.
- After the treatment period of 16 weeks, the subjects will enter a follow-up period of 4 weeks prior to the End of Study visit.

3.5 Cohort E (Ianalumab)

This cohort will comprise approximately 40 subjects; 30 subjects will receive the investigational treatment and 10 subjects will receive matching placebo.

- On Day 1, ianalumab CCI mg or its corresponding placebo (CCI injections of CCI mL) will be administered by CCI injection (CCI) by trained site personnel. Prior to the first administration of study treatment, study subjects must receive pre-medication CCI CCI or equivalent administered orally. See Section 6.1.2 for more details. Clinical assessments will be performed as well as PK, target engagement, immunogenicity, pathway and disease biomarkers and safety assessments. Subjects will be discharged from the site on the same day after completion of all assessments, provided there are no safety concerns. Following the first administration, subjects should be observed at the site for potential injection related reactions for at least CCI hours, or longer at the discretion of the Investigator.

- Subjects will return to the study center (from Day 29 (Week 5) to Day 85 (Week 13) to receive CCI mg s.c. CCI

Safety and selected efficacy assessments will be conducted during these visits and PK, target engagement, immunogenicity and pathway/disease biomarker samples will be collected.

4 Rationale

4.1 Rationale for study design

This proof of concept study in moderate to severe HS subjects is designed as an adaptive platform study to allow ineffective treatment cohorts to be closed early and avoid unnecessary exposure of subjects. In addition, it will allow the inclusion of new innovative treatments which can be directly compared, in a field with high medical need. This may result in an improved and more efficient inclusion of subjects. The slightly different inclusion criteria per study cohort permit a coordinated screening, and thus subjects may benefit from different therapeutic approaches and more opportunities to participate in investigational research and earlier access to potentially beneficial therapies (see Woodcock, LaVange 2017). Despite the lack of universally recognized severity criteria, a minimum of 3 inflammatory lesions has been accepted in the past to describe moderate to severe HS patients (Kimball et al 2016). This threshold has been used for defining the minimal inclusion criteria for Cohort B and D with an oral treatment LYS006 or remibrutinib respectively, since there is no regulatory precedent for oral treatments. Injectables are generally used in patients with higher severity as compared to oral treatments. Thus, a minimum of 5 inflammatory lesions is selected for Cohort A with iscalimab, Cohort C with MAS825 and Cohort E with ianalumab.

The primary objective is to show efficacy of the selected investigational treatments, in HS subjects after 16 weeks of treatment in comparison to placebo. After the 16-week treatment period, a follow up period of 12 weeks is included to observe whether the effect can be sustained or increased after 16 weeks of treatment. This period also covers the safety follow-up period of iscalimab, LYS006, MAS825 and ianalumab. For ianalumab there will be a mandatory follow up period of 16 weeks (20 weeks from the last treatment), followed by a conditional follow up period for up to 84 weeks for a total maximum follow up period of 2 years.

The EoS visit will be performed 2 years after the last dose of the study treatment have passed. After achieving the B cell recovery, conditional follow-up may be stopped and the EOS visit performed at any point. If B cell counts have not recovered at 2 years after the last dose of the study treatment, the follow-up may stop and the EOS visit may be performed.

B cell recovery is defined as when CD19+ B cell counts return to ≥80% of baseline value or 50 cells/µL (Genovese et al 2008), whichever occurs earlier.

CCI An additional urine pregnancy test will also be done for women of childbearing potential 5 months after the last treatment in Cohort C (MAS825).

Blinding of subjects and investigators allows for an unbiased assessment of subjective readouts such as lesion counts in HS or global CCI scores, as well as adverse events.

Clinical assessments available for HS are not universally recognized. A recent Cochrane review (Ingram et al 2016) stated that 12 randomized prospective trials included in the review utilized 16 physician-reported instruments. The study includes multiple clinical endpoints, to better evaluate the properties of these selected endpoints:

- For this study, the simplified HiSCR was selected as the primary endpoint. The original HiSCR used in the phase 3 clinical trials conducted with adalimumab (Kimball et al 2016) has been validated, but may include some potential limitations, notably as it has been shown recently that investigators have difficulties in reliably assessing abscesses and sinus tracts and that the inter-rater variability is high (presentation at IDEOM meeting, Washington, USA 2018). The simplified HiSCR is defined as 50% decrease in the total number of abscesses plus inflammatory nodules, without any increase in draining fistulae. However, in contrast to the original HiSCR, increases in abscesses are allowed to constitute a clinical response, if the previous conditions are met.
- The inflammatory lesions of HS will be counted as individual lesions (inflammatory nodules, abscesses and draining fistulae) in the typical anatomical areas. In addition to the count, a global assessment scale (Hidradenitis Suppurativa - CCI or CCI as well as a composite score CCI or CCI will be used. Abscesses and nodules will also be presented as AN Counts.
- Several patient reported outcomes will be used, including the CCI and the CCI (at selected sites). Finally, as from a subject's perspective skin related pain is the most important symptom, the numerical rating scale (NRS) for pain is included.
- As CCI is now recognized as a symptom in HS patients, CCI has been included in Cohort D and E CCI
- In addition, in Cohorts D and E a new scale the CCI will be used as described by CCI

4.2 Rationale for dose/regimen and duration of treatment

The median treatment duration of comparative HS trials in a recent Cochrane review was 16 weeks (Ingram et al 2016). This was also the duration of a similar placebo-controlled phase 2 study with adalimumab, recently approved for the treatment of HS (Kimball et al 2012) while another placebo-controlled trial was up to 24 weeks in a very similar HS population (Tzanetakou et al 2016). Placebo treatment may have some effect on the disease, reflecting the natural history, regression to the mean effects or a tighter clinical management of the subjects in part also due to concomitant medication. In this trial, use of topicals for wound care is allowed, as well as short term (< 2 weeks) antibiotics, which can be used if medically justified (as outlined in Section 6.2).

Clinically significant worsening of HS necessitating a prohibited medical, surgical or physical treatment may lead to premature discontinuation of the concerned subject (as outlined in Section 9.1).

4.2.1 Cohort A (iscalimab)

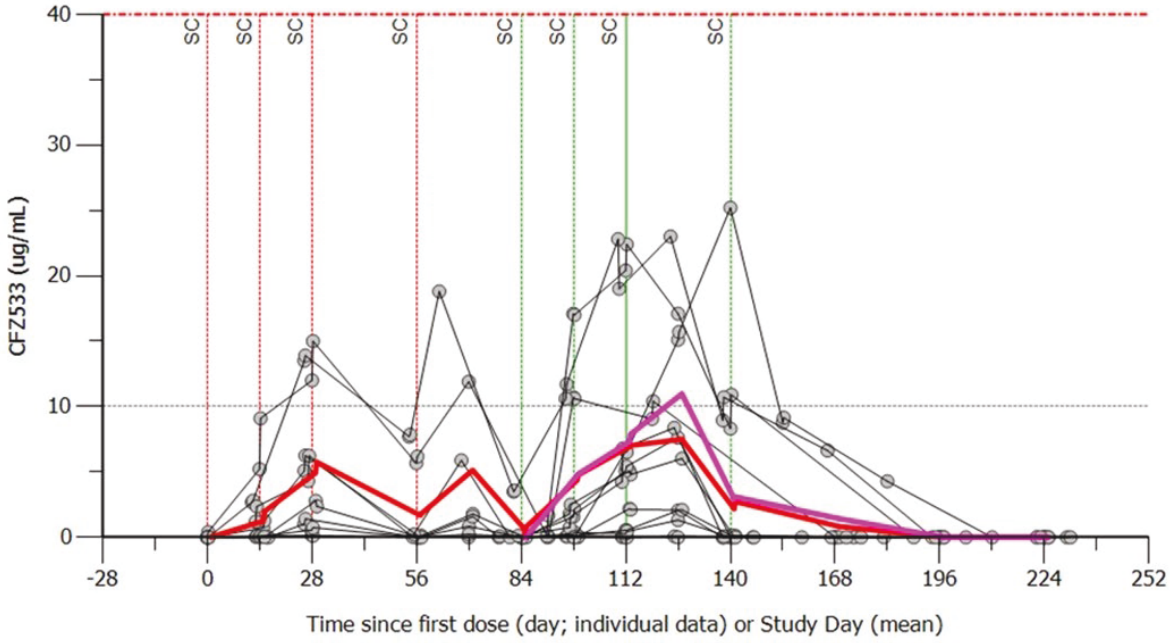
At each dosing visit, HS subjects will receive 600 mg iscalimab s.c. (2 injections of 2 mL).

During the **loading phase of the study** (from Day 1 (Week 1) to Day 29 inclusive (Week 5)), iscalimab will be administered **weekly** s.c. (Q1W; 5 doses).

HS subjects present with a high inflammatory status which is likely to be associated with high CD40 expression and therefore the loading phase is justified to overcome the efficient CD40-mediated elimination of iscalimab when iscalimab is administered s.c. in conditions where CD40 expression in tissues is likely to be elevated.

This has been demonstrated in Study CCFZ533X2203 in pSS subjects. In Cohort 1 (s.c. regimen; Figure 4-1) most subjects demonstrated lower than expected PK profiles due to efficient pre-systemic CD40-mediated elimination, likely in the interstitium, lymphatic capillaries and/or lymph nodes. As CD40 receptors have been reported to be upregulated on parenchyma in inflamed tissues, an increased level of CD40 receptors is likely to be the origin of the efficient pre-systemic CD40-mediated elimination of iscalimab. As mentioned before, iscalimab is subject to target mediated elimination, and elevated CD40 expression is associated with high elimination rate of iscalimab if CD40 receptors are not fully saturated.

Figure 4-1 Study CCFZ533X2203 in pSS patients: preliminary iscalimab plasma concentration-time profiles from Cohort 1 (3 mg/kg s.c. regimen) demonstrating the efficient pre-systemic CD40-mediated elimination of iscalimab after s.c. if CD40 receptors are not fully saturated

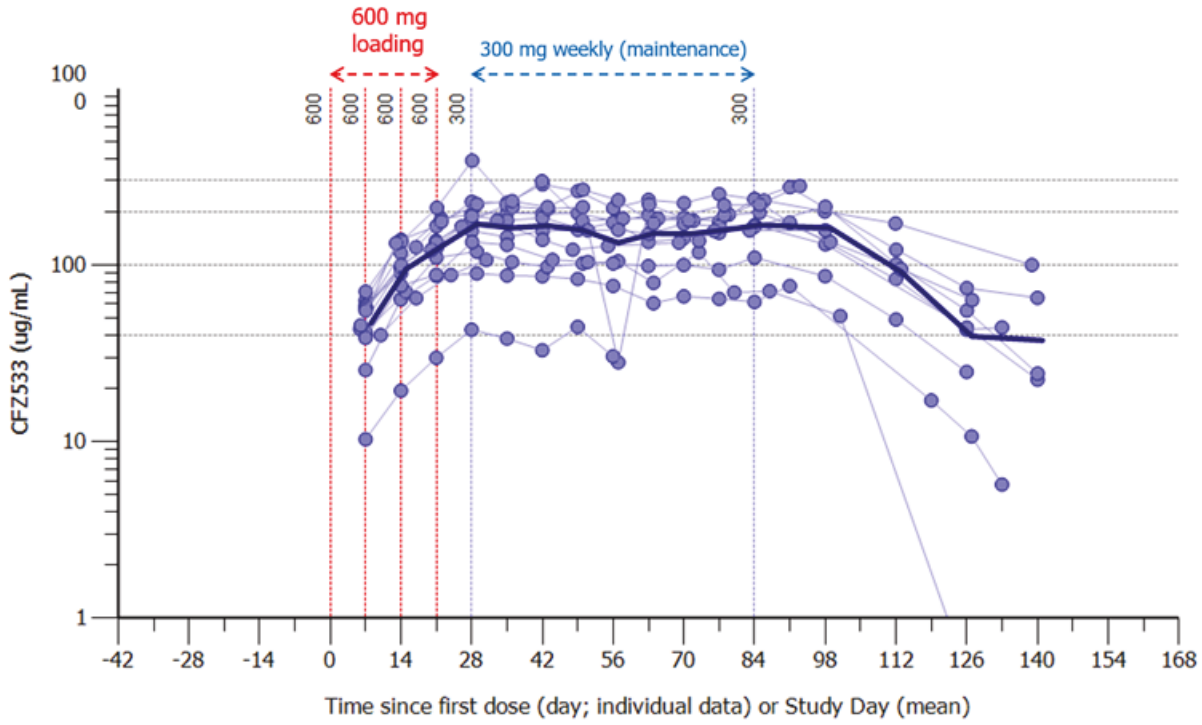


In Study CCFZ533X2203-Cohort 1, iscalimab was administered at 3 mg/kg s.c. on Study Day 1, 15, 29, and 57 in the placebo-controlled period, and on Study Day 85, 99, 113, and 141 in the open-labelled period. Most subjects demonstrated lower than expected PK profiles. Only a few subjects had iscalimab concentrations ≥10 µg/mL, and all of them had iscalimab concentrations well below 40 µg/mL, a threshold associated with complete suppression of germinal center development and T cell dependent antibody response in non-human primates (more details in the Investigator's Brochure). Individual (gray dots and lines) and mean data (red and purple lines) are presented. Red line: Subjects received iscalimab during the placebo-controlled and the open labelled periods. Purple line: Subjects received iscalimab only during the open-labelled period.

In HS subjects, the CCI mg s.c. weekly regimen during the loading period is expected to provide, at start of treatment, rapid and complete CD40-CD40L pathway blockade in target tissues.

In Study CCFZ533X2203, to demonstrate that an s.c. regimen was able to deliver steady state trough plasma concentrations similar to Cohort 2 (i.v. regimen; positive PoC) and had the ability to overcome the CD40-mediated elimination of iscalimab, Cohort 3 was introduced: CCI mg s.c. weekly on 4 occasions (loading), followed by CCI mg s.c. weekly on 9 occasions (maintenance; Figure 4-2). Preliminary data indicated that this regimen was safe and well tolerated.

Figure 4-2 **Study CCFZ533X2203 in pSS subjects: preliminary iscalimab plasma concentration-time profiles in Cohort 3 demonstrating that a s.c. loading and maintenance regimen has the ability to overcome CD40-mediated elimination of iscalimab**



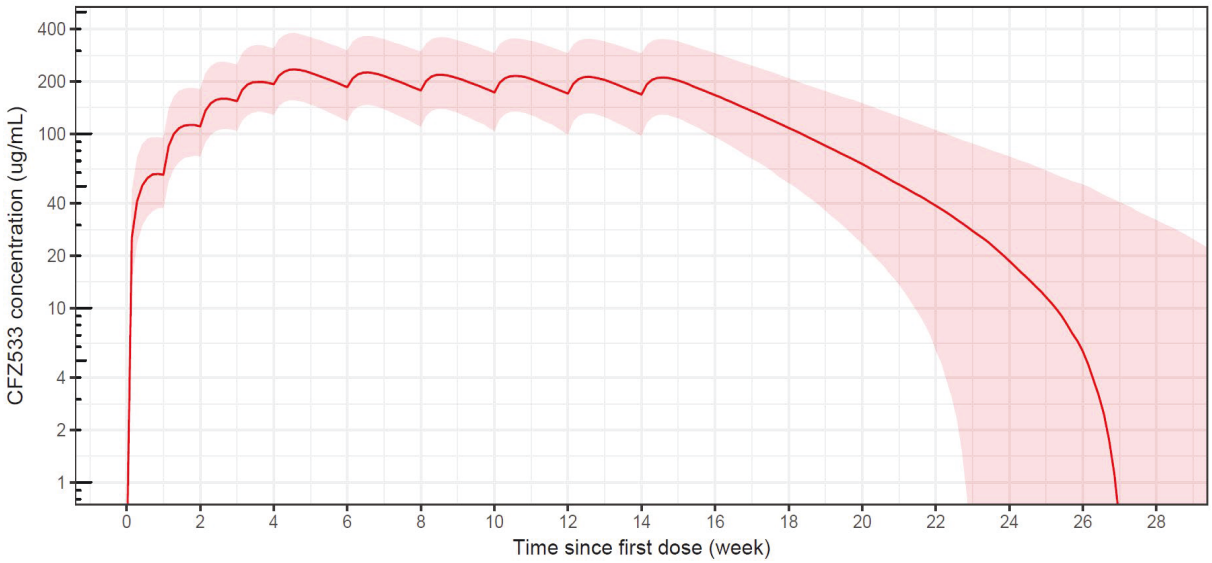
In Study CCFZ533X2203-Cohort 3 (interim/preliminary data), iscalimab was administered at CCI mg s.c. on Study Day 1, 8, 15 and 22 for the loading phase (red vertical bars), and at CCI mg s.c. CCI y from Study Day 29 to Study Day 85. Individual (blue dots) and mean (thick blue line) plasma concentration data are presented.

During the **maintenance phase of the study** (from Day 43 (Week 7) to Day 99 (Week 15)) iscalimab will be administered at CCI mg s.c. CCI

TheCCI mg CCI maintenance regimen is expected to deliver steady state trough plasma concentrations of about 160-170 µg/mL (Figure 4-3), which is slightly above those observed in Study CCFZ533X2203-Cohort 2 (10 mg/kg IV regimen) in pSS subjects. In Study CCFZ533X2203-Cohort 2, steady state iscalimab trough plasma concentrations of CCI µg/mL were associated with clinical efficacy, such as clinical improvement of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), and suppression of a biologically relevant biomarker CXCL13 (chemokine CXC ligand 13 protein; a marker of germinal center activity).

In HS (a follicular skin disease with deep dermal nodules/boils (in apocrine gland-bearing skin) and abscesses), tissue penetration of iscalimab is key and is likely to require higher plasma exposure as compared to pSS.

Figure 4-3 Predicted time-course of plasma iscalimab concentrations in HS patients



The line represents the predicted time-course of plasma iscalimab concentrations for the typical patient; the band represents the 90% prediction interval (90% of the patients' concentration is expected in that area).

4.2.1.1 Target engagement after last dose

Based on the predicted median iscalimab plasma concentration-time profile in HS subjects (Figure 4-3), about 10 weeks after the last dose (administered on Day 99), iscalimab plasma concentrations are expected to be <CCI µg/mL with no expected pharmacodynamic activity in target tissues like germinal centers (more details in the Investigator Brochure). A 14-week washout period after the last dose (EOS on Day 197) is acceptable considering the uncertainties in the predicted PK profiles.

4.2.2 Cohort B: LYS006

In this cohort, a dose of CCI mg CCI is proposed to explore the efficacy and safety of LYS006 in HS.

The main potential safety risk identified in LYS006 preclinical safety studies, was CCI and CCI; these adverse effects determined the NOAEL selection for both preclinical species. In 16-week toxicity studies, the NOAEL was established at 100 mg/kg/day in the dog and 15 mg/kg/day in the rat, with total drug Cmax-based safety margins of 34 and 29, respectively, as compared with the proposed dose of 20 mg b.i.d. in this study. At this dose, a CCI is expected as suggested by the data from healthy volunteers of the first in human study (CLYS006X2101). In this FiH study, 80 mg b.i.d. was well tolerated over 12 days without detection of CCI CCI. This clinical safety margin of at least 4 should allow for potentially higher variability in pharmacokinetics and urinary excretion in the trial population.

A dose-dependent increase in incidence and severity of CCI was seen in a 16-week dog study at doses ≥30 mg/kg/day (at Cmax-values ≥ 5 times higher than observed at a clinical dose of CCI mg CCI.). Mildly decreased CCI in dogs administered 100 mg/kg/day (at Cmax-based exposure multiples of 34) were suggestive of decreased CCI formation, but not considered adverse due to the absence of correlating microscopic findings in CCI.

Steady-state leukotriene A4 hydrolase (LTA4H) target inhibition assessed *ex-vivo* in trough blood samples was on average CCI% at CCI mg CCI, CCI% at CCI mg CCI and CCI% at CCI mg CCI.. Therefore, CCI mg CCI. is selected as a pharmacodynamically active dose hypothesised to generate a maximal clinical response. Whilst the degree of LTA4H target inhibition may be lower in skin and other tissues, there is no specific reason such as slow or restricted drug distribution or high LTA4H turnover currently hypothesised to cause a major difference from the blood compartment. Selection of a dose higher than CCI mg CCI. appears unjustified considering the high degree of target inhibition at this dose level and the increasing risk of CCI CCI at higher dose levels.

In the FiH trial, a very high fluctuation between peak and trough concentrations was observed. High peak plasma concentrations are associated with CCI and may constitute a potential safety concern. The present study applies a b.i.d. posology to reduce peak concentrations whilst maintaining high levels of LTA4H target inhibition. Moreover, as seen in the FiH trial, dosing together with food intake (standard breakfast, tested at 10 mg) decreased Cmax of LYS006 by approximately 40% with little impact on AUC. Thus, dosing with food, as proposed in this study, is expected to reduce peak plasma and CCI concentrations to a similar extent and will therefore further decrease the likelihood of CCI CCI, which was not observed at higher doses up 80 mg b.i.d. in the FiH study.

4.2.3 Cohort C (MAS825)

During the CCI mg of MAS825 will be administered s.c. CCI (from Day 1 (Week 1) to Day 29 (Week 5)) (CCI; CCI doses).

During the **maintenance phase of the study** (from Day 29 (Week 5) to Day 85 (Week 13)) MAS825 will be administered at CCI mg s.c. CCI doses).

The model used to predict the dynamics of the anti-IL-1β/IL-18 CCI antibody and its targets in serum consists of a general competitive binding model for the IL-18 arm CCI) and the previously published model of CCI adjusted to CCI CCI arm with a novel model describing the free and total CCI. To predict the dynamics of CCI in response to the application of CCI, the model established in the clinical CCI study was used (CCI) and the CCI PK parameters and binding affinities were updated accordingly. To adjust the CCI concentrations in CCI patients, we used the synthesis and clearance parameters of this CCI listed in the CCI clinical study CCI The model is based on in-house *in vitro* and published human data from free and total IL-18 serum concentrations from patients across several autoimmune diseases (Weiss et al 2018). Based on this, a dosing schedule of CCI s.c. is predicted to result in the simultaneous

reduction of CCI IL-1β and IL-18 levels in serum and effective neutralization of IL-1β as well as IL-18 is expected.

Figure 4-4 CCI

Figure 4-5 CCI
CCI

MAS825 is evaluated in a FiH single dose ascending study up to CCI mg/kg i.v. in healthy volunteers without any drug related SAEs. The pharmacokinetics (PK) of MAS825 in human follows human CCI based on CCI data and is CCI CCI to soluble ligand cytokine target(s). MAS825 showed a CCI in exposure matching the predicted human PK (evaluated up to CCI mg/kg i.v.). The predicted human PK parameters of MAS825 are: clearance (CL) = CCI L/d, volume of distribution (Vd) = CCI L (for a 70-kg human subject) or CCI L/kg; half-life (T1/2) = CCI days. Preliminary analysis of PK profiles from the FiH study has CCI of CCI of MAS825 due to the formation of anti-drug antibodies (ADA).

Based on recent subcutaneous data from the FiH study, bioavailability and absorption rate constants were adjusted due to these findings and used in the prediction of the subcutaneous PK.

Figure 4-6 CCI

The MAS825 dose of CCI mg CCI s.c. is further justified by:

The dose is predicted to lead to rapid and simultaneous neutralization of all systemic free IL-1β and IL-18. The exposure after CCI mg s.c. CCI IC90 for IL-1β and IL-18 for more than CCI days after a single dose.

The dose and the projected Cmax is lower than the well tolerated MAS825 dose administered to healthy volunteers and COVID-19 patients with no identified safety concerns (CCI mg/kg i.v.).

The predicted exposure for humans for CCI mg s.c. CCI of MAS825 is approximately CCI -fold lower for AUC and approximately CCI -fold lower for Cmax to the non-clinical NOEL of CCI mg/kg s.c. in CCI .

CCI has been administered to healthy subjects in doses up to CCI mg/kg CCI and was well tolerated. PoC studies in pulmonary sarcoidosis and atopic dermatitis patients with CCI mg/kg i.v. CCI are currently ongoing. In the atopic dermatitis study an arm with a roughly three fold lower dose of CCI mg s.c. CCI is included.

CCI is approved in doses up to CCI mg every CCI In the 26-week toxicology study in CCI), CCI mg/kg, twice a week had no adverse events with no observed effect level.

4.2.4 Cohort D (remibrutinib)

In this cohort, two doses, CCI mg CCI. and CCI mg CCI., are proposed to explore the efficacy and safety of remibrutinib in adult HS patients.

Based on the safety data from the completed and ongoing remibrutinib trials, the clinical safety profile of remibrutinib is favorable and fully supports the selected doses of CCI mg CCI. and CCI mg CCI. The dose of CCI mg CCI has been used in several studies in different indications, such as AD, asthma, pSS, as well as in CSU. In the primary endpoint analysis of the dose-range finding Phase 2b study CLOU064A2201 in CSU, where the dose range of CCI mg CCI. to CCI mgCCI was tested, most adverse events (AEs) were mild in severity, without any patterns of clustering or dose-dependency. Ongoing clinical safety review of CLOU064A2201E1, the ongoing long-term extension study of CLOU064A2201, which has a 52-week treatment period with CCI mg remibrutinib CCI., was consistent with the core study CLOU064A2201 safety profile and did not reveal any safety signals. In addition, the clinical safety data from the completed Phase 1 studies, which tested doses of remibrutinib up to CCI mg CCI and CCI mgCCI was favorable and did not raise any concerns. For more detailed information on the safety profile of remibrutinib, please see Section 4.5 and the IB.

In the dose-range finding study CLOU064A2201 with 311 adult CSU patients, the efficacy of remibrutinib was assessed versus placebo for the following dose regimens: CCI mg CCI., CCI mg CCI., CCI mg CCI., CCI mg CCI., CCI mg CCI., CCI mg CCI The treatment duration was 12 weeks and the primary endpoint was change in weekly urticaria activity score (UAS7) from baseline at Week 4. At the time of the primary endpoint analysis, there were 301 participants (40-47 per arm) in the full analysis set with a UAS7 score at Week 4, and 233 participants (29-37 per arm) with a UAS7 score at Week 12. The treatment groups were overall well balanced in terms of demography and baseline disease characteristics.

The study demonstrated clinical efficacy of remibrutinib in the treatment of CSU, with all tested doses showing superior efficacy over placebo at Week 4. A dose-response relationship was established for the CCI. and CCI remibrutinib dosing regimens compared to placebo with respect to the change from baseline in UAS7 score at Week 4, with the dose-response plateau already achieved at CCI mg for CCI. dosing (CCI mg total daily exposure) and at CCI mg for CCI dosing CCI mg total daily exposure).

Figure 4-7 CCI

A CCI dosing regimen is supported from a pharmacokinetics, pharmacodynamics and mode-of-action perspective, in order to ensure sustained BTK inhibition over 24 hours, considering the relatively fast turn-over of the covalent BTK-remibrutinib complex in tissue (see Investigator´s Brochure for details). Furthermore, CCI dosing leads to a faster onset of action and steady state.

Taken together, all tested remibrutinib dosing regimens demonstrated superior efficacy in treating signs and symptoms of CSU compared to placebo, when assessing the mean change from baseline in UAS7. Based on the data from CLOU064A2201, CCI mg CCI was selected as the optimal dosing regimen for the treatment of CSU, a disease primarily driven by mast cell activation and degranulation. However, the mechanism of action and primary target may be different in HS as compared to CSU. We hypothesize that the scientific rationale of BTK inhibition in HS is related to B cell and plasma cells, as these can be found in tertiary lymphoid organs in lesional tissue (Gudjonsson et al 2020). BTK turn-over is potentially higher in B cells located in tertiary lymphoid organs of HS lesions compared to skin mast cells and sufficient target tissue penetration might be more difficult to achieve in HS compared to CSU, due to the fibrotic tissue remodeling as well as abscess and fistula tract formation typically present in HS. Thus, for Cohort D, we will explore not only the dose of CCI mg CCI., which was selected for the CSU indication but also CCI mg CCI, which, as mentioned above, is well covered from a safety perspective and can potentially offer higher tissue penetration with higher tissue BTK occupancy (see IB).

Translational PK/PD model simulations were used to predict human peripheral tissue occupancy (e.g. spleen and lymph node) of remibrutinib assuming absence of relevant inter-species differences in turn-over and drug-potency. The PK/PD model was focused on B cells, which are, as described above, hypothesized to be the relevant primary target of remibrutinib

in HS. B cells are typically residing in lymph nodes and in the spleen, besides a circulating fraction. In HS, B cells are also present in so called 'tertiary lymphoid organs' in HS lesional tissue, resembling key lymph node and germinal center characteristics. It can be assumed that B cells residing in spleen, lymph nodes or tertiary lymphoid organs in HS lesions show a faster BTK turn-over compared to circulating B cells in peripheral blood. The model predicts that overall significantly higher BTK occupancy can be achieved using a CCI dosing regimen. While a trough BTK occupancy of approximately 70-95% is predicted in human tissue for the CCImg CCI dosing regimen, the CCImg CCI dosing regimen is predicted to achieve ≥90% trough BTK occupancy (for more information refer to the IB).

While B cells are hypothesized to be the leading target of BTK inhibition in HS, there are also other relevant immune cells types present in HS lesions, in which BTK is expressed and indispensable for Fc epsilon receptor (FcεR1) or Fc gamma receptor (FcγR) signaling, such as macrophages or mast cells. BTK inhibition in these cells might further contribute to a potential efficacy of remibrutinib in the treatment of HS.

Single doses lower than CCI mg did not elicit high, sustained (>24h), near complete (>90%) BTK occupancy in all subjects in a first in human study (see the IB). Thus, based on multiple dosing and experience in CSU, another skin disease, both doses of CCImg CCI. CCI mg CCI remibrutinib could have the potential to elicit a therapeutic response in HS patients.

In total, approximately 771 adult subjects have been enrolled into clinical studies with remibrutinib (as of March 2021), out of which at least 650 subjects were exposed to at least one dose of remibrutinib. The clinical safety profile fully supports both dosing regimens, CCImg CCI as well as CCI mg CCI (see Section 4.5 and the IB), with a favorable safety profile and no dose-dependent safety signals.

4.2.5 Cohort E (Ianalumab)

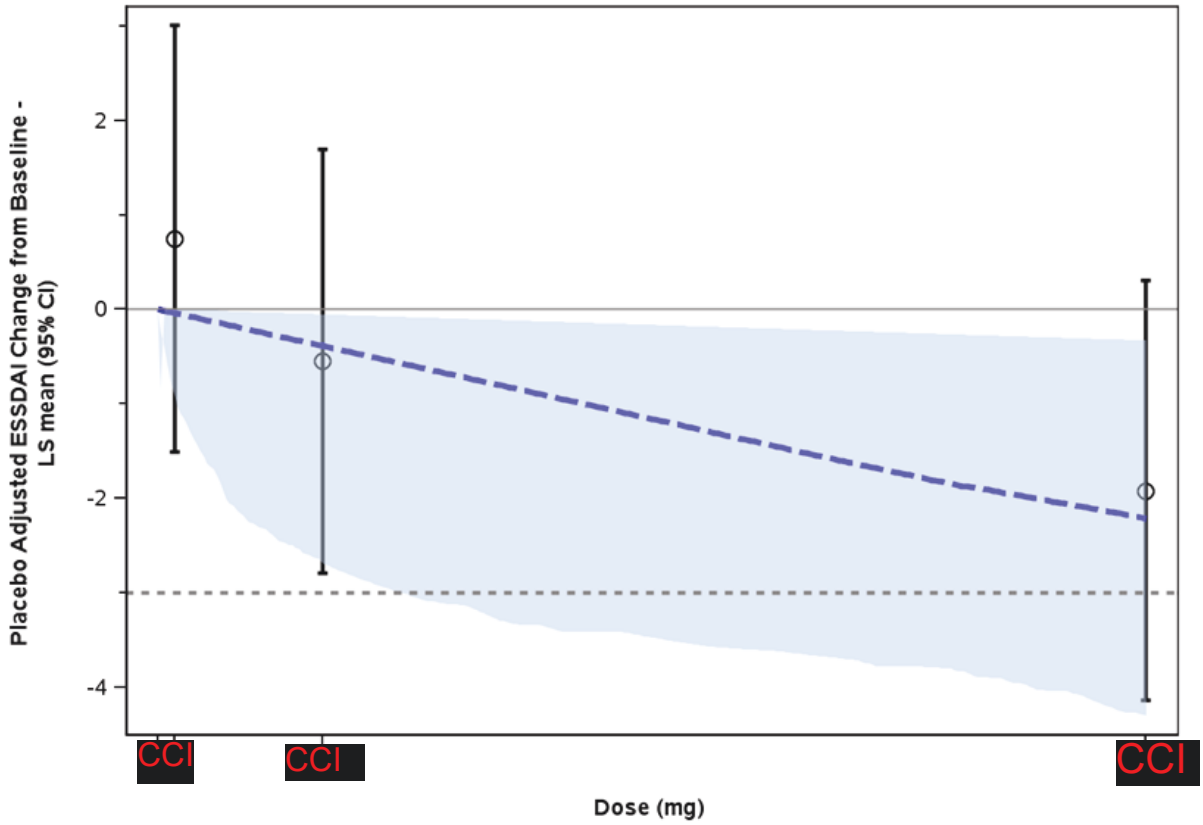
In this cohort, ianalumab CCImg s.c. CCI is proposed to explore the efficacy and safety of ianalumab in adult HS patients.

The rationale for the proposed dose regimen relies on the safety profile of completed and on-going clinical studies with ianalumab in pSS, SLE, RA, AIH, IPF and results of a Phase 2b study in patients with pSS (CVAY736A2201), where three ianalumab doses CCI mg, CCI mg and CCImg) administeredCCI over 6 months were studied and compared to placebo. CCI has a favorable safety profile and no dose-related safety observations other than mostly mild to moderate, local injection site reactions have been observed. These clinical results in ianalumab-treated patients with pSS suggest that additional therapeutic benefits are obtained by maintaining sustained BAFF-R blockade over the dosing interval in addition to rapid and sustained depletion of circulating B cells, justifying the CCI regimen for treatment in this Phase 2 study in HS patients. In the paragraphs below, we describe dose-response modelling, exposure-response exploration based on data from patients with pSS, and additional evidence to support the proposed dose.

Dose-response relationship for ESSDAI based on phase 2b data at Week 24 (CVAY736A2201)

The primary objective of study CVAY736A2201 was met and a statistically significant dose response relationship was observed in ESSDAI change from baseline at Week 24 (Figure 4-8). The best clinical efficacy and best benefit/risk for patients was seen at the highest dose level of CCI mg s.c. administered CCI

Figure 4-8 Dose-response modelling (MCP-Mod) for ESSDAI at Week 24 (study CVAY736A2201)



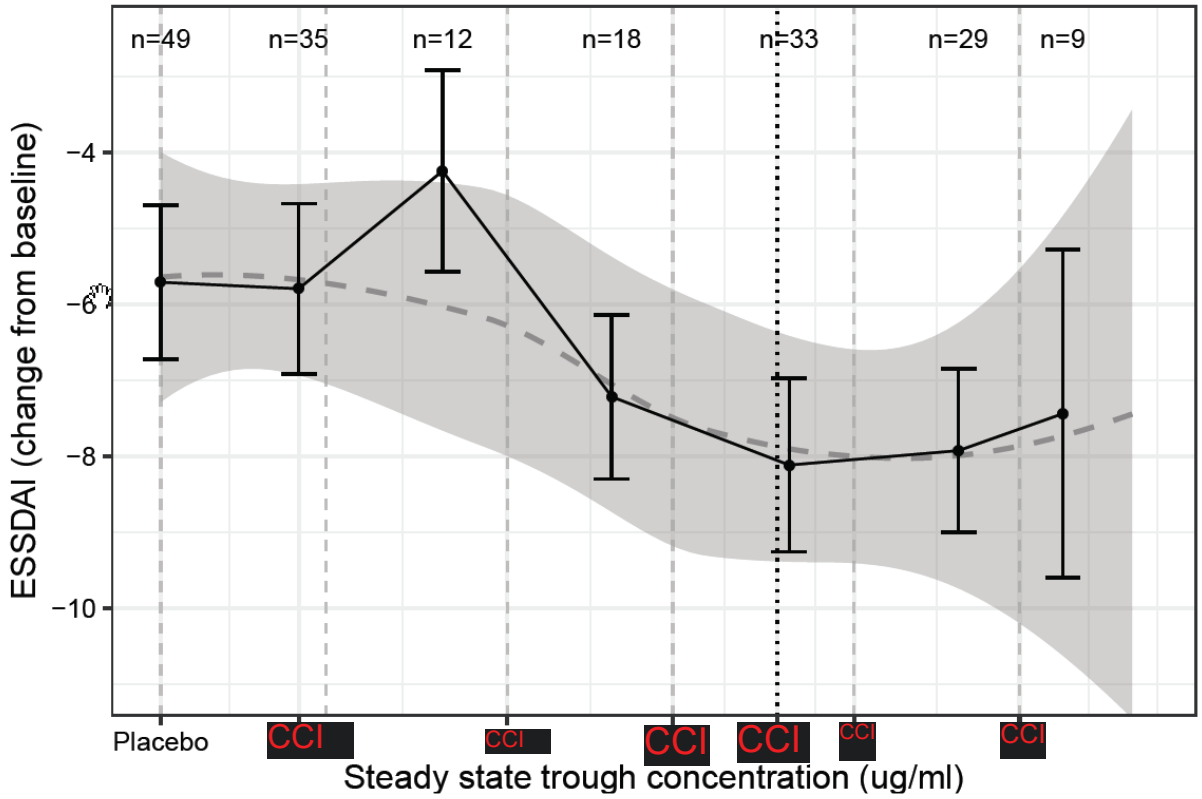
Placebo-adjusted change from baseline of ESSDAI versus dose (open circles and associated confidence interval) and model mean curve at Week 24 (blue dashed line). Solid horizontal line represents baseline; dashed horizontal line represents minimal clinically important change (MCII) of 3 points. The simulated dose-response is based on model average method through bootstrappingtechnique.

Exposure-response relationship for ESSDAI based on phase 2b data at Week 24 (CVAY736A2201)

Due to the high placebo effect and variability in the ESSDAI response, it was not possible to establish a robust exposure-response model. Hence, an exploratory cross-sectional exposure-response analysis of ESSDAI change from baseline at Week 24 was performed. Individual patient data at Week 24 (including placebo, CCI and CCI mg dose levels) were used to characterize the relationship between observed trough ianalumab concentrations and ESSDAI

change from baseline (Figure 4-9). Despite the large variability of ESSDAI responses, there was a clear trend towards a sigmoid exposure-response relationship, which appears to plateau at exposures above ~0.6 µg/mL. There was evidence that exposures higher than those achieved with CCI mg CCI will not translate into additional clinical benefit. Acknowledging that the dose level of CCI mg CCI was not part of the primary efficacy analysis, our PK simulations suggest that the maximum clinical efficacy won't be reached with CCI mg CCI for a substantial number of patients, whereas CCI mg CCI is most likely to achieve maximum clinical efficacy.

Figure 4-9 Exposure-response relationship for ESSDAI (study CVAY736A2201)



Exposure-response relationship for ESSDAI (difference from baseline) at Week 24 based on data from dose levels Placebo, CCI and CCI mg from study CVAY736A2201. The exposure was split into six bins (equally sized ranges on log-scale, delimited by vertical dashed lines), with "n" showing the number of data points in each bin. Data are given as mean +/- standard error within each bin. Dashed line and grey area indicate loess smooth on individual data. Concentrations at zero refer to placebo patients. Concentrations at CCI µg/mL are below the limit of quantification (LOQ).

Further support for the choice of dose and regimen: The pharmacokinetic properties of ianalumab support a fixed dose for all patients CCI [redacted] .In the phase 2b dose-range study in Sjögren's syndrome the primary endpoint ESSDAI was maximized with ianalumab CCI mg CCI and stimulated salivary flow showed greater improvement on ianalumab CCI mg CCI as compared to lower doses.

Ianalumab CCI mg CCI provides B cell depletion, suggestive of sustained BAFF-R blockade based on biomarker results. Ianalumab CCI mg CCI has a favorable safety profile; there are no dose-related safety observations other than mostly mild-to-moderate, local injection site reactions.

Hidradenitis Suppurativa patients have higher body weight compared to patients with Sjögren's syndrome and tend to have lower exposure of therapeutic mAbs compared to other patient categories supporting the ianalumab CCI mg CCI dose to be tested in HS.

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

Adalimumab (Humira®), a TNFα inhibitor for s.c. injection, is the only drug currently approved for HS. No oral drug is currently approved for the treatment of HS and/or has clearly proven its efficacy. This study does not include a direct active comparator per cohort but instead compares investigational treatments to a corresponding placebo. While topical treatments and short term antibiotics are allowed, relevant systemic treatments used for HS are not allowed during the treatment phase, in line with what was done previously (Kimball et al 2016). The inclusion of placebo allows for a direct and unbiased estimate of the effect of the investigational treatment, which is important when no objective clinical assessment scores are available and clinical endpoints are rather subjective and can thus be influenced by beliefs or convictions. The use of a placebo arm also ensures an unbiased comparison of safety data with that of the actively treated population, and better reflects the natural history of the disease, which is still largely unknown and is thus difficult to predict (since only relatively few RCT data are available in this specific HS subject population). Inclusion of a placebo group clearly helps with establishing the efficacy and thus the usefulness of the proposed investigational treatments, specifically in early proof of concept trials (Singer 2004). Placebo controlled trials have been conducted previously in HS subjects for a duration up to 16 weeks (Tzanetakou et al 2016, Kimball et al 2012, Kimball et al 2016). The overall randomization ratio for investigational treatment to placebo is 2:1 in Cohorts A and B and 3:1 for Cohort C and E, which limits the number of subjects who will receive a placebo in this trial. For Cohort D, since a second dose is added, a randomization of 3:3:1 (active: active: placebo) is proposed. Only 10 patients will be exposed to placebo to ensure a double blind design, with 60 patients exposed to active. Both active doses will be compared to the pooled placebo group.

4.4 Purpose and timing of interim analyses/design adaptations

Two interim analyses (IA) are planned **for each cohort**:

- One IA to assess efficacy and safety, to avoid unnecessary exposure of subjects to compounds that have no, or marginal, chances to be effective (Section 12.4.2). This IA will be conducted when approximately half the planned subjects have completed 16-weeks of treatment, and
- One IA after all subjects have completed all planned assessments of the concerned cohort, because it is possible that different cohorts may complete enrolment at different times. These end-of-cohort interim analyses are intended to help with the planning of later steps in the development program of each treatment.

Additional IAs may be conducted to support decision making, concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns. If the recruitment rate is higher than expected, the first planned IA can be missed and only the end of cohort IA will be conducted.

Additional information is presented in Section 12.7 (Interim Analyses).

4.5 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific stopping rules, are included in this protocol. Recommended guidelines for supportive management of study-drug induced adverse events are provided in Section 16.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and adequate post-treatment safety follow-up to capture any potential late occurring AEs. Refer to the IBs for more detailed information of the investigational treatments used in this trial.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should be excluded from participation in the study.

4.5.1 Cohort A (Iscalimab)

4.5.1.1 Potential benefit of treatment with iscalimab

To date, only one drug (adalimumab) has been approved for the treatment of HS where a high unmet medical need still exists. Current standard of care therapies comprise topical care, conventional antibiotics, and immunosuppressive therapies, which are not fully efficacious in most subjects. Based on the scientific rationale for targeting the CD40 pathway in HS and the data available for iscalimab, CD40 inhibition by iscalimab has a potential to treat subjects with HS.

4.5.1.2 Potential risks associated with exposure to iscalimab

Currently, limited data exists regarding the use of agents that block the CD40/CD40L pathway. Preclinical and data from the Phase 1 and 2 programs for iscalimab and data from compounds acting on the same pathway (CD40/CD40L) have been taken into account to estimate the potential risks associated with iscalimab. The current edition of the IB also provides detailed instructions regarding the risks and their mitigation.

4.5.1.2.1 Vaccinations

Vaccination of subjects during iscalimab treatment and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of the antibody. Reduced or absent immunization effectiveness may be expected during treatment and for 14 weeks post treatment For subjects participating in this study, all vaccinations should be up to date based on local guidelines and an appropriate duration to illicit an immune response, prior to inclusion. Administration of live vaccines or

attenuated agents will be prohibited within a 2-month period before first dosing with iscalimab in the current study, during study treatment and for at least 14 weeks after the last dose.

4.5.1.2.2 Teratogenicity

As iscalimab's reprotoxicity potential is not fully characterized yet (see current IB of CFZ533), women of child bearing potential are only to be included if they follow highly effective contraception. Women will be monitored during the trial participation with serum pregnancy tests at screening and EoS, and urine pregnancy tests during the trial. If the subject is confirmed to become pregnant, the treatment must be discontinued.

4.5.2 Cohort B (LYS006)

4.5.2.1 Potential benefit of treatment with LYS006

Currently, limited data exists regarding the use of agents that block LTA4H. Another LTA4H inhibitor, acebilustat from Celtaxsys, is in a clinical study in 200 cystic fibrosis subjects (NCT02443688), where preliminary summary results became available recently, referring to a successful outcome and move to phase 3 (Celtaxsys Inc. Press-release 2018). Another study in 124 acne subjects was earlier completed (NCT02385760), though results are not yet available. Zileuton is an upstream acting oral 5-Lipoxygenase (5-LO) inhibitor, approved for treating asthma with similar but less selective pharmacology. Neutrophils, the main cellular target for LYS006, are abundant in HS lesions. Internal data show that the LTA4H pathway, in particular 5-LO, is observed and shows signs of activation in HS histological samples. In the absence of predictive preclinical disease tests, it seems likely that the inhibiting chemoattraction of neutrophils may exhibit a potential clinical effect in HS.

4.5.2.2 Potential risks associated with exposure to LYS006

Overall, LYS006 was well tolerated in the single and multiple ascending dose cohorts in a total of 121 enrolled healthy volunteers. Doses up to 80 mg b.i.d. were well tolerated, while for this present study, daily dosing of CCI mg CCI. is planned. The current edition of the IB also provides detailed instructions regarding the risks and their mitigation.

4.5.2.2.1 CCI

CCI was observed with increasing doses in preclinical studies. From these preclinical studies, it can be reasonably assumed that the risk of LYS006 CCI increases when CCI It is expected that CCI will precede CCI damage. CCI were not observed in LYS006 treated subjects in the FIH despite close monitoring with doses up to 80 mg b.i.d. and under stressed conditions (CCI .. Thus, it is not anticipated that any CCI induced by LYS006 will be observed during the present trial at the dose of CCI mg CCI. Nevertheless, CCI and LYS006 CCI CCI assessment will be performed on samples collected. Any CCI event or changes in CCI will also be monitored closely.

To lower the peak concentration of LYS006 in the CCI, LYS006 capsules are to be taken twice daily (b.i.d.), in the morning and in the evening. In addition, during the FiH study, the administration of LYS006 with food was associated with decreased maximal concentrations of LYS006 in plasma CCI. Therefore, LYS006 should be always taken with a glass of fluid (typically water) during or shortly after a meal and subjects instructed to drink at least 1.5 liter (L) /day during the duration of the trial.

4.5.2.2.2 Teratogenicity

As per CTGF recommendation related to contraception and pregnancy testing in clinical trials (Clinical Trial Facilitation Group September 2014. Recommendations related to contraception and pregnancy testing in clinical trials), LYS006 is considered unlikely to cause human teratogenicity/ fetotoxicity in early pregnancy. However, in order to harmonize eligibility criteria between cohorts, highly effective contraception for women of childbearing potential (WoCBP) will be kept as a requirement for both cohorts in this study.

No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4/5 was observed in human hepatocytes *in vitro*, therefore no human drug-drug interaction with oral or systemic hormonal contraception is anticipated.

The use of condoms for male participants is not required.

4.5.2.2.3 Vaccinations

There is currently no clear evidence that blockade of LTA4 hydrolase would interact significantly with vaccination responses. Thus, the impact of LYS006 on vaccine response is expected to be low. However, studies investigating vaccine response in the presence of LYS006 have not been conducted.

4.5.3 Cohort C (MAS825)

4.5.3.1 Potential benefit of treatment with MAS825

To date, only one drug (adalimumab) has been approved for the treatment of HS where a high unmet medical need still exists. Current standard of care therapies comprise topical care, conventional antibiotics, and immunosuppressive therapies, which are not fully efficacious in most subjects. Based on the scientific evidence of upregulation of both IL-1ß and IL-18 in HS lesions (Kelly et al 2015), as well as the encouraging data in a small proof of concept trial with an anti-IL-1R antagonist (Tzanetakou et al 2016), there is some evidence that blockade of IL-1ß and IL-18 CCI may be beneficial to patients with HS. However, as this is the first time that MAS825 is tested in HS patients, it is unknown if a benefit and its extent can be confirmed.

4.5.3.2 Potential risks associated with exposure to MAS825

Currently, limited data exists regarding the use of agents that CCI agents IL-1ß and IL-18. The current edition of the IB for MAS825 also provides detailed instructions regarding the risks and their mitigation.

4.5.3.2.1 Vaccination

Data are lacking to confirm immunization effectiveness during treatment and for 14 weeks post treatment with MAS825, however interference is not expected. For subjects participating in this study, all vaccinations should be up to date based on local guidelines and an appropriate duration to illicit an immune response, prior to inclusion.

Administration of live vaccines or attenuated agents will be prohibited within a 2-month period before first dosing with MAS825, during study treatment, and for at least 14 weeks after the last dose.

4.5.3.2.2 Women of Child bearing potential (WoCBP)

There is no available reproductive toxicity data for MAS825 nor clinical experience with the mAb in human pregnancies.

Similar to other IgG antibodies, MAS825 may have FcRn-mediated, cross-placental transfer. The potential of placental transfer can be influenced by many factors (maternal level of the total IgG and specific antibodies and their subclasses, gestational age and placental integrity) (Palmeira et al 2012).

Women of child-bearing potential (WoCBP) can be included in the MAS825 patient trials where the risk-benefit is considered favorable (i.e., studies in which there is potential benefit from CCI), if they fulfil the following criteria:

- Practice highly effective contraception for at least 3 months prior to study enrollment;
- Have a negative pregnancy test at the time of enrollment;
- Practice highly effective contraception during treatment with MAS825; and
- Practice highly effective contraception for 5 months following treatment with MAS825, when it is predicted that CCI have come back to the values prior to treatment.

Pregnant women are excluded from all MAS825 clinical trials.

4.5.4 Cohort D (remibrutinib)

4.5.4.1 Potential benefit of treatment with remibrutinib

BTK inhibition is a new therapeutic principle for the treatment of HS that significantly differs from currently available treatment options in terms of its mode of action and route of administration. Because of its central role in B cell receptor (BCR) signaling and pro-inflammatory Fc-receptor function, BTK inhibition has recently emerged as an attractive approach for selective immune modulation (Kaul et al 2021). BTK is expressed in selected cells of the adaptive and innate immune system, including B cells, macrophages, mast cells, basophils, and thrombocytes.

The role of BTK in regulating BCR signaling strength is the rationale to explore BTK inhibitors in B cell driven diseases, such as rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus (SLE), as well as B cell lymphomas, like chronic lymphocytic leukemia, leading to the approval of ibrutinib, acalabrutinib, and zanubrutinib by several regulatory agencies,

including the US Food and Drug Administration (Kaul et al 2021). Hidradenitis suppurativa is a potential candidate to be included in this list.

Indeed, in HS lesional skin, several authors have demonstrated that macrophages, plasma and B cells are present and predominant in HS skin Shah 2017, Altman, Criswell 2021, Gudjonsson et al 2020, Frew et al 2020, Musilova 2020. In particular B cells seem to be more prominent in chronic lesions and around tunnel structures, where tertiary lymphoid structures are found as well (van Straalen et al 2022, Frew et al 2020). B cells and B cell signature are present in HS (Frew et al 2020, Musilova 2020, Rumberger 2020) and BCR was considered activated through the detection of pBTK and pSYK in HS lesional skin (Gudjonsson et al 2020). In an *in vitro* model in IgG/IgM stimulated B cells, Gudjonsson et al 2020 showed that BTK induced changes could be decreased with BTKi, such as acalabrutinib or ibrutinib.

In several publications, autoantibodies have been detected and more commonly observed in patients with HS (Ross and Ballou 2021, Roediger 2022), which may hint to an increased B cell activity. Carmona-Rivera et al 2022 identified specific IgG autoantibodies that recognize circulating and tissue antigens in HS and suggest an autoimmune mechanism. Presence of autoantibodies was correlated with HS disease severity.

In addition to the above that may apply to the BCR- and FcγR mediated signaling of the BTK pathway, List et al 2019, but as well van der Zee et al 2012 showed that mast cells are upregulated in HS patients.

Thus, a CCI scientific rationale exists to test a BTK inhibitor, such as remibrutinib, in HS patients, where no approved oral treatment is currently available and alternatives include adalimumab or surgery.

Remibrutinib did show promising results in CSU patients in a recent phase 2b study as compared to placebo and will proceed to larger phase 3 program in CSU and as well in MS. Based on the above described scientific rationale and its efficacy on B cells, macrophages possibly mast cells and the promising clinical efficacy in CSU, CCI that remibrutinib may show a reduction of HS lesions over time.

4.5.4.2 Potential risks associated with exposure to remibrutinib

Based on the mode of action of remibrutinib, pre-clinical safety information, drug-drug-interaction studies, and the review of currently available literature as well as safety information of approved BTK inhibitors (e.g. ibrutinib, acalabrutinib and zanubrutinib), the following potential risks of remibrutinib have been identified (see below). Of note, several safety risks noted for ibrutinib and acalabrutinib, two BTK inhibitors approved for the treatment of B cell malignancies (mantle cell lymphoma, chronic lymphatic leukemia, Waldenstroem´s disease), are less likely related to the pharmacology of BTK inhibition, but rather to the underlying hemato-oncologic diseases being treated and their associated comedications and complications, such as tumor lysis syndrome, second primary malignancies etc. Therefore, when comparing the safety risks between the approved BTK inhibitors and remibrutinib, the underlying condition of the treated patient population must be taken into consideration. Furthermore, ibrutinib and acalabrutinib have a different target selectivity profile compared to remibrutinib (Angst et al 2020). The current edition of the IB also provides detailed instructions regarding the risks and their mitigation.

4.5.4.2.1 Infections

BTK is an important signaling kinase downstream of cell surface receptors and expressed in a number of cell types of the adaptive and innate immune system, including B cells, macrophages, basophils and mast cells. In the completed and ongoing clinical trials with remibrutinib, infections were well balanced between the remibrutinib and placebo arms. Most of the infections observed were mild to moderate and did not lead to a change in study treatment. In the primary endpoint analysis of the Phase 2b study CLOU064A2201, infections rates were comparable between any remibrutinib arm (22.8%) and the placebo arm (21.4%). Most infections reported in the remibrutinib arms were mild in severity and did not lead to treatment discontinuation.

All participants in remibrutinib clinical trials are monitored closely for signs and symptoms of infections while in the trial. Patients with a known history of chronic recurrent or active ongoing infections are excluded from the trial (refer to Section 5.2 for details).

4.5.4.2.2 Vaccination

Immune modulation of B cells via BTK inhibition is expected to affect the response to vaccination, and thus during treatment with remibrutinib, vaccination may be less effective. Therefore, it is recommended to have any necessary vaccinations completed 2 weeks prior to enrollment in the study. However, the use of live attenuated vaccines should be avoided 2 months before, during, and for 4 weeks after the last dose of remibrutinib (see Section 6.2.2).

4.5.4.2.3 Risk for bleeding

In patients with B cell malignancies (chronic lymphatic leukemia, Waldenstroem´s disease, mantle cell lymphoma) treated with the BTK inhibitors ibrutinib or acalabrutinib, major bleeding events (i.e. serious events, gastrointestinal bleeding) were reported. However, the underlying hemato-oncologic diseases of these patients, the prevalence of anti-coagulant/anti-platelet comedication use and the association with such complications should be taken into consideration. No relevant increase in bleeding risk has been observed in patients with X-linked agammaglobulinemia (XLA), an inborn genetic deficiency of BTK (Quek et al 1998, Futatani et al 2001, von Hundelshausen, Siess 2021). Furthermore, BTK inhibition does not have any impact on the plasmatic coagulation system and plasmatic coagulation was not affected in the human Phase 1 study up to the highest tested dose of CCI mg remibrutinib. In the completed and ongoing trials with remibrutinib only few mild and moderate bleeding events were reported. In the primary analysis of the Phase 2b study CLOU064A2201, 13 (4.9 %) non-serious bleeding events were reported on any remibrutinib dose compared to one event on placebo (2.4 %). None of the events reported on remibrutinib was serious or severe. There was a single mild event (petechiae) leading to treatment discontinuation. Blood cell counts (including thrombocytes), hemoglobin and coagulation status will be closely monitored throughout the trial. Patients with a known history of bleeding disorders, or with a history of clinically relevant gastrointestinal bleeding and patients requiring anti-platelet or anticoagulant therapy (other than aspirin up to 100 mg/day or clopidogrel) are excluded from the trial; the use of dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel) is prohibited (see details in Section 5.2 and Section 6.2.2). In case of a significant bleeding event, remibrutinib must be discontinued immediately.

4.5.4.2.4 Other potential risks

For detailed information on potential risks and other effects on QT intervals, myelomodulation, drug-drug interaction and reproductive toxicity associated with remibrutinib, please refer to the current IB of remibrutinib.

4.5.5 Cohort E (Ianalumab)

For the latest information on benefit risk of ianalumab please see the latest version of the ianalumab Investigators Brochure (IB).

4.5.5.1 Potential benefits of treatment with ianalumab

With currently only one drug (adalimumab) approved for HS there is a high unmet medical need in HS and among HS patients who do not respond to adalimumab lesional B cells and plasma cells are enriched compared non-responders (Hambly 2023). Indeed, in lesional HS skin plasma cells and B cells are predominantly present (Shah 2017, Altman, Criswell 2021, Gudjonsson et al 2020, Frew et al 2020, Musilova 2020). In particular B cells seem to be more prominent in chronic lesions and around tunnel structures, where tertiary lymphoid structures are found as well (van Straalen et al 2022, Frew et al 2020). B cells and B cell signature are present in HS (Frew et al 2020, Musilova 2020, Rumberger 2020) with BCR-activation demonstrated through the detection of pBTK and pSYK (Gudjonsson et al 2020, Rumberger 2020) and recently autoantibodies correlating with disease severity and duration have been demonstrated in HS patients (Macchiarella et al 2022). Little is known about the survival factors supporting the persistence of immune cells in HS lesions but increased B cell activating factor (BAFF) expression has recently been demonstrated. In HS lesions, BAFF receptor expression is most prominent in B cells and plasma cells with a strong correlation between BAFF expression and B cells and plasma cells (Sabat 2022). Taken together, targeting BAFF receptors with ianalumab in HS seems to be justified based on the scientific rationale above and the promising clinical efficacy seen in primary Sjögren's patients.

4.5.5.2 Potential risks associated with exposure to ianalumab

The identified safety risks of ianalumab are injection-related reactions (systemic and local) and upper respiratory tract infections. Potential risks that have been observed with different B Cell depleting agents include infections (hepatitis B reactivations, opportunistic infections, such as progressive multifocal leukoencephalopathy (PML)), neutropenia, allergic reactions, immunogenicity, lower response to vaccinations, malignancies and reproductive toxicity. Since B cell depletion can last several months or even years after last treatment with B cell depleting agents, monitoring requirements are put forth to be adhered to during the post-treatment safety follow-up period and are detailed below.

4.5.5.2.1 Injection-related reactions (systemic and local reactions)

These reactions are anticipated based on the mode of action of ianalumab, whereby B cell killing leads to release of intracellular cytokines by antibody-dependent cellular cytotoxicity (ADCC).

Mild-to-moderate, systemic injection-related reactions including symptoms such as headache, fever/pyrexia, shivering/chills, mild nausea, dizziness, rash, flushing, myalgia, fatigue and

tachycardia have occurred in ianalumab single dose and multiple dose studies. Reactions typically occur within 30 minutes and up to 24 hours after the first administration of ianalumab. Symptoms were most often observed after the first ianalumab dose but new-onset and recurrent reactions after repeated dosing have occasionally been reported. Symptoms either did not require any treatment or were manageable with paracetamol, antihistamines and corticosteroids. In the current study, mandatory premedication with a fixed dose of predniso(lo)ne prior to the first dose of the study treatment will be given to attenuate development and intensity of potential injection-related reactions (local and systemic). Patients are required to stay at the clinic until at least 4 hours after first dose of the study treatment. Patients must be observed/clinically monitored during this period for symptoms of possible injection-related reactions. Patients must be instructed to promptly report symptoms occurring within 24 hours after study treatment administration.

In the dose-ranging study CVAY736A2201, participants with Sjögren's syndrome received pre-medication with methylprednisolone i.v. (CCI mg or CCI mg) prior to the first dose of the study treatment. In the ianalumab CCI mg arm, systemic reactions were observed in 8.5% (4/47) of patients treated with ianalumab compared to 4.1% (2/49) of patients in placebo arm. Majority of the systemic reactions reported (4/47) in patients dosed with ianalumab CCI mg were of mild intensity (6.4%, 3/47). There was no severe systemic reaction in the patients dosed with ianalumab CCI mg. Symptoms included dizziness, headache, fever, chills, rash, flushing, nausea, myalgia, fatigue, tachycardia, and hypotension. As in the previous studies, symptoms either did not require treatment or were manageable with paracetamol, antihistamines and steroids. The site reactions were dose-dependent, with approximately 60% of participants experiencing a reaction at the CCI mg dose. Most were mild or moderate in severity (46.8%, 10.6%, respectively). There was a single case of a severe local injection-related reaction in a participant who received ianalumab CCI mg which led to study treatment discontinuation. Symptoms included erythema, swelling, pain, itching/pruritus, rash and tenderness around the injection site. Some local injection reactions have been reported with a delayed onset and lasting up to several weeks. The majority of local reactions did not require treatment or were managed symptomatically as warranted.

4.5.5.2.2 Infections

The potential of ianalumab to increase the risk of infections has been identified (see IB Section 7). The risk of infection may increase if ianalumab is combined with corticosteroids or strong immunosuppressive drugs. In this study, predniso(lo)ne is prohibited except for the mandatory pre-medication administered at the first IMP administration. The Investigator should remind the patient of the risk of infections and ask them to promptly report any symptoms of infections. Subjects in this study will be monitored regularly and carefully for signs and symptoms which might indicate an infection.

In the CCI the incidence of the Infections and Infestations System Organ Class during the double-blind, placebo-controlled period (first blinded treatment period up to Week 24) was comparable between the all-exposed ianalumab group (51.8%, 73/141) and placebo (59.2%, 29/49). Overall, during the entire study period (including the post-treatment follow up period), the combined incidence across all ianalumab doses (all-exposed) of the Infections and Infestations System Organ Class was 74.5%. The most

commonly reported infections occurring ≥5% by preferred terms were nasopharyngitis, upper respiratory tract infection, urinary tract infection, sinusitis, bronchitis, oral herpes and conjunctivitis, with no relation to dose. The majority of the events were non-serious, mild to moderate events that were self-limiting or responded promptly to treatment and did not lead to study drug discontinuation. There were three infection AEs that led to study treatment discontinuation (non-serious bronchitis, herpes zoster and a serious event of wound infection). The proportion of patients with serious infections was small and showed no dose-response relationship: [redacted] mg (2.1%, 1/47), [redacted] mg (4.3%, 2/47), [redacted] mg (6.4% 3/47), [redacted] mg (4.3%, 2/47). COVID-19 has similar impact on the risk-benefit as other infections. Any immunosuppressive/immunomodulatory agent may be associated with an increased risk of infections. Therefore, the risk of becoming infected or potentially developing a severe respiratory illness may be further increased in patients who are treated with ianalumab.

During the COVID-19 pandemic, there have been serious and non-serious events of COVID-19 infections reported. As of 24-Sep-2023, 8 SAEs of confirmed COVID-19 infections were reported. Of these, four were fatal (reported from the CVAY736A2101, CVAY736B2201, CVAY736Y2102 and CVAY736J12101 studies) with other potential contributory factors were present (e.g. obesity, diabetes, hypertension, or cancer). All SAEs of COVID-19 infections were assessed as not related to ianalumab by the investigator. Based on review of all COVID-19 cases, no new safety signals were detected.

As of 24-Sep-2023, there were no disseminated opportunistic infections in patients treated with ianalumab.

4.5.5.2.3 Allergic reactions

Although no allergic reactions following i.v. or s.c. administration were observed so far, the potential to develop an allergic reaction in a predisposed subject cannot entirely be ruled-out. Routine monitoring as for other biological treatments is warranted, as described in the ianalumab IB.

4.5.5.2.4 Immunogenicity

Anti-drug antibodies (ADAs) are assessed in all participants across all clinical trials with ianalumab. Only limited signs and symptoms of immunogenicity have been observed thus far in participants exposed to ianalumab. Administration of any mAb, independent of the antibody specificity for antigen, carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of neutralizing ADAs. Other potential clinical manifestations can include local skin reactions at the injection site, pyrexia and an influenza-like syndrome. In study [redacted] the incidence of treatment emergent [redacted] was [redacted]%, [redacted]%, [redacted]% and [redacted]% in the [redacted], [redacted], [redacted] and [redacted] mg dose groups respectively. [redacted] participants with treatment emergent [redacted] in the [redacted] mg dose group had none-or-no sustained B cell depletion. [redacted] participants with treatment emergent [redacted] in the other dose groups had [redacted]. There was no evidence of a relationship between development of treatment emergent [redacted] and AEs as referred to preferred terms in the Standardized Medical dictionary for regulatory activities (MedDRA) Query 'Hypersensitivity' and preferred term 'Injection site reaction'. Especially, there was no trend observed towards a higher frequency of injection-related

reactions (both local and systemic) in participants with treatment emergent ADAs. Most of the patients with injection related reactions had no signal of ADAs. CCI [redacted]

4.5.5.2.5 Vaccinations

In immune suppressed patients, live vaccinations may cause serious adverse events and vaccination success may be attenuated. No data exists on the effect of ianalumab on response to vaccinations. It is recommended that patients receive appropriate vaccinations in accordance with current immunization guidelines, at least 2 weeks prior to the first administration. After a live vaccine is administered, exposure to the first dose of ianalumab (randomization) should not occur within 4 weeks. For further information please refer to the Vaccination Guidance for ianalumab (provided to study sites).

4.5.5.2.6 Malignancies

There is a risk of malignancies in immunocompromised patients in general, including patients receiving immunosuppressive therapies and/or patients who were immunocompromised from prior therapies. Patients with autoimmune disorders are also prone to develop specific types of cancer, depending on type of autoimmune disease. (Jung et al 2020, Ju et al 2023, Liang et al 2014, Brito-Zerón et al 2017, Zintzaras et al 2005, Nocturne, Mariette 2015, Tansel et al 2017, Jensen et al 2022, Danielsson Borssén et al 2015, Rees et al 2016, Clarke et al 2021). Based on the description of individual cases of malignancies reported from clinical trials with ianalumab, and the confounding factors present (e.g. underlying disease, prior/concomitant treatment with immunosuppressants), a causal association with ianalumab cannot be established at this time. However, given that patients receiving immunosuppressive therapies are at increased risk of malignancies and based on the safety information from other anti-CD20 mAb and BAFF inhibitor therapies, 'Malignancy' is considered as a potential risk for ianalumab. Based on overall data analysis to date, the benefit-risk profile of ianalumab remains unchanged. In ongoing non-oncology studies, there exists long-term treatment-free safety follow-up of patients until B cell count recovery thresholds are met (up to 2 years post-treatment). During this time, all SAEs including any malignant neoplasm, are collected allowing for further evaluation of this important potential risk of malignancy.

4.5.5.2.7 Reproductive toxicity

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

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

the impact of B cell depletion on the safety and effectiveness of vaccines, are unknown (Sangle et al 2013).

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy occurs during the study, and of the importance of contraceptive measures. Before enrollment, they must agree that in order to participate in the study, they must adhere to highly effective contraception requirements for the duration of the study treatment and 6 months after its discontinuation, as outlined in the protocol's exclusion criteria Section 5.2. If there is any question that the subject will not reliably comply, she should not be entered or continue in the study.

4.5.6 Study related/ non cohort specific risks and benefits

Additional risks are related to the procedures of the trial, such as blood sampling and CCI [redacted] sampling. During the collection of blood samples, subjects may experience pain and/or bruising at the injection site. In addition, although rare, localized clot formation, infections and nerve injuries may occur. Lightheadedness or fainting may also occur during or after the blood draw. CCI [redacted]

4.5.6.1 Treatment of Adverse Events

Treatment for adverse events should follow general guidelines for standard-of-care, and is at the discretion of the investigator or treating physician (please refer to Section 16). Please also refer to Section 6.6.2.

Subjects with clinically significant worsening of their disease are to be discontinued from study treatment (see Section 9.1.1) if prohibited treatments (Table 6-3) are needed to treat their symptoms.

4.5.6.2 Blood sample volume

Approximately 250mL (Cohort B), 300 mL (Cohort A), 405 mL (Cohort C), 200 mL (Cohort D) or 500 mL (Cohort E) of blood is planned to be collected over a period of 33 weeks (up to 121 weeks for Cohort E), from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in Section 8 (Assessment Schedules).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and Central Laboratory Manual.

See Section 8.5.3.9 on the potential use of residual samples.

5 Population

Subjects included in this study are adult male and female subjects of 18 to 65 years of age (inclusive), presenting with moderate to severe HS diagnosed with recurrent inflammatory lesions for at least 12 months. At randomization (pre-dose on Day 1), subjects need to have at least 5 inflammatory lesions (abscesses and nodules) in at least 2 anatomical areas to be included in Cohort A (iscalimab), Cohort C (MAS825) and Cohort E (ianalumab) and at least 3 inflammatory lesions in at least two anatomical areas to be included in Cohort B (LYS006) and Cohort D (remibrutinib). Most of the other eligibility criteria are the same or very similar between the cohorts. Differences in eligibility criteria are based on the differences in the pharmacological profiles of the respective drugs, such as the need to monitor CCI and CCI for LYS006.

A total of approximately 240 subjects will be enrolled in the study. Approximately 45 subjects will be enrolled in Cohort A (iscalimab) and approximately 40 to 45 subjects will be enrolled in Cohort B (LYS006) with approximately 40 subjects being enrolled in Cohort C (MAS825), approximately 70 subjects being enrolled into Cohort D (remibrutinib) and approximately 40 subjects being enrolled into Cohort E (ianalumab). Within each cohort approximately 30 subjects will receive the investigational treatment and approximately 15 subjects will receive the matching placebo in Cohorts A and B, with approximately 10 receiving placebo in Cohort C, D and E. However, in Cohort D an additional arm is included for a second dose level, therefore approximately 60 subjects in Cohort D will receive remibrutinib: approximately 30 patients will receive CCI mg CCI. and approximately 30 patients will receive CCI mg CCI

The investigator must ensure that all subjects being considered for the study meet the eligibility criteria. Subject selection is to be established by checking through all eligibility criteria as specified below. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a subject from enrollment into the study. Waivers for deviations from these criteria are not allowed to be given or granted.

5.1 Inclusion criteria

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

#	Detail of Inclusion	Cohort				
1	Written informed consent must be obtained before any assessment is performed.	A	B	C	D	E
2	Male and female patients, 18 to 65 years of age (inclusive), with clinically diagnosed HS for at least 12 months prior to Screening.	A	B	C	D	E
3	Patients with moderate to severe HS, as per evaluation at screening and randomization (values obtained pre-dose on Day 1 are used to determine cohort eligibility):					
	• A total of at least **5 inflammatory lesions**, i.e., abscesses and/or inflammatory nodules.	A		C		E

#	Detail of Inclusion	Cohort				
	• A total of at least **3 inflammatory lesions**, i.e., abscesses and/or inflammatory nodules.		B		D	
	• No more than 15 fistulae.	A	B	C	D	E
	• At least two anatomical areas need to be involved with HS lesions.	A	B	C	D	E
5	Able to communicate well with the investigator, able to understand and comply with the requirements of the study and:	A	B	C	D	E
	1. able and willing to participate in Cohort A and conduct study visits as per the Cohort A visit schedule.	A				
	2. able and willing to participate in Cohort B and conduct study visits as per the Cohort B visit schedule.		B			
	3. able and willing to participate in Cohort C and conduct study visits as per the Cohort C visit schedule.			C		
	4. able and willing to participate in Cohort D and conduct study visits as per the Cohort D visit schedule.				D	
	5. able and willing to participate in Cohort E and conduct study visits as per the Cohort E visit schedule.					E
6	Subjects must have a minimal body weight of 50 kg (inclusive) at screening.	A	B	C	D	E

5.2 Exclusion criteria

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

#	Detail of Exclusion	Cohort				
1	Use of other investigational drugs at the time of screening, or within 30 days or 5 half-lives of randomization, whichever is longer; or longer if required by local regulations.	A	B	C	D	E

#	Detail of Exclusion	Cohort				
2	Use/receipt of the following treatments during the specified time frames: 1. Use of IL12 and IL23 blocking biologics such as ustekinumab or guselkumab within the last 6 months prior to randomization. 2. Use of B cell targeting or B cell depleting biologics or similar such as rituximab or belimumab within 12 months prior to randomization; For patients who received these drugs earlier, B cell count must be within normal range at screening. 3. Use of biological immunomodulating agents other than above (e.g., adalimumab, secukinumab, etanercept, infliximab, etc.) within 3 months or 5 half-lives (whichever is longer) prior to randomization. 4. If spironolactone or other anti-androgens (such as finasteride, cyproterone acetate, etc.) are used (for HS or other conditions, such as PCOS), only patients who have been on a stable dose for the last 3 months prior to randomization and who are planning to continue for the duration of the study are eligible. 5. Use of systemic antibiotics for HS in the last week prior to randomization. 6. Surgical and physical treatment (such as laser, intense light and photodynamic therapy) for HS in the last 4 weeks prior to randomization. Surgical treatment does not include sporadic excisional biopsies. 7. Use of any other systemic treatment for HS in the last 4 weeks prior to randomization (such as retinoids or other immunmodulating therapies, e.g., methotrexate, cyclosporine A, corticosteroids, PDE4 inhibitors). 8. Receipt of any high-dose injected corticosteroid bolus (>1mg/kg) within 3 months prior to randomization. 9. Use of cyclophosphamide within the last 6 months prior to randomization 10. Use of any systemic JAK inhibitors (such as tofacitinib or upadacitinib) or BTK inhibitors (such as ibrutinib and acalabrutinib) within 4 weeks or 5	A	B	C	D	

#	Detail of Exclusion	Cohort				
	half-lives (whichever is longer) prior to randomization.					
2a	Use/receipt of the following treatments during the specified time frames: 1. Use of IL12, IL23 or TNF-α blocking biologics such as ustekinumab, guselkumab, adalimumab, etanercept and infliximab within the last 6 months prior to randomization. 2. Any B-cell depleting therapies, other than ianalumab (e.g., rituximab, other anti-CD20 mAb, anti-CD22 mAb, or anti-CD52 mAb) administered within 1 year prior to randomization, or as long as B cell count is less than the lower limit of normal or baseline value prior to receipt of B cell-depleting therapy (whichever is lower). 3. Use of IL-17 blocking biologicals such as secukinumab within 3 months or 5 half-lives (whichever is longer) prior to randomization. 4. If spironolactone or other anti-androgens (such as finasteride, cyproterone acetate, etc.) are used (for HS or other conditions, such as PCOS), only patients who have been on a stable dose for the last 3 months prior to randomization and who are planning to continue for the duration of the study are eligible. 5. Use of systemic antibiotics for HS in the last week prior to randomization. 6. Surgical and physical treatment (such as laser, intense light and photodynamic therapy) for HS in the last 4 weeks prior to randomization. Surgical treatment does not include sporadic excisional biopsies. 7. Use of any other systemic treatment for HS (such as retinoids or other immunomodulating therapies, e.g., methotrexate, corticosteroids, PDE4 inhibitors) in the last 4 weeks prior to randomization. Patients receiving methotrexate at a weekly dose more than 25 mg or hydroxychloroquine more than 400 mg daily or leflunomide at a non-stable dose, in the last 3 months prior to randomization.					E

#	Detail of Exclusion	Cohort				
	8. Receipt of any high-dose injected corticosteroid bolus (>1mg/kg) or cyclosporine A within 3 months prior to randomization. 9. Use of CTLA4-Fc Ig (abatacept), cyclophosphamide, intravenous IgG, plasmapheresis, iscalimab (anti-CD40) or belimumab (anti-BAFF mab) within the last 6 months prior to randomization 10. Use of any systemic JAK inhibitors (such as tofacitinib or upadacitinib) or BTK inhibitors (such as ibrutinib and acalabrutinib) within 4 weeks or 5 half-lives (whichever is longer) prior to randomization.					
3	WoCBP, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for the subsequent 14 weeks after the last study drug administration for Cohort A (iscalimab) and the subsequent 2 weeks after the last study drug administration for Cohort B (LYS006) and D (remibrutinib). In **Cohort C**, WoCBP will be asked to adhere to highly effective contraception from **at least 3 months prior** to first drug administration **and until 5 months after the final dose** (Day 225 to Day 253), when a pregnancy test will be conducted. In **Cohort E**, WoCBP will be required to adhere to highly effective contraception during dosing and for 6 months after the final dose (Day 253 to Day 281). Highly effective contraception methods include: • Total heterosexual abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are **not** acceptable methods of contraception. • Female sterilization (surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation) at least 6 weeks prior to randomization. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment	A	B	C	D	E

#	Detail of Exclusion	Cohort				
	• Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%). For example, hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been treated with the same pill and dose for a minimum of 3 months prior to randomization. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.					
4	Pregnant or nursing (lactating) women at screening or randomization, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.	A	B	C	D	E
5	Any severe, progressive or uncontrolled medical or psychiatric condition or other factors at randomization that in the judgment of the investigator prevent the patient from participating in the study.	A	B	C	D	E

#	Detail of Exclusion	Cohort				
6	At screening, history or symptoms of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases with the following exceptions: 1. history of basal cell carcinomas and/or up to 3 squamous cell carcinomas of the skin, if successful treatment has been performed, with no signs of recurrence; 2. actinic keratoses, if present at screening, should be treated according to standard therapy before randomization.	A	B	C	D	E
7	History of auto-immune or immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result at screening.	A	B	C	D	E
8	Positive serology for:					
	1. hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc) or hepatitis C antibodies at screening	A	B	C	D	E
	2. IgM for Cytomegalovirus (CMV) in the absence of positive CMV IgG, or quantifiable CMV DNA by PCR (patients with detectable but NOT quantifiable DNA test result may be eligible for the study) at screening	A				
9	Signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days of randomization. Infections are considered controlled if appropriate therapy has been instituted and, at the time of Screening, no signs of infection progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. 1. COVID-19 specific: If in line with health and governmental authority guidance, it is highly recommended during a pandemic, that PCR or comparable approved methodology for COVID-19 is completed within 1 week prior to first dosing. The physician needs to consider whether or not to do the test and/or interpret test results, in case the patients would have received a vaccine for SARS-CoV-2. If testing is	A	B	C	D	E

#	Detail of Exclusion	Cohort				
	performed, negative test results are required prior to enrolment into the study. Additional testing may occur at the discretion of the investigating physician. COVID-19 testing should be completed via nasal or throat swabs or other approved route. If testing is not performed, the investigator must document their discussion with the patient/ parent/ caregiver regarding testing, and the rationale for not testing, in the source documentation.					
10	Any condition, that would result in a significantly elevated risk for infections, as judged by the investigator, e.g.:					
	1. Receipt of live/ attenuated vaccinations within the 2 month period before randomization and willing to withhold any future live/attenuated vaccines until 14 weeks after the last dose	A		C		
	2. Receipt of live/attenuated vaccinations within the 2 month period before randomization until 4 weeks after the last dose				D	
	3. Any other current, active or latent infection susceptible to reactivation, at randomization	A	B	C	D	E
	4. Receipt of live/attenuated vaccinations within the 4 week period before randomization until the end of the follow up period.					E
11	Evidence of active or latent tuberculosis as assessed by Quantiferon testing at screening	A	B	C	D	E
12	History of drug abuse or unhealthy alcohol use within the 12 months prior to randomization. In the case of drug use, the Investigator must determine if a subject's drug use qualifies as drug abuse. Unhealthy alcohol use is defined as five or more drinks on the same occasion on each of 5 or more days in the past 30 days.	A	B	C	D	E
13	Donation or loss of 400 mL or more of blood within 8 weeks prior to randomization, or longer if required by local regulation.	A	B	C	D	E
14	Inability or unwillingness to undergo repeated venipunctures (e.g., due to poor tolerability or lack of access to veins).	A	B	C	D	E

#	Detail of Exclusion	Cohort				
15	Patients who are at significant risk for thromboembolic events based on their medical history and as judged by the investigator, and who are not under appropriate treatment at randomization, in particular patients with antiphospholipid syndrome or with a history of a positive test for antiphospholipid antibodies.	A				
16	Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:					
	1. Inflammatory bowel disease, peptic ulcers, gastrointestinal bleeding including rectal bleeding		B		D	
	2. Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection)		B		D	
	3. Pancreatic injury or pancreatitis Lipase and amylase must not be above the upper limit of normal at screening		B			
	4. Liver disease or liver injury as indicated by clinical symptoms and clinically relevant abnormal liver function tests at screening. As a guidance, abnormal values for ALT (SGPT), AST (SGOT), and alkaline phosphatase are considered those exceeding 1.5ULN, in particular if two or more liver values are increased. Serum total bilirubin must not be above 1.2 x the upper limit of normal at screening	A A	B B		D	E
	5. Subjects with evidence of existing hematological abnormalities at screening: Hemoglobin levels below 8.0 g/dL White blood cell count below 2.0 x 10^9/L Absolute Neutrophil Count below 1.5 x 10^9/L, and/or Platelet count below 100 x 10^9/L			C		
	6. Subjects with evidence of existing hematological abnormalities at screening: Hemoglobin below 10 g/dl				D	

#	Detail of Exclusion	Cohort				
	White blood cell count: below 3 x 10^9/L Absolute Neutrophil count: below 1.5 x 10^9/L Platelets: below 100 x 10^9/L					
	7. Subjects with evidence of existing hematological abnormalities at screening: Hemoglobin below 8.0 g/dL White blood cell count: below 2 x 10^9/L Absolute Neutrophil count: below 1.5 x 10^9/L Platelets: below 50 x 10^9/L					E
17	History of hypersensitivity or allergy to any constituent of the investigational compounds or related compounds of the respective cohort.	A	B	C	D	E
	In addition, history of hypersensitivity or allergy to inhibitors of LTA4H or LTB4.		B			
	History of hypersensitivity to drugs of similar chemical classes to ianalumab (e.g., mAb of IgG1 class) or to any of the constituents of the study drug ([redacted]CCI					E
18	Patients receiving concomitant medication(s) that is/are known to inhibit OAT3 (see Table 6-3) and that cannot be discontinued or replaced by safe alternative medication at least 5 half-lives or 1 week (whichever is longer) prior to randomization and for the duration of the study.		B			
19	Intentionally blank - removed by Protocol Amendment 1.					
20	[redacted]CCI		B			
21	Subjects with eGFR <60 mL/min/1.73 m^2 (estimated by MDRD) at screening.		B			
22	Difficulty in urination and/or obstructive urine outflow symptoms at screening or randomization; history or presence of impaired renal function as indicated by clinically significant abnormal creatinine or BUN and/or urea values, or clinically significant abnormal urinary constituents (e.g. albuminuria) at screening.		B			
23	• Intentionally blank - removed by Protocol Amendment 4.					
24	Evidence of clinically significant cardiovascular (such as but not limited to myocardial infarction, unstable				D	

#	Detail of Exclusion	Cohort				
	ischemic heart disease, NYHA Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), disease that in the investigator's opinion, would compromise the safety of the subject, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the subject					
25	Uncontrolled disease states, such as asthma, where flares are commonly treated with oral or parenteral corticosteroids				D	
26	Significant bleeding risk or coagulation disorders e.g.: • Use of anti-platelet medication [including dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel)] within two weeks prior to randomization. • Note: monotherapy with acetylsalicylic acid up to 100 mg/day or clopidogrel is not exclusionary. • Use of anticoagulant medication [for example, warfarin or Novel Oral Anti-Coagulants (NOAC)] within 2 weeks prior to randomization • History of gastrointestinal bleeding, e.g. in association with use of nonsteroidal anti-inflammatory drugs (NSAID), that was clinically relevant • International Normalized Ratio (INR) of more than 1.5 at screening • Major surgery within 8 weeks prior to randomization or planned major surgery for the duration of study treatment				D	
27	Use of any of the following within two weeks prior to randomization: • Strong CYP3A4 inhibitors • Moderate CYP3A4 inhibitors • Strong CYP3A4 inducers • Moderate CYP3A4 inducers				D	
28	History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects, such as: Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia or clinically				D	

#	Detail of Exclusion	Cohort				
	significant second or third degree atrioventricular block without a pacemaker History of familial long QT syndrome or known family history of Torsades de Pointes. Cardiac arrythmias requiring anti-arrythmic treatment with Class Ia or Class III anti-arrhythmic drugs which prolong QT interval (See Table 6-3 for list).					
29	Resting QTcF ≥450 msec (male) or ≥460 (female) at screening or randomization				D	
30	Intentionally blank - removed by Protocol Amendment 9					
31	History of major organ, hematopoietic stem cell or bone marrow transplant					E

6 Treatment

6.1 Study treatment

The investigational drugs, e.g. iscalimab, LYS006, MAS825, remibrutinib, ianalumab and their corresponding matching placebos, will be prepared by Novartis and supplied to the investigational site as double-blinded medication kits. Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment, are outlined in the Site Operations Manual.

6.1.1 Investigational and control drugs

- For iscalimab, the dosage form of the supplied drug is a "ready to use" aqueous buffered sterile solution, also referred to as "CFZ533 150 mg/ml solution for injection (liquid in vial or "LIVI")". The 6 mL glass vial contains 1.2 mL of a "ready to use" 150 mg/mL solution of iscalimab and the excipients L-histidine, sucrose, and polysorbate 20, pH 6.0 ± 0.5. The placebo control, selected for this study, is a solution with a matching composition of inactive excipients.
- For LYS006, the dosage form of the supplied drug is a capsule which contains 5 mg LYS006. The placebo control, selected for this study, has a matching composition of inactive excipients. Drug and matching placebo will be administered orally in accordance with the specified study procedures.
- For MAS825, the dosage form of the supplied drug is a CCI mg/mL concentrate for solution for injection. In addition to the active ingredient, the MAS825 drug product also contains CCI and CCI The placebo control, selected for this study, is a solution for injection without any active ingredients.
- For remibrutinib, the dosage form of the supplied drug is a film-coated tablet with a strength of CCI mg and CCI mg, respectively. The placebo control, selected for this study, has a matching composition of inactive excipients. As the tablet size depends on the

content, and CCI mg and CCI mg have different sizes, each patient in Cohort D will receive one large size tablet and one smaller size tablet to ensure a double blind design. Drug and matching placebos will be administered orally in accordance with the specified study procedures.

- For ianalumab, the dosage form of the supplied drug is a 'ready to use' aqueous buffered sterile solution, also referred to as VAY736 CCI mg/mL solution for injection (liquid in vial or 'LIVI'). This formulation is stored in 6 mL glass vials and consists of ianalumab (VAY736) CCI mg per 1 mL, CCI [redacted] The placebo control, selected for this study, is a solution for injection without any active ingredients. Drug and placebo will be administered s.c in accordance with the specified study procedures.

Table 6-1 Overview of study medication

Study Drug Name/ Unit dose	Formulation	Route of Administration	Packaging	Provided by
Cohort A				
Iscalimab 150 mg/mL*	Solution for injection / infusion	Subcutaneous	6 ml, Type I glass vials, double blind	Novartis
Placebo 0 mg/mL*	Solution for injection / infusion	Subcutaneous	6 ml, Type I glass vials, double blind	Novartis
Cohort B				
LYS006 5 mg	Hard Gelatin Capsule	Oral	Double blind subject kits	Novartis
Placebo 0 mg	Hard Gelatin Capsule	Oral	Double blind subject kits	Novartis
Cohort C				
MAS825 CCI mg/mL*	Solution for injection / infusion	Subcutaneous	6 ml, Type I glass vials, double blind	Novartis
Placebo 0 mg/mL*	Solution for injection	Subcutaneous	6 ml, Type I glass vials, double blind	Novartis

Study Drug Name/ Unit dose	Formulation	Route of Administration	Packaging	Provided by
Cohort D				
Remibrutinib CCI mg	Tablet	Oral	Double blind/dummy subject kits	Novartis
Remibrutinib CCI mg	Tablet	Oral	Double blind/dummy subject kits	Novartis
Placebo to remibrutinib CCI mg	Tablet	Oral	Double blind/dummy subject kits	Novartis
Placebo to remibrutinib CCI mg	Tablet	Oral	Double blind/dummy subject kits	Novartis
Cohort E				
Ianalumab CCI mg/1mL*	Solution for injection / infusion	Subcutaneous	6 ml, Type I glass vials Double blind, subject kits	Novartis
Placebo 0 mg/1mL*	Solution for injection / infusion	Subcutaneous	6 ml, Type I glass vials Double blind, subject kits	Novartis

*The vials contain up to a 20% overfill to allow for a complete withdrawal of the labeled amount of Iscalimab/MAS825 or placebo. A pharmacist or authorized designee is required to prepare the study drug. Instructions for the storage and handling of study medication vials, and preparation of injection solution are described in the SOM (which is provided as a separate document).

Clinical supplies are to be dispensed only in accordance with the specified study procedures

6.1.2 Additional study treatments

For Cohorts A, B, C and D no additional treatment beyond investigational drugs and control drugs are included in this trial.

For Cohort E:

1 to 2 hours prior to the first administration of the study treatment, study subjects must receive pre-medication with 50 mg predniso(lo)ne or equivalent administered orally. The purpose of corticosteroid pre-medication is to mitigate potential cytokine release-related signs and symptoms associated with rapid depletion of circulating B cells. After the initial dose, corticosteroid pre-medication will not be required for subsequent injections of the study treatment. Predniso(lo)ne may be provided by the investigational site.

Table 6-2 Additional study treatment

Treatment Title	Glucocorticoids (ATC code: H02AB)
Treatment Description	As pre-medication (refer to Section 6.1.2)
Type	Drug
Dose Formulation	Tablet/capsule according to locally approved label
Unit Dose Strength(s)	50 mg predniso(lo)ne or equivalent
Dosage Level(s)	According to locally approved label
Route of Administration	According to locally approved label
Use	Pre-medication
Authorization status of the AxMP in EEA	Yes
Sourcing	Provided centrally by or on behalf of the sponsor or locally by the study site
Packaging and Labeling	Locally available authorized product will be used

At the investigator's discretion, in addition to predniso(lo)ne, paracetamol (acetaminophen) at doses not exceeding 1000 mg p.o. and/or oral second generation antihistamines (e.g., loratadine) may be administered.

After the first administration of the study treatment, all subjects must remain at the study site/doctor's office for at least 4 hours to enable safety monitoring for potential injection-related reactions. Such monitoring will not be required at subsequent visits.

6.1.3 Treatment arms/group

Subjects will be assigned to one of the following cohorts:

- **Cohort A**: iscalimab, 600 mg (2 injections of 2 mL) s.c. weekly for 4 weeks then bi-weekly, or its corresponding placebo (2 x 2 mL) s.c. weekly then bi-weekly

or

- **Cohort B**: LYS006, CCI mg CCI or its corresponding placebo b.i.d. p.o.

or

- **Cohort C**: MAS825, CCI mg s.c. CCI CCI for 4 weeks then CCI, or its corresponding placebo (2 x 1.5 mL) s.c. CCI and then CCI

or

- **Cohort D**: remibrutinib, CCI mg CCI. and matching placebo for CCI mg p.o., or CCI mg CCI and matching placebo for CCI mg p.o., or their matching placebo for CCI mg and matching placebo for CCI mg CCI. p.o.
- **Cohort E**: ianalumab, CCI CCI) s.c. CCI or its matching placebo CCI s.c. CCI

Within each cohort, subjects will be randomized to the investigational treatment arm or its corresponding placebo in a 2:1 ratio for Cohort A and B and a 3:1 ratio for Cohort C and E. As a second dose regimen will be used in Cohort D, the randomization will be 3:3:1 (remibrutinib CCI mg CCI: CCI mg CCI: placebo). The maximum treatment duration will not exceed 16 weeks.

Cohort allocation will be performed by the IRT system. If a subject is only eligible for one open cohort, they will be allocated 100% to that cohort. If the subject is eligible for more than one open cohort, the IRT will randomly allocate the subject to a cohort. The sponsor can set the cohort allocation ratio to favor any of the cohorts but this favoring to any one cohort will not exceed 80%.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All prescription medications, over-the-counter drugs and significant non-drug therapies (including surgery, excision and incisions, laser therapy and photodynamic therapy, physical therapy and blood transfusions) administered or taken within 6 months prior to the start of the study and during the study, must be recorded on the CRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant therapy must be individually assessed against all exclusion criteria/prohibited medications and non-drug therapies. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new therapy to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

For information regarding the potential impact of study treatment on vaccination success, please refer to Section 4.5.1.2.1 (Cohort A), Section 4.5.2.2.3 (Cohort B) Section 4.5.3.2.1 (Cohort C), Section 4.5.4.2.2 (Cohort D) and Section 4.5.5.2.5 (Cohort E).

6.2.2 Prohibited medications and non-drug therapies

Use of the treatments displayed in the table below is NOT allowed after randomization, unless otherwise specified. If medically justified, the investigator can prescribe appropriate prohibited medication or non-drug therapy after the EOT visit. A list of medications and non-drug therapies where caution needs to be exercised and certain action need to be taken are listed below Table 6-3.

Table 6-3 Prohibited medications and non-drug therapies

Medication or non-drug therapy	Action taken (if taken during study treatment period)
Use of other investigational drugs	To be discussed with Sponsor on case by case basis
Any systemic immunosuppressant or immunomodulator, such as but not limited to: • Corticosteroids • Cyclosporine A • Methotrexate • Cyclophosphamide • Biologics such as adalimumab, secukinumab, bimekizumab, bermekimab, etanercept, infliximab, ustekinumab, guselkumab, rituximab, belimumab, iscalimab (cohort E only), etc. • Systemic JAK inhibitors (such as tofacitinib or upadacitinib) or BTK inhibitors (such as ibrutinib and acalabrutinib)	Discontinue study treatment
Locally injected corticosteroids	Acceptable, if sporadic use (other than in HS lesions). Discontinue treatment if more than 3 injections are needed during study period
Spironolactone or other anti-androgens (such as finasteride, cyproterone acetate, etc.)	Can be used but must be on stable dose for the last 3 months prior to randomization and planning to continue for the duration of the study. To be discussed with Sponsor on case by case basis if new therapy is initiated or existing therapy is changed during the treatment period.
Any long term (>2 weeks) treatment with systemic antibiotics	Consider discontinuing study treatment if required antibiotic treatment is significantly longer than 2 weeks. To be discussed with Sponsor on case by case basis
Other systemic treatments for HS, including but not limited to: • Retinoids (such as isotretinoin), • Dapsone • Metformin • Oral zinc	To be discussed with Sponsor on case by case basis For metformin, a close monitoring of blood glucose is suggested
Surgery for HS	Acceptable, if localized, once during the treatment period. Discontinue study treatment if large excision (more than one lesion) and/or larger area treatment Other cases to be discussed with Sponsor on case by case basis

Medication or non-drug therapy	Action taken (if taken during study treatment period)
	For Cohort D: If major surgery is planned, which includes systemic or local anesthesia, please discontinue study drug treatment for 7 days prior to the intervention and until the risk for bleeding is considered over.
Physical treatment for HS, including laser, intense light and photodynamic therapy	Discontinue study treatment
Only for Cohort A,C, D and E Live/ attenuated vaccines	Discontinue study treatment Other approved (including HA conditional marketing authorization) vaccines e.g. killed, inactivated, subunit, nucleic acid (e.g. DNA, mRNA) may be permitted according to investigator's discretion and per local guidance.
Only for Cohort B Concomitant systemic medication inhibiting OAT3 such as: Probenecid, Gemfibrozil, Teriflunomide, Cimetidine and Diclofenac	Discontinue study treatment
Only for Cohort D Anti-platelet medication, **except** for **monotherapy** with acetylsalicylic acid up to 100 mg per day **or** clopidogrel. Note: the use of dual anti-platelet therapy (e.g. acetylsalicylic acid **+** clopidogrel) is prohibited.	Discontinue study treatment
Only for Cohort D Anticoagulant medication such as warfarin or Novel Oral Anti-Coagulants (NOAC)	Discontinue study treatment
Only for Cohort D Strong or Moderate CYP3A4 inhibitors Examples (non-exhaustive)[1]: aprepitant, amprenavir, boceprevir, casopitant, ceritinib, clarithromycin, cimetidine, ciprofloxacin, cobicistat, conivaptan, crizotinib, darunavir, diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, fluconazole[2], idelalisib, imatinib, indinavir, isavuconazole[2], istradefylline, itraconazole[2], josamycin, ketoconazole[2], lefamulin, letermovir, Magnolia vine (Schisandra sphenanthera), mibefradil, mifepristone, nefazodone, nelfinavir, netupitant, nilotinib, posaconazole[2], ravuconazole[2], ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, tofisopam, troleandomycin, tucatinib, verapamil voriconazole[2], voxelotor	Discontinue study treatment

Medication or non-drug therapy	Action taken (if taken during study treatment period)
Only for Cohort D Strong or Moderate CYP3A4 inducers Examples (non-exhaustive) [1]: apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampicin, rifapentine, St. John's wort (Hypericum perforatum), asunaprevir, beclabuvir, daclatasvir, bosentan, cenobamate, dabrafenib, elagolix, efavirenz, etravirine, lesinurad, lersivirine, lopinavir, nafcillin, primidone, rifabutin, talviraline, telotristat ethyl, thioridazine,	Discontinue study treatment
Only for Cohort D Class Ia or Class III anti-arrhythmic drugs which work by prolonging QT interval. Ia: qunidine, procainamide, disopyramide, hydroquinidine III: bretylium, amiodarone, ibutilide, sotalol, dofetilide, vernakalant, dronedarone	Discontinue study treatment

[1]The lists provided are not exhaustive. References: University of Washington Drug Interaction database (www.druginteractioninfo.org): Database search October, 2021.

[2]Exclusions of concomitant antifungal treatment only apply to oral/parenteral administration.

The following medications and non-drug therapies are NOT prohibited during the treatment period (if medically indicated):

- Topical antibiotics (such as clindamycin) and antiseptics, standard wound care.
- Oral antibiotics may be used, but for no longer than 2 weeks as rescue treatment in case of skin infection during the treatment period.
- Incision OR excision of one HS lesion, if medically indicated to relieve the subject.
- Pain medication, such as nonsteroidal anti-inflammatory drugs and opiates.

6.2.3 Other medications having potential interactions with remibrutinib (Cohort D only)

Note: use of the following medications may otherwise be excluded. Please consult Table 6-3.

Table 6-4 Other medications having potential interactions with remibrutinib

Medication or non-drug therapy	Action taken (if taken during study treatment period)
Intestinal BCRP or P-gp substrates which have a narrow therapeutic index Examples (non-exhaustive)[1]: baricitinib, daunorubicin, doxorubicin, mitoxantrone, digoxin, docetaxel, eribulin, everolimus, pazopanib, sirolimus, sorafenib, tacrolimus, talazoparib, tolvaptan, venetoclax	Use with caution. Co-administer in a staggered dosing approach (3hrs after remibrutinib).
Substrates of **systemic** efflux and uptake transporters OAT3 or OATP1B1 Examples (non-exhaustive):1 paclitaxel, pemetrexed, topotecan, carboplatin, cisplatin, oxyplatin, sorafenib	Use with caution. Monitor patients and adjust the dose of the concomitant drug(s) as required.
OCT1 substrates Examples (non-exhaustive)[1]: ranitidine, metformin	Use with caution. Monitor patients and adjust the dose of the concomitant drug(s) as required. Metformin: subjects to monitor their blood glucose levels after co-administration with remibrutinib and discontinue remibrutinib treatment in case of uncontrolled glucose
Drugs with known QT prolongation effect Examples (non-exhaustive)[1]: aclarubicin, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, cesium chloride, chloroquine, chlorpromazine, chlorprothixene, cilostazol, cisapride, citalopram, cocaine, domperidone, donepezil, droperidol, escitalopram, flecainide, gatifloxacin, grepafloxacin, halofantrine, haloperidol, hydroxychloroquine, ibogaine, levofloxacin, levomepromazine (methotrimeprazine), levomethadyl acetate, levosulpiride, meglumine antimoniate, mesoridazine, methadone, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, propofol, roxithromycin, sertindole, sevoflurane, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, vandetanib	Use these drugs with caution keeping in mind these risk factors: 1. QT effects of other co-prescribed drugs 2. Electrolyte imbalances (such as hypokalemia, hypomagnesemia) 3. Any impact on their clearance or metabolism (e.g. CYP450 inhibition) Subjects on these medications should be educated to report symptoms like palpitations, light-headedness, or dizziness and ECG should be conducted for such symptoms.

[1]The lists provided are not exhaustive. References: University of Washington Drug Interaction database (www.druginteractioninfo.org): Database search October, 2021.

6.2.4 Rescue medications and non-drug therapies

If skin infections or an exacerbation of HS lesions occur, the investigator may choose to treat with permitted medications and non-drug therapies in order to avoid discontinuation of the subject from the study treatment. Examples include:

- Conservative and topical wound care and dressings,
- Oral treatment with antibiotics, which should target involved bacteria if known and be no longer than 2 weeks in duration

No specific rescue medication is planned to be used for this trial. However, several standard of care (SOC) medications can be used to alleviate signs and symptoms of HS, such as antibiotics or biologics (Section 6.2.4). According to the European Guidelines (Zouboulis et al 2015), locally recurring lesions can be treated by classical surgery or LASER techniques, whereas medical treatment either as monotherapy or in combination with radical surgery is more appropriate for widely spread lesions. Medical treatment in HS may include antibiotics (such as clindamycin plus rifampicine, tetracyclines), acitretin, biologics (adalimumab, infliximab), hormonal treatment, dapsone and other biologics such as IL-17A blockers.

Please refer to Table 6-3 for prohibited treatments during the study. During the follow-up period, if medically indicated, SOC HS treatments, including surgery, may be used.

See respective IB for recommended treatment of specific adverse events.

6.2.5 Restrictions for study subjects

Highly strenuous physical exercise (e.g. weight training) should be avoided until after Study Completion evaluation, particularly prior to and during study visits. Subjects may otherwise continue with their usual level of physical activity.

Whenever possible, excessive sweating such as sauna and/or visit to countries with very hot climate should be restricted in particular for subjects enrolled in Cohort B (LYS006). If not, the subjects should be reminded to drink sufficiently. Subjects enrolled in Cohort B should be reminded that the intake of the medication should always be with a glass of liquid and during or within 15 minutes after meals. Sufficient water intake should be ensured during the whole day.

In addition, all subjects should not donate blood during the course of the study.

6.2.5.1 Dietary restrictions and smoking

Standard of care recommendations should be applied with regards to smoking habits and weight loss. Smoking habits will be recorded throughout the study.

Body weight will be recorded as indicated in the Assessment schedules.

6.2.5.2 Other restrictions

Not applicable

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see the 'subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Randomization may be performed only after a subject's study eligibility is confirmed on Day 1.

Subjects only eligible for one cohort will be assigned directly to the corresponding cohort; while subjects eligible for more than one cohort will be randomized to a cohort.

In Cohort B, a stratification factor (baseline lesion count >=5 or 3-4) will be utilized, to cap the number of subjects with 3-4 lesions at randomization (pre-dose on Day 1) to a maximum number of 15 subjects, which is expected to minimize the impact of any potential differences in placebo response between cohorts due to different baseline lesion count. When the number of subjects allocated to one cohort reaches the planned 45, the enrollment for this cohort will be closed and subjects in screening afterwards will only be evaluated for eligibility into another cohort.

Based on interim analysis data of the primary endpoint, placebo effect was observed to be similar between Cohort A (injectable) and Cohort B (oral compound). Due to this reason the stratification based on the number of baseline lesion count was not applied for Cohort D.

After cohort allocation, subjects will be randomized to the investigational treatment or placebo arm with a ratio of 2:1 in Cohorts A and B, 3:1 in Cohort C and E and 3:3:1 in Cohort D. For any prematurely terminated cohort, all ongoing subjects in both treatment arms in this cohort will be discontinued and not be replaced. The enrollment into this cohort will also be stopped. The IRT system will be set up for the allocation of eligible subjects, and for distribution and assignment of the study medication (see Site Operations Manual for details).

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. The randomization number is only used to identify which treatment the subjects have been randomized to receive. For information on subject numbering, please see 'Subject numbering' section in the SOM.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below. However both subject and investigator will know to which cohort (Cohort A, B, C, D or E) the subject has been assigned.

Within a cohort, the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.6.3).

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-5.

For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. PK/PD modeler) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other individuals (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

Following final database lock all roles may be considered unblinded.

Table 6-5 Blinding and unblinding plan

Role	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis	Final analysis per cohort
Subjects	B	UI	B	UI*
Site staff	B	UI	B	UI*
Field monitor	B	UI	B	UI*
Unblinded Pharmacovigilance sponsor staff	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	UI	UI	UI

Role	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis	Final analysis per cohort
All other sponsor staff and external consultants not identified above (trial team, project team, management & decision boards (including DMC), support functions)	B	UI	UI	UI

B Blinded ; UI Unblinded at individual level ; UI*For the respective closing cohort only

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted. Should this occur for any reason, the Investigator should discuss the option to restart treatment with the Sponsor.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Cohort A (iscalimab), Cohort C (MAS825) and Cohort E (ianalumab):

Information about study medication administered to the subject should be captured in the source document at each visit and in the eCRF.

Since the study treatment will be administered to the subject during the clinic visits by the investigator and/or designated study personnel only, it is the responsibility of the site staff to adequately capture all study treatment dispensed and used in the Drug Accountability Log.

Cohort B (LYS006) and Cohort D (remibrutinib):

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable to take the study treatment as prescribed for any reason.

Compliance will be assessed by the investigator and/or designated study personnel at each visit, using information provided by the subject. In addition, pill counts should be done at all drug dispensation and drug return visits. This information should be captured in the source document at each visit and in the eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

6.6.2.1 HS related events

6.6.2.1.1 Skin infections

If skin infections or an exacerbation of HS lesions occur, the investigator may choose to treat with conservative topical wound care and dressings, or may also consider oral treatment with antibiotics, which should target the involved bacteria, if known, and be no longer than 2 weeks in duration, in order to avoid discontinuation of the subject from the study. Rescue treatments are detailed in Section 6.2.3. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.6.2.1.2 Inflammatory skin lesions

If medically indicated, an HS lesion may be incised or excised once during the 16 week treatment period to relieve the subject. The surgery (incision or excision, etc.) needs to be recorded in the subject CRFs.

For cohort D: if surgery is indicated, the Investigator should take into account a potential bleeding risk of remibrutinib, in particular in case of additional risk factors, such as inherent risk of bleeding, or concomitant therapy with anti-platelet or anti-coagulant therapies (see Section 6.6.2.5).

6.6.2.2 Cohort A (iscalimab)

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion.

In this study, iscalimab will be administered as subcutaneous injections. No infusion or injection reactions have been noted in the Phase 1 and Phase 2 clinical program with iscalimab so far; however, investigators should be aware of the possibility and be prepared to treat such events.

Subjects will be monitored after the first injection at the site for approximately 1 hour post dose or longer, if needed at the discretion of the Investigator, to ensure adequate safety monitoring. In case of any signs of an acute reaction, clinical treatment may be provided as determined by the treating physician on a case-by-case basis and depending on the severity, using symptomatic treatment, anti-histamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

For the management of allergic reaction, anaphylaxis and cytokine release, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE/v5, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Use of rescue medication must be recorded on the Concomitant medications / Significant non-drug therapies eCRF after start of study drug.

6.6.2.3 Cohort B (LYS006)

There are no known expected AEs associated with LYS006 that would warrant specific treatment. Necessary medication as well as surgical or physical treatment used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.6.2.4 Cohort C (MAS825)

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion.

In this study, MAS825 will be administered as subcutaneous injections. Some injection site hemorrhage in 2 out of 6 subjects has been noted, but no dose related infusion site reactions have been noted after i.v. administration, thus injection site reactions may be observed.

Subjects will be monitored after the first injection at the site for approximately 1 hour post dose or longer, if needed at the discretion of the Investigator, to ensure adequate safety monitoring. In case of any signs of an acute reaction, clinical treatment may be provided as determined by the treating physician on a case-by-case basis and depending on the severity, using symptomatic treatment, anti-histamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

For the management of hypersensitivity or allergic reaction, anaphylaxis and cytokine release, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE/v5, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Use of rescue medication must be recorded on the Concomitant medications / Significant non-drug therapies eCRF after start of study drug.

6.6.2.5 Cohort D (Remibrutinib)

There are no dose related adverse event associated with remibrutinib that would need specific treatment. In case of a significant bleeding event, remibrutinib (LOU064) must be discontinued immediately. Platelet transfusion may be considered in emergency. Although not yet established as a rescue therapy, platelet transfusion has been shown in a small pilot study to have beneficial effects on hemostasis when administered after elimination of ibrutinib (another BTK inhibitor) from blood (Levade et al 2014). Currently, there is no scientific evidence to support the use of fresh frozen plasma for the treatment of bleeding adverse events related to remibrutinib.

In the same context, whenever surgery is needed, and a significant bleeding risk is identified, remibrutinib should be stopped. Please, refer to IB for additional details.

As this risk is not considered major, some smaller surgical interventions such as incisions, it may not be necessary to stop the treatment in order to alleviate pain and or disease burden. The observation for the signs of bleeding is recommended post intervention.

6.6.2.6 Cohort E (ianalumab)

If warranted, mild-to-moderate local and systemic injection related reactions can be managed according to symptoms and their severity (e.g., cooling, topical creams/gels, patches, paracetamol, antihistamines etc.) at investigator discretion. It is recommended that sites of administration are alternated, avoiding any body areas where there has been a recent local reaction. If a study subject experiences a severe systemic or local injection related reaction, management should be guided by general principles of treating the respective condition, including intensive care admittance, if warranted.

Subjects will be monitored after the first injection at the site for a minimum of 4 hours post dose or longer, if needed at the discretion of the Investigator, to ensure adequate safety monitoring. As with any biologic treatment, subjects should be monitored for signs and symptoms of anaphylaxis, including urticaria, rash, dyspnea, hypotension, chest pain, fever, and chills. Hypersensitivity reactions should be treated with antihistamines and glucocorticoids, and depending on severity, these subjects may also require 100% oxygen, volume expansion, catecholamines and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of ianalumab may be considered, depending on the subjects condition.

The investigator should carefully assess for signs and symptoms which might indicate an infection, remind the participant of the risk of infections and ask them to promptly report any symptoms of infections. Subjects with bacterial skin infections should be monitored closely. When evaluating a subject with a suspected infection, it is recommended the most sensitive test should be used (e.g., culture, PCR for direct pathogen detection). If a subject is evaluated for unexpected neurological or psychiatric symptoms (e.g., cognitive deficit, behavioral changes, visual disturbances or any other neurologic signs and symptoms), infectious causes should be considered in consultation with infectious disease experts as appropriate, and brain MRI and/or CSF examinations including cellular, biochemical and microbiological analyses (e.g., herpes virus, John Cunningham virus) performed as needed.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email

confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency.

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section. Please refer to the Study Operations Manual (SOM) for Cohort A (iscalimab) and Cohort C (MAS825) study drug preparation. No specific preparation for Cohort B (LYS006), Cohort D (remibrutinib) or Cohort E (ianalumab) study drug is necessary.

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

See the Site Operations Manual for further details. Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

If a subject will miss a visit and a home visit is not possible e.g. in the case of an epidemic or pandemic that limits or prevents on-site study visits (e.g. COVID-19 pandemic), delivery of IMP directly to a participant's home is generally permitted **for Cohort B and D only and on one occasion only**, in the event that the Investigator has decided that:

1. an on-site visit by the participant is not appropriate or possible, AND
2. it is in the best interest of the participant's health to continue administration of the study treatment even without performing an on-site visit.

In the event that on site visits can be replaced by home visits, and key assessments are able to be performed, home delivery of IMP is also permitted, for either cohort. In such a case there are no restrictions on the permissible number of home deliveries. See Section 8 for information regarding home visits.

In either case implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be dispensed as per the IRT system.

Cohort A

- Iscalimab and its matching placebo will be administered to the subject via two subcutaneous injections (2 x 2 mL) every one or two weeks during the subjects dosing visits at the study center. No dosing should occur on an outpatient basis except during an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, visits by site staff to a patient's home may be arranged in order to continue study treatment per protocol, as permitted by local regulations.

Cohort B

- LYS006 and its matching placebo will be taken orally by the subject twice daily, in the morning and in the evening.
- It is recommended that LYS006 and its matching placebo are taken during or shortly after a meal with a glass of water. At dosing visits, a snack may substitute for a meal.
- On treatment visit days, morning doses should be administered at the study site to enable pre-dose assessments. Every reasonable effort should be made to ensure that visits are held early enough in the day to enable on-site morning dose administrations. If a visit MUST be held after a subject's morning dose administration, the following procedures should be followed:
  1. The morning dose should be taken by the subject with their morning meal prior to the visit. The subject should record the time of dose administration.
  2. No dose will be administered during the visit. At the visit, the subject will be asked to provide the time of morning dose administration, which will be entered into the CRF.
  3. No changes are to be made to the procedures performed at the visit.
  4. The evening dose should be administered outpatient at the normal time.
- All other administrations will occur on an outpatient basis.
- LYS006 or matching placebo doses should be taken approximately 12 hours apart, with morning and evening meals. Any missing dose should be taken as soon as possible unless the next dose is scheduled within the next 6 hours, in which case the missed dose should be skipped.

Cohort C

- MAS825 and its matching placebo will be administered to the subject via CCI subcutaneous injections CCI mL) every CCI during the subjects dosing visits at the study center. No dosing should occur on an outpatient basis except during an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, visits by site staff to a patient's home may be arranged in order to continue study treatment per protocol, as permitted by local regulations.

Cohort D

Every subject should take CCI film-coated tablets (CCI) in the CCI with an approximate CCI interval at approximately the same time CCI The study medication may be taken with or without a

meal but subjects should adhere to their choice throughout the study. If taken without food, the study medication should be taken with a glass of water (250 ml) at least 2 hours after the last meal and 1 hour before the next meal. Subjects should be instructed to swallow whole tablets and not to chew or break them.

On treatment visit days, CCI doses should be administered at the study site to enable pre-dose assessments. Every reasonable effort should be made to ensure that visits are held early enough in the day to enable on-site CCI dose administrations. If a visit MUST be held after a subject's CCI dose administration, the following procedures should be followed:

1. The CCI dose should be taken by the subject with their CCI meal prior to the visit. The subject should record the time of dose administration.
2. No dose will be administered during the visit. At the visit, the subject will be asked to provide the time of CCI dose administration, which will be entered into the CRF.
3. No changes are to be made to the procedures performed at the visit with the exception of the PK samples. In this situation, the PK sample should **not** be obtained if the patient has already taken their CCI dose before arriving at the study site.
4. The CCI dose should be administered outpatient at the normal time.

On treatment visit days with PK assessments, doses should be administered at the study site after the subject has fasted for 12 hours. Fasting should continue until after the 90 minute PK sample has been obtained.

Cohort E

Ianalumab and matching placebo will be administered to the subject via CCI subcutaneous injections CCI mL) CCI at the study center. No dosing should occur on an outpatient basis except during an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, visits by site staff to a patient's home may be arranged in order to continue study treatment per protocol, as permitted by local regulations.

7 Informed consent procedures

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

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 (R2) GCP Guideline 2016 and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drugs can be found in the respective IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drugs that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be re-discussed with the subject.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Ensure subjects are informed of the contraception requirements outlined in Section 5.2 (Exclusion criteria).

The study includes an optional CCI component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the investigator presents this option to the subject, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent. Declining to participate in these CCI will in no way affect the subject's ability to participate in the main research study.

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

In case Home Nursing is implemented during an epidemic or pandemic, a separate Home Nursing consent document must be used in addition to the main ICF.

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8 Visit schedule and assessments

Subjects should be seen for all visits/assessments as outlined in the Assessment Schedules:

- All Subjects (Table 8-1)
- Cohort A (Table 8-2)
- Cohort B (Table 8-3)
- Cohort C (Table 8-4)
- Cohort D (Table 8-5)
- Cohort E (Table 8-6 and Table 8-7)

Missed or rescheduled visits should not lead to automatic discontinuation. The following should be considered:

- If a subject cannot attend a visit as per the schedule, they should attend as soon as possible for the scheduled assessments that were due to be completed at the missed visit.
- If a subject cannot attend the site until the next scheduled visit, consider contacting the subject by phone to determine if there have been any adverse events or changes to concomitant medications. See Section 8.5.1 for information on how to deal with PROs. If practically possible and allowed by local regulation, drug for Cohort B (LYS006) and Cohort D (remibrutinib) may shipped directly to a subject (see Section 6.7). If there is a possibility that the subject may miss more than one visit either consecutively or non-consecutively, this should be discussed with the Sponsor. Every attempt must be made to have the subject on site for visits 102 (day 8), 199 (day 113) and 299 (day 197 – end of study).
- If there are restrictions on travel in a county or region e.g. in the case of an epidemic or pandemic, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. IMP should be provided to the subject by the site staff or shipped to the subject if permitted (see Section 6.7). Phone calls, virtual contacts (e.g. teleconsult) may also be considered where appropriate in addition to home visits by site staff/nursing service.

Subjects who prematurely discontinue the study treatment for any reason should be scheduled for a visit as soon as possible. Where possible, they should return for the assessments as defined in their respective assessment table. If not possible, all of the assessments listed for the final visit should be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Specifications for and timing of each assessment are detailed in the protocol. The methods and recording of each assessment may be outlined in the Site Operations Manual.

Table 8-1 Assessment Schedule: Screening

Visit Name	**Screening**
Visit Number[1]	**1**
Days	**Up to Day -35 to Day -1**
Informed Consent Form(s)	X
CCI consent	X
Inclusion / Exclusion criteria	S
Pregnancy test (blood test)	X
Demography	X
Physical Examination	S
Vital Signs	X
Body Height	X
Body Weight	X
Smoking habit	X
Medical history/current medical conditions	X
Hepatitis, CMV , Lupus anticoagulant and HIV Screen	S
Electrocardiogram (ECG)	X
Clinical Chemistry	X
Hematology	X
Urinalysis	X
Coagulation Panel (aPTT, PT, INR)	X
hsCRP, IgA, IgM, IgG, sBAFF	X
Quantiferon test	X
COVID-19 test[3]	S
Blood collection for B cell count (TBNK)	X
Concomitant medications	X
Adverse Events[4]	X
Serious Adverse Events	X
HS lesion count	X
CCI	X
Anatomical HS regions involved	X
New or flared existing boils	X
Skin Pain NRS	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Removed in PA4 therefore N/A
[3] COVID test performed at a separate visit within 7 days of treatment if a COVID test is in line with health and governmental authority guidance
[4] Including HS lesion flares

Table 8-2 Assessment Schedule, Cohort A: iscalimab

Epoch	Treatment											Post-Treatment Follow-Up		
Visit Name	Treatment											Non-Treatment		EOS
Visit Numbers[1]	101	102	103	104	105	106	107	108	109	110	199	201	202	299[2]
Days	1[3]	8 ±2	15 ±2	22 ±2	29 ±2	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	141 ±5	169 ±5	197 ±5
Inclusion / Exclusion criteria	S													
Pregnancy test[4]	X	X	X		X		X		X		X	X		X
Physical Examination	S				S		S				S			S
Vital Signs	X	X	X		X		X		X		X	X		X
Body Weight	X						X				X			X
Smoking habit	X				X						X			X
Hurley score	X													
Electrocardiogram (ECG)	X	X			X		X				X			X
Clinical Chemistry	X[5]	X	X		X		X		X		X	X		X
Hematology	X	X			X		X		X		X			X
Urinalysis	X	X	X		X		X		X		X	X		X
Coagulation Panel	X						X				X			
hsCRP	X	X	X		X		X		X		X	X		X
Drug administration	X	X	X	X	X	X	X	X	X	X				
Concomitant medications	X													
Adverse Events[6]	X													
Serious Adverse Events	X													
HS lesion count	X	X	X		X		X		X		X	X		X
CCI														
Anatomical HS regions involved	X	X	X		X		X		X		X	X		X
New or flared existing boils	X	X	X		X		X		X		X	X		X
CCI														

Epoch	Treatment											Post-Treatment Follow-Up		
Visit Name	Treatment											Non-Treatment		EOS
Visit Numbers[1]	101	102	103	104	105	106	107	108	109	110	199	201	202	299[2]
Days	1[3]	8 ±2	15 ±2	22 ±2	29 ±2	43 ±3	57 ±3	71 ±3	85 ±3	99 ±3	113 ±3	141 ±5	169 ±5	197 ±5
CCI														
Skin Pain NRS	X	X	X		X		X		X		X	X		X
PK blood collection[8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity blood collection[8,9]	X		X				X					X	X	X
PD blood collection - Soluble CD40[8]	X		X		X		X		X		X	X	X	X
Biomarkers blood collection[11]	X	X			X				X		X			X
CCI														
Randomization	X													

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 Subjects who discontinue the study early should have the same assessments performed as for the end of study visit 299 (EOS).

3 All Day 1 assessments should be performed/collected pre-dose (not required for Exploratory CCI

4 Blood test at EOS or last study visit; urine tests done at other indicated visits.

5 Subject should be fasted for at least 6 hours prior to collection

6 Including HS lesion flares

7 Selected sites only

8 Pre-dose sampling on dosing days - All subjects

9 In case of suspected event due to immunogenicity, an additional (unscheduled) PK and an additional IG sample should be collected as close as possible to the event

10 Optional CCI collection requires a separate consent and can be collected at or after D1

11 Biomarkers blood collection including Serum and Plasma

Table 8-3 Assessment Schedule, Cohort B: LYS006

Epoch	Treatment							Post-Treatment Follow-Up	
Visit Name	Treatment							Non-Treatment	EOS
Visit Numbers[1]	101	102	103	104	105	106	199	201	299[2]
Days	1[3]	8 ±3	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	141 ±5	197 ±5
Inclusion / Exclusion criteria	S								
Pregnancy test[4]	X	X	X	X	X	X	X	X	X
Physical Examination	S			S	S	S			S
Vital Signs	X	X	X	X	X	X	X	X	X
Body Weight	X					X			X
Smoking habit	X				X		X		X
Hurley score	X								
Electrocardiogram (ECG)	X	X		X	X	X			X
Hematology	X	X		X	X	X	X		X
Clinical Chemistry	X[5]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
CCI									
hsCRP	X	X	X		X	X	X		X
Drug administration	X	X	X	X	X	X	X		
Concomitant medications	X								
Adverse Events[7]	X								
Serious Adverse Events	X								
HS lesion count	X		X	X	X	X	X	X	X
CCI									
Anatomical HS regions involved	X		X	X	X	X	X	X	X
New or flared existing boils	X		X	X	X	X	X	X	X
CCI									

Epoch	Treatment							Post-Treatment Follow-Up	
Visit Name	Treatment							Non-Treatment	EOS
Visit Numbers[1]	101	102	103	104	105	106	199	201	299[2]
Days	1[3]	8 ±3	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	141 ±5	197 ±5
Skin Pain NRS	X		X	X	X	X	X	X	X
PK blood collection - pre-dose[9]	X	X	X	X	X	X	X	X	X
CCI									
Biomarkers urine collection[11]	X	X	X	X	X	X	X	X	X
Soluble biomarkers blood collection[8,12]	X	X		X		X		X	X
Biomarkers blood collection[15]	X	X		X		X	X		X
CCI									
Randomization	X								

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 Subjects who discontinue the study early should have the same assessments performed as for the end of study visit 299 (EOS).

3 All Day 1 assessments should be performed/collected pre-dose (not required for Exploratory CCI)

4 Blood test at screening and EOS or last study visit; urine tests done at other indicated visits

5 Subject should be fasted for at least 6 hours prior to collection

6 Central lab: full micro panel on on-site samples and CCI detection on at-home samples; Local lab may perform CCI detection on on-site and/or at-home samples if deemed necessary and in consultation with the Sponsor. At-home CCI samples are only collected at the visits defined for the "CCI " assessment.

7 Including HS lesion flares

8 Selected sites only

9 The sample volume will be immediately separated into 2 tubes: 1 tube for blood PK analysis and 1 tube for plasma preparation and plasma PK analysis.

10 For treatment visits, the CCI sample will be collected at home the day prior to the visit, 2-4 h after study drug evening dose intake. The sample will be kept at room temperature. For post-treatment visits, the CCI samples will be obtained on the day of the visit.

11 Protein levels of potential kidney damage biomarkers.

12 Analysis from ex-vivo stimulated and non-stimulated whole blood, including LTB4.

13 Collection from region with inflammatory nodular skin lesions (peri-lesional).

14 Optional CCI collection requires a separate consent and can be collected at or after D1

15 Biomarkers blood collection including Serum and Plasma

Table 8-4 Assessment Schedule, Cohort C: MAS825

NOTE: Blood samples should be taken after the subject has been fasting for at least 6 hours.

Epoch	Treatment						Post-Treatment Follow-Up			Post study
Visit Name	Treatment						Non-Treatment		EOS	Pregnancy test
Visit Numbers[1]	101	102	103	104	105	199	201	202	299[2]	
Days	1[3]	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	141 ±5	169 ±5	197 ±5	239 ±14
Inclusion / Exclusion criteria	S									
Pregnancy test[4]	X	X	X	X	X	X	X		X	S
Physical Examination	S		S	S		S			S	
Vital Signs	X	X	X	X	X	X	X		X	
Body Weight	X			X		X			X	
Smoking habit	X		X			X			X	
Hurley score	X									
Electrocardiogram (ECG)	X		X	X		X			X	
Clinical Chemistry	X	X	X	X	X	X	X		X	
Hematology	X	X	X	X	X	X	X		X	
Urinalysis	X		X	X	X	X	X		X	
hsCRP	X	X	X	X	X	X	X		X	
Drug administration	CCI									
Concomitant medications	X									
Adverse Events[5]	X									
Serious Adverse Events	X									
HS lesion count	X	X	X	X	X	X	X		X	
CCI										
Anatomical HS regions involved	X	X	X	X	X	X	X		X	
New or flared existing boils	X	X	X	X	X	X	X		X	
CCI										

Epoch	Treatment						Post-Treatment Follow-Up			Post study
Visit Name	Treatment						Non-Treatment		EOS	Pregnancy test
Visit Numbers[1]	101	102	103	104	105	199	201	202	299[2]	
Days	1[3]	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	141 ±5	169 ±5	197 ±5	239 ±14
Skin Pain NRS	X	X	X	X	X	X	X		X	
PK blood collection[7,8]	CCI									
Immunogenicity blood collection[7,8]	X	X		X			X	X	X	
PD blood collection - target engagement BM[7]	CCI									
Biomarkers blood collection[10]										
CCI (optional)	X					X				
Biomarkers skin tape strips	X		X		X	X				
CCI										
Randomization	X									

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 Subjects who discontinue the study early should have the same assessments performed as for the end of study visit 299 (EOS). A urine pregnancy test should be performed 5 months after the last treatment of MAS825

3 All Day 1 assessments should be performed/collected pre-dose (not required for Exploratory CCI)

4 Blood test at EOS or last study visit if subjects participation stops early; urine tests done at other indicated visits. Post study safety contact pregnancy test can be done by posting pregnancy test kit and a telephone follow up.

5 Including HS lesion flares

6 Selected sites only

7 Pre-dose sampling on dosing days - All subjects

8 In case of suspected event due to immunogenicity, an additional (unscheduled) PK and an additional IG sample should be collected as close as possible to the event

9 Optional CCI collection requires a separate consent and can be collected at or after D1

10 Biomarkers blood collection including Serum.

Table 8-5 Assessment Schedule, Cohort D: Remibrutinib

Epoch	Treatment						Post-Treatment
Visit Name	Treatment						EOS
Visit Numbers[1]	101	102	103	104	105	199	CCI
Days	1[3]	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	±5
Inclusion / Exclusion criteria	S						
Pregnancy test[4]	X	X	X	X	X	X	X
Physical Examination	S		S	S	S		S
Vital Signs	X	X	X	X	X	X	X
Body Weight	X					X	X
Smoking habit	X					X	X
Hurley score	X						
Electrocardiogram (ECG)	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
Clinical Chemistry	X[5]	X	X	X	X	X	X
Coagulation Panel	X		X		X	X	
Urinalysis	X	X	X	X	X	X	X
hsCRP, IgA	X	X		X	X	X	X
Drug administration	X	X	X	X	X	X	
Concomitant medications	X						
Adverse Events[6]	X						
Serious Adverse Events	X						
HS lesion count	X	X	X	X	X	X	X
CCI							
Anatomical HS regions involved	X	X	X	X	X	X	X
New or flared existing boils	X	X	X	X	X	X	X
CCI							

Epoch	Treatment						Post-Treatment
Visit Name	Treatment						EOS
Visit Numbers[1]	101	102	103	104	105	199	CCI
Days	1[3]	15 ±3	29 ±3	57 ±3	85 ±3	113 ±3	±5
CCI							
Skin Pain NRS CCI	X	X	X	X	X	X	X
CCI							
Biomarkers blood collection (BTK)	X	X	X		X	X	X
Biomarkers blood collection (serum and plasma)	X	X	X		X	X	X
CCI							
Randomization	X						

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 Subjects who discontinue the study early should have the same assessments performed as for the end of study visit 299 (EOS).

3 All Day 1 assessments should be performed/collected pre-dose (not required for Exploratory CCI)

4 Blood test at screening and EOS or last study visit; urine tests done at other indicated visits

5 Subject should be fasted for at least 12 hours prior to collection. Samples to be taken pre-dose, then 45 and 90 minutes post dose.

6 Including HS lesion flares

7 Selected sites only

8 Optional CCI collection requires a separate consent and can be collected at or after D1

Table 8-6 Assessment Schedule, Cohort E: Ianalumab Treatment and Mandatory Follow-up periods

Epoch	Treatment							Post-Treatment Follow-Up			
Visit Name	Treatment							Mandatory (non- treatment)			
Visit Numbers[1]	101	102[2]	103	104	105	106	199	201	202	203	204
Days	1	15 ±3	29 ±3	57 ±3	85 ±3	88[10] ±3	113 ±3	141 ±5	169 ±5	197 ±5	225 ±5
Inclusion / Exclusion criteria	S										
Pregnancy test[3]	X	X	X	X	X		X	X	X	X	X
Physical Examination	S		S	S			S				
Vital Signs	X	X	X	X	X		X	X	X	X	X
Body Weight	X			X			X				
Smoking habit	X						X				
Hurley score	X										
Electrocardiogram (ECG)	X	X	X	X	X		X	X	X	X	X
Hematology	X	X	X	X	X		X	X	X	X	X
Clinical Chemistry	X	X	X	X	X		X	X	X	X	X
Urinalysis	X		X	X	X		X	X			X
hsCRP, IgA, IgM, IgG CCI	X		x		X		X			X	X
Drug administration	CCI										
Corticosteroid induction	X										
Concomitant medications	X										
Adverse Events[4]	X										
Serious Adverse Events[9]	X										
HS lesion count	X	X	X	X	X		X	X	X	X	X
CCI											
Anatomical HS regions involved	X	X	X	X	X		X	X	X	X	X
New or flared existing boils	X	X	X	X	X		X	X	X	X	X
CCI											

Epoch	Treatment							Post-Treatment Follow-Up			
Visit Name	Treatment							Mandatory (non- treatment)			
Visit Numbers[1]	101	102[2]	103	104	105	106	199	201	202	203	204
Days	1	15 ±3	29 ±3	57 ±3	85 ±3	88[10] ±3	113 ±3	141 ±5	169 ±5	197 ±5	225 ±5
CCI											
Skin Pain NRS CCI	X	X	X	X	X		X	X	X	X	X
PK blood collection[6, 7]	CCI										
Immunogenicity (ADA) [6, 7]											
CCI											
Randomization	X										

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 All Day 1 assessments should be performed/collected pre-dose (not required for Exploratory CCI)

3 Blood test at screening and EOS or last study visit; urine tests done at other indicated visits

4 Including HS lesion flares

5 Selected sites only

6 For both PK and IG Samples to be collected pre-dose unless otherwise stated.

7 In case of hypersensitivity reaction, an unscheduled sample needs to be collected for PK and IG

8 Optional CCI collection requires a separate consent and can be collected at or after D1

9 All SAEs occurring until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). See Section 10.1.3.

10 PK sample on Day 88 should be taken 3 days +/- 1 day after the dose on Day 85

Table 8-7 Assessment Schedule, Cohort E: Ianalumab Conditional Follow-up period

Epoch	Post-Treatment Follow-Up						
Visit Name	Conditional (B cell dependent)						
Visit Numbers[1]	210	220	230	240	250	260	299[2] (EOS)
Days	309 ±7	393 ±7	477 ±7	561 ±7	645 ±7	729 ±7	813 ±7
Pregnancy test[3]	X	X	X	X	X	X	X
Physical Examination	S	S	S	S	S	S	S
Vital Signs	X						X
Body Weight							X
Smoking habit							X
Electrocardiogram (ECG)							X
Hematology							X
Clinical Chemistry							X
Urinalysis							X
CCI							
Concomitant medications	X						
Adverse Events[4]	X						
Serious Adverse Events[6]	X						
HS lesion count	X	X	X	X	X	X	X
CCI							
Anatomical HS regions involved	X	X	X	X	X	X	X
New or flared existing boils							X
CCI							
Skin Pain NRS CCI	X	X	X	X	X	X	X

Epoch	Post-Treatment Follow-Up						
Visit Name	Conditional (B cell dependent)						
Visit Numbers[1]	210	220	230	240	250	260	299[2] (EOS)
Days	309 ±7	393 ±7	477 ±7	561 ±7	645 ±7	729 ±7	813 ±7
Immunogenicity (ADA)		X					X
CCI							

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded in the source documentation only

1 Visit structure given for internal programming purpose only

2 Subjects who discontinue the study early should have the same assessments performed as for the end of study visit 299 (EOS).

3 Blood test at screening and EOS or last study visit; urine tests done at other indicated visits

4 Including HS lesion flares

5 Selected sites only

6 All SAEs occurring until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). See Section 10.1.3.

8.1 Screening

It is permissible to re-screen a subject if s/he fails the initial screening e.g. due to washout period- of concomitant medication; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after he/she has screen failed. All eligibility criteria must be re-checked, based on the most recent data available, and met prior to enrollment of the subject into the study.

All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. An exception may be granted for those subjects who screen failed due to the temporary halts of enrolment due to epidemics or pandemics. If a subject fails screening but is re-screened, the subject will be assigned a new subject number.

Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

For screening failures (initial or after re-screening), information on what data should be collected is outlined in the Site Operations Manual.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. See the SOM for the list of information to be collected for screening failures. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Section 10.1.2, Section 10.1.3). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Data to be collected will include general subject demographics, relevant medical history and current medical conditions prior to study entry, diagnosis and other variables believed to influence HS severity or response to treatment, such as weight and smoking status, details of prior anti-HS treatment, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 6 months prior to first dose of study drug must be recorded on the eCRF. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2.1 Hurley score

The Hurley score (Revuz 2009) will be collected to understand the characteristics of the patient population enrolled in this study.

Table 8-8 Hurley score

Hurley's classification	
Grade I	Abscess formation, single or multiple without sinus tracts and cicatrization
Grade II	Recurrent abscesses with tract formation and cicatrization. Single or multiple, widely separated lesions
Grade III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area

8.3 Efficacy

Efficacy assessments are specified below, with the methods for assessment and recording, specified in the Study Operations Manual. Assessments will be performed and samples collected at the timepoint(s) defined in the Assessment schedule Section 8. As clinical efficacy measures are rater dependent, each evaluator should be appropriately trained and qualified for these assessments.

Every effort should be made to ensure that the same evaluator should assess and count the lesions for a subject throughout the study. Clinical Outcome measures will assess the HS severity in different areas of the body and also the numbers and types of lesions in the different anatomical areas. Due to the inter- and intra- rater variability inherent to every subjective grading system, every effort should be made to keep the same evaluator per subject. As HS lesions are complex and difficult to distinguish, it is highly recommended that only experienced raters evaluate the subjects and that palpation on top of inspection is used to define the numbers of distinct lesions.

The counting is to be done by lesion type and by counting area. For each assessment, the evaluator will be recorded in the source documentation and CRF and change of evaluator should be taken into account.

8.3.1 Hidradenitis suppurativa lesion count

Individual lesions counts will be performed as outlined in the Assessment schedules. The lesion count will include all observed typical HS lesions at the given timepoint and in the typical anatomical areas and will be recorded in the CRFs. The HS lesions are:

- Inflammatory nodules (N) that are typically tender, erythematous, possibly pyogenic granuloma lesions typically of more than 1 cm in diameter.
- Abscesses (A) that are often inflammatory, fluctuant, with or without drainage, tender or painful. The fluctuant character must be confirmed by palpation.
- Draining fistulae (F) are synonyms for sinus tracts or tunnels; draining fistulae have a visible communications to the skin surface, and visible drainage, such as purulent fluid or lymphatic liquid.
- Non-draining fistulae (NF) are identified fistulae without visible drainage.

- Non-inflammatory nodules (NN) are dense lesions of more than 1 cm in diameter that are typically neither tender nor painful and lack peri-lesional or lesional redness.

8.3.2 Hidradenitis suppurativa clinical response (HiSCR)

The HiSCR is defined by the status of three types of HS specific lesions, which are abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulae (sinus tracts, with communications to the skin surface, draining purulent fluid, also called tunnel). The proposed definition of responders to treatment (HiSCR achievers) is at least a 50% reduction in abscesses and nodules (Ans), no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline (Kimball et al 2014, Kimball et al 2018).

A **simplified HiSCR50** is proposed for this study as primary endpoint and is defined as follows:

1. at least a 50% reduction in abscesses and inflammatory nodules (Ans),
2. no increase in the number of draining fistulas from baseline

This definition is used to reflect the difficulty in clinically distinguish abscesses reliably from inflammatory nodules. The score will be derived from the individual lesion counts of abscesses and nodules (and fistulae) at scheduled visits as indicated in Assessments schedule and as such will not be recorded in the CRF.

Additionally to facilitate comparisons with other trials, the following HiSCRs will be derived:

- The simplified HiSCR75
  a. at least a 75% reduction in abscesses and inflammatory nodules (Ans),
  b. no increase in the number of draining fistulas from baseline
- The original HiSCR (or HiSCR50)
  c. at least a 50% reduction in abscesses and inflammatory nodules (Ans),
  d. no increase in the number of draining fistulas from baseline
  e. no increase in the number of abscesses
- HiSCR75:
  f. at least a 75% reduction in abscesses and inflammatory nodules (Ans),
  g. no increase in the number of draining fistulas from baseline
  h. no increase in the number of abscesses
- HiSCR90:
  i. at least a 90% reduction in abscesses and inflammatory nodules (Ans),
  j. no increase in the number of draining fistulas from baseline
  k. no increase in the number of abscesses

8.3.3 Anatomical HS regions involved

The following HS affected anatomical areas will be recorded in the CRF:

- right and left axillary (armpit),
- right and left gluteal (perianal),
- right and left inguinal-femoral (groin),
- right and left submammary (breast),
- perineal,
- others (any other HS-affected anatomical areas, to be identified by investigator)

These anatomical areas are to be assessed for the location of HS lesions (abscesses, draining fistulas, non-draining fistulas, inflammatory nodules, and non-inflammatory nodules).

8.3.4 CCI

CCI

The scores will be recorded in the CRF.

Figure 8-1 CCI

CCI

8.3.5 CCI

CCI

[redacted]

8.3.6 CCI

CCI

[redacted]

8.3.7 CCI

CCI

[redacted]

8.3.8 Appropriateness of efficacy assessments

As described in Section 4.1 several clinical efficacy parameters have been used in the past to assess HS, without a universally recognized endpoint. For this study, the simplified HiSCR (Hidradenitis Suppurativa Clinical Response) was selected as primary endpoint.

In addition, since the main goal for a medical intervention is to reduce inflammation and consequent pain and HS severity and symptoms, the primary clinical endpoint focuses on inflammatory HS lesions (inflammatory nodules, abscesses and fistulae).

Other clinical endpoints are used to examine CCI

CCI Subjects will be asked to evaluate their own while the skin pain NRS will assess the primary symptom of HS, skin

related pain. CCI [redacted]

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedules (Section 8) detailing when each assessment is to be performed.

During an epidemic or pandemic that limits or prevents on-site study visits regular phone or virtual calls will occur (as per the Assessment schedule or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

For details on AE collection and reporting, refer to Section 10.1.

Table 8-9 Safety Assessments

Assessment	Description
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital sign	Vital signs include body temperature (recorded in °C), BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Height information will be collected at screening only.

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, coagulation panel and clinical chemistry blood and urine specimens collected as part of screening and safety monitoring (as detailed in the Assessment schedule (Table 8-1, Table 8-2, Table 8-3, Table 8-4 ,Table 8-5, Table 8-6 and Table 8-7). With the exception of local CCI [redacted] results, only laboratory results from the central laboratory can be used to determine subject's eligibility for the study. During the course of the study, unscheduled assessments can be performed if clinically indicated.

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol** but is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

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

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Details on the collection, and shipment of samples and the reporting of results by the central laboratory are provided to the investigators in a separate Laboratory Manual.

8.4.1.1 Blood specimens

Table 8-10 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), MCH, MCHC, MCV, For Cohort E only: CCI CCI
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose, serum ketones (Cohort C only) eGFR will also be calculated for Screening and Cohort B and E subjects. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated
Coagulation	International normalized ratio [INR]), activated Partial thromboplastin time (aPTT), Prothrombin time (PT)
Serology	HbsAg, HbcAb, hepatitis C antibodies, HIV, CMV, Lupus anticoagulant, Quantiferon
Additional tests	CCI
Pregnancy Test	Serum / Urine pregnancy test

8.4.1.2 Urine specimens

All Cohorts:

During visits at the clinic, a midstream urine sample (approx. 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments and allow proper assessments.

Protein, creatinine, microalbumin, protein-creatinine ratio (PCR) and albumin-creatinine ratio (ACR) measurements will be performed at the Central Lab.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed at the central lab: Specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

Screening, Cohort A, C, D and E:

A microscopic panel will be performed by the central lab in the case of select dipstick results, as specified in the Central Laboratory Manual.

CCI only:

In CCI additional CCI samples will also be collected at home, the day prior to on-treatment visit days at the clinic, per the schedule outlined for CCI" in the Assessment schedule (Table 8-3). These samples will be collected CCI after study drug intake in the evening and will be sent to a central laboratory for CCI see Section 8.5.2.2)

The following will be systematically performed for CCI subjects, per the schedule outlined for "CCI in the Assessment schedule (Table 8-3):

- Central lab CCI panel, on on-site and at-home CCI samples

If CCI are detected, additional analyses including exploratory biomarker analysis may be implemented (see Study Operations Manual/Laboratory Manual for details).

All CCI samples should ideally be kept at body/room temperature until local and/or central analysis.

8.4.2 Electrocardiogram (ECG)

A central reading of standard 12-lead ECGs will be implemented. Full details of all procedures relating to the ECG collection and reporting are contained in the core laboratory technical manual or in the Site Operations Manual. For cohort D, ECGs will be recorded in triplicates.

PR interval, QRS duration, heart rate, RR, QT, QTcF (Fridericia QT) will be collected.

Clinically significant abnormalities must be reported in the AE CRF.

8.4.3 Pregnancy and assessments of fertility

At screening and EOS (or last visit), a serum pregnancy test will be performed centrally.

Throughout the study, local urine pregnancy test are sufficient. Additional urine pregnancy tests may be required, if a reason occurs such as subject reports delay in menstruation.

A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. For Cohort C, all WoCBP are required to continue the highly effective contraception until 5 months after the last treatment with MAS825 (refer to Chapter 7.9 of the MAS825 IB). Between Day 225 and 253 a urine pregnancy test will be conducted (pregnancy test can be provided to the subject at the EoS visit and the test completed at home) and results communicated to the site. See Section 10.1.4 for guidance on pregnancy reporting and follow-up. For **Cohort E**, all WoCBP are required to continue the highly effective contraception during treatment and until 6 months after the last treatment with ianalumab. Between Day 253 and 281 a urine pregnancy test will be conducted (pregnancy test can be provided to the subject at visit 204 and the test completed at home) and results communicated to the site. See Section 10.1.4 for guidance on pregnancy reporting and follow-up.

8.4.4 Other safety evaluations

8.4.4.1 Quantiferon test

A QuantiFeron test will be performed and read at screening (or within 6 months prior to randomization) in order to evaluate the infection with tuberculosis (TB). The test may be repeated if test result is ambiguous. A positive QuantiFeron test at screening will exclude the subjects from participation in the study.

T-SPOT or other types of ELISPOT assays based on interferon-gamma release may also be used for tuberculosis diagnosis as per local practice.

Precautions against tuberculosis should be handled according to the best medical practice consistent with the local standards in each country with prior consultation with Novartis. Subjects requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the subject to enter the study).

Results will be available as source data and will not be recorded within the eCRF.

8.4.4.2 CMV and SARS-CoV-2 (COVID-19)

CMV

Guidance to investigators:

CMV infections will be recorded as Adverse Events and on the CMV-specific CRF. CMV infection is identified by assessments of laboratory and/or clinical sign/symptoms. Cytomegalovirus disease is defined according to published criteria (Ljungman et al 2017) as described below.

a. ACTIVE CYTOMEGALOVIRUS INFECTION is defined as a detectable cytomegalovirus viral load in the absence of signs or symptoms attributable to cytomegalovirus. Active cytomegalovirus infection can be the result of cytomegalovirus reactivation or primary cytomegalovirus infection.
b. PROVEN DISEASE: For pneumonia, central nervous system (CNS) disease, gastrointestinal disease, hepatitis, nephritis, cystitis, myocarditis, pancreatitis, and disease in other organs, definite tissue-invasive disease requires the correct clinical syndrome combined with the detection of cytomegalovirus in tissue samples (or in bronchoalveolar lavage fluid for pneumonia) by virus isolation, immunohistochemical analysis, in situ hybridization, or conventional histologic features. Detection of cytomegalovirus by PCR alone is not sufficient.
    - Cytomegalovirus viral syndrome requires fever (oral temperature >38°C) for two or more days within a 4-day period, neutropenia or thrombocytopenia, and the detection of cytomegalovirus in the blood by culture or the detection of antigen, DNA, or RNA. Human herpes virus -6 (HHV-6) infection needs to be excluded.
    - For central nervous system (CNS) disease, detection of cytomegalovirus in cerebro-spinal fluid (CSF) samples by culture or PCR is sufficient.
    - For retinitis, typical cytomegalovirus lesions must be confirmed by an ophthalmolo-gist; detection of cytomegalovirus is not required.
c. PROBABLE DISEASE requires the correct clinical syndrome but the detection of cytomegalovirus cannot be confirmed as outlined above.

Detection during screening and treatment period (only Cohort A):

1. At study screening, subjects with active viral infections (quantifiable CMV DNA by PCR or positive IgM in the absence of a positive IgG) will not be eligible for randomization in Cohort A.
2. During treatment in Cohort A: In case of suspicion of CMV infection, CMV serology and PCR will be performed as soon as possible and the subject should not receive treatment until confirmed negative. Treatment will be discontinued if confirmed.

SARS-CoV-2 (COVID-19)

Local guidelines and regulations need to be strictly followed regarding the screening and monitoring of the new coronavirus called SARS-CoV-2 (COVID-19).

8.5 Additional assessments

8.5.1 Patient Reported Outcomes (PROs)

During an epidemic or pandemic that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible the PRO data collection may be done by sending the subject the diaries/questionnaires by email or post or if possible, the PRO may be completed by telephone interview.

8.5.1.1 Skin Pain Numerical Rating Scale (NRS)

CCI [redacted]

Results will be transcribed into the CRF by site personnel.

8.5.1.2 CCI [redacted]

CCI [redacted]

Results will be transcribed into the CRF by site personnel.

8.5.1.3 CCI [redacted]

CCI [redacted]

Results will be transcribed into the CRF by site personnel.

8.5.1.4 CCI [redacted]

CCI [redacted]

Figure 8-2 CCI

8.5.1.5 CCI

CCI

8.5.1.6 New or flared existing boils

The number of new boils or existing boils which flare up in the past four weeks, provides a good representation of the inflammatory load and disease-burden experienced by patients with HS that has a strong impact on the patients' discomfort (Hessam et al 2018). Subjects will be asked at scheduled visits (as described in the Assessment schedules – see Section 8) to report this number for the past 4 weeks approximately.

8.5.2 Pharmacokinetics

During an epidemic or pandemic that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible the collection of samples may be modified by Novartis and will be communicated to the Investigator.

8.5.2.1 Cohort A (iscalimab)

PK blood samples will be collected at the timepoints defined in the Assessment schedule (Table 8-2). Follow instructions outlined in the SOM and Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

PK samples will be obtained from all subjects (iscalimab-, and placebo-treated) to maintain blinding, but the analysis (free iscalimab concentration in plasma) will only be conducted for iscalimab-treated subjects.

Iscalimab plasma concentrations will be determined using a validated target-based sandwich ELISA method. The lower limit of quantification (LLOQ) is 0.03 µg/mL in undiluted human plasma. The data and details of the analytical methods will be provided in the Bioanalytical Data Report. Concentrations below the LLOQ will be reported as 'zero' and missing data will be labeled as such in a Bioanalytical Data Report.

8.5.2.2 Cohort B (LYS006)

PK samples will be collected at the timepoints defined in the Assessment schedule (Table 8-3). Follow instructions outlined in the Site Operations Manual and Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

The collection of enriched PK blood samples may be stopped once samples from approximately 8 subjects randomized in the LYS006 cohort have been received by the unblinded PK bio-analyst.

For pre-dose PK blood samples and enriched PK blood samples, the subjects should arrive with their study drug kits at the study center before the morning dose administration. Study drug administration will be done during, or shortly after meals as described in Section 6.7.

CCI samples will be collected from all subjects, CCI CCI during the treatment period (apart from Study Day CCI

The subjects will be asked to CCI , take the evening dose as usual (Section 6.7), and CCI .

As with CCI samples collected at the study center, the CCI samples collected CCI should ideally be kept at room temperature until shipment to the central laboratory and its analysis.

LYS006 concentrations will be determined in plasma CCI by a validated LC-MS/MS method. The anticipated lower limits of quantification (LLOQ) are 0.1 ng/mL for plasma and 5.00 ng/mL for CCI. In addition, LYS006 concentrations will be determined in blood samples in an exploratory way.

Remaining plasma, CCI or blood from PK samples may be used for metabolite investigations / exploratory work.

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in a Bioanalytical Data Report. Due to the b.i.d. dosage regimen, for enriched PK blood profiles, pre-dose concentration (Cmin,ss) will be used as 12 h post-dose concentration, for AUC calculation.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol. Pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher). The linear trapezoidal rule will be used for AUC calculation.

8.5.2.3 Cohort C (MAS825)

PK blood samples will be collected at the timepoints defined in the Assessment schedule (Table 8-4). Follow instructions outlined in the SOM and Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

PK samples will be obtained from all subjects (MAS825 and placebo-treated) to maintain blinding, but the analysis (MAS825 concentration in serum) will only be conducted for MAS825-treated subjects.

MAS825 serum concentrations will be determined using a validated target-based sandwich ELISA method. The lower limit of quantification (LLOQ) is CCI ng/mL in human serum. The data and details of the analytical methods will be provided in the Bioanalytical Data Report. Concentrations below the LLOQ will be reported as 'zero' and missing data will be labeled as such in a Bioanalytical Data Report.

8.5.2.4 Cohort D (remibrutinib)

PK blood samples will be collected at the timepoints defined in the Assessment schedule (Table 8-5). Follow instructions outlined in the SOM and Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

PK samples will be obtained from all subjects (remibrutinib and placebo-treated) to maintain blinding, but the PK analysis and calculation of respective PK parameters will only be conducted for remibrutinib treated subjects.

Remibrutinib blood concentrations will be determined using a validated LC-MS/MS method. The lower limit of quantification (LLOQ) is CCI ng/mL in human blood. The data and details of the analytical methods will be provided in the Bioanalytical Data Report. Concentrations below the LLOQ will be reported as 'zero' and missing data will be labeled as such in a Bioanalytical Data Report.

8.5.2.5 Cohort E (ianalumab)

Pharmacokinetic (PK) samples will be collected at the visits defined in Table 8-6 and Table 8-7 Schedule of Assessments. At each visit indicated, a blood sample will be taken prior to dosing by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

PK samples will be obtained in all participants to maintain blinding but ianalumab concentrations will be evaluated only in the participants that receive ianalumab.

A validated ELISA will be used to determine ianalumab serum concentrations in the clinical trial participants. The anticipated LLOQ is CCI µg/mL. Concentrations of ianalumab will be expressed in µg/mL.

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

8.5.3 Biomarkers

Biomarker samples will be collected at the time points defined in the Assessment schedules (Table 8-2, Table 8-3, Table 8-4, Table 8-5, Table 8-6 and Table 8-7). Instructions regarding sample collection, numbering, processing and shipment will be provided in the Site Operations Manual and Central Laboratory Manual.

Detailed descriptions of the assays will be provided in the bioanalytical data reports.

8.5.3.1 Exploratory soluble biomarkers

Plasma and serum samples will be collected for the analysis of pathway-related markers, including but not limited to CCI Cohort A, or CCI in Cohort B and CCI CCI in Cohort C and CCI in Cohort D and CCI in Cohort E. Whole blood samples will be collected and stored for the assessment of BTK occupancy (based on free BTK) if warranted by the outcome of clinical endpoints.

These samples may also be used for the analysis of disease-related markers such as CCI CCI CCI which will be conducted depending on the overall study results, results obtained in other studies or new findings in the literature.

If performed, data from profiling (hypothesis-free) platforms will be reported separately from the CSR (e.g. CSR addendum).

8.5.3.2 Skin tape strips samples (Cohort B and C)

Skin tape strips samples will be collected using adhesive non-invasive tapes (D-Squame tape). Tape strips will be used to explore pathway activation and disease activity in skin. To do so, analyses will include soluble biomarkers related to state of inflammation, cell infiltrates and activation, such as but not limited to CCI or pathway and mechanistic markers such as CCI and CCI (Cohort C). The final selection of markers will be based on assays availability at the time of analysis.

8.5.3.3 Soluble blood biomarkers (Cohort B only)

The inflammatory leukotriene LTB4, as a product of LTA4H, directly related to the enzymatic activity inhibited by LYS006, will be measured in whole blood with and without stimulation by Calciumionophore S and N, mobilizing intracellular Ca^{2+}-levels. Other related eicosanoid markers and other disease- or pathway-related markers will be also analyzed in the same samples. The sampling of whole blood with and without ex-vivo stimulation will be performed at selected, appropriately equipped and specifically trained centers only.

8.5.3.4 Exploratory CCI biomarkers (Cohort B only)

Protein levels of exploratory CCI may be assessed, in particular in case of suspicion of a CCI, assessed by related clinical assessment (refer to Section 16.2) related to the presence of CCI. The list of markers may be changed or expanded, if it is recognized that more relevant or additional biomarkers should be assessed during the conduct of the study.

8.5.3.5 Cellular Biomarkers Cohort E (Ianalumab)

CCI

samples will be collected at each indicated visit in Table 8-1, Table 8-6 and Table 8-7 Assessment Schedules.

CCI are intended to be used for the exploratory assessment of the relationship of ianalumab exposure and PD

CCI at visits after end of treatment may determine the end of the conditional follow up period and end of study.

8.5.3.6 CCI Cohort E

Effects of ianalumab CCI may be assessed by CCI. The assessment may include the assessment of theCCI

8.5.3.7 Exploratory CCI (optional)

The study includes an optional CCI

CCI

CCI assessments may include analysis of specific panel of CCI , such as CCI

For subjects in Cohort B (LYS006) soluble biomarkers in CCI will be measured to explore CCI
CCI and for Cohort C, specific markers may be considered such as CCI

The analysis of CCI samples will be triggered depending on the number of obtained samples.

8.5.3.8 Exploratory CCI (optional)

The study includes an optional CCI

As technology changes over time, the most appropriate technology will be used at the time the exploratory CCI research is performed. This may include the study of the CCI .

8.5.3.9 Use of residual biological samples

Residual blood, skin tape strip or CCI samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include but is not limited to using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

8.5.4 Immunogenicity (Cohort A, C and E only)

Detection of anti-iscalimab (Cohort A) or anti-MAS825 (Cohort C) or anti-ianalumab (Cohort E) antibodies

The immunogenicity of multiple s.c. doses of iscalimab (Cohort A) as well as MAS825 (Cohort C) and anti-ianalumab (Cohort E) will be assessed via the quasi-quantitative analysis of anti-iscalimab antibodies in plasma for Cohort A or anti-MAS825 and anti-ianalumab antibodies in serum for Cohort C and E.

Blood samples collected for immunogenicity testing will be obtained from all subjects and analysis will be performed for active- and placebo-treated subjects (to assess the rate of pre-existing anti-drug antibodies - ADAs) of the corresponding Cohorts A, C and E. The details of sample processing, handling, storage, shipment and analytical method will be described in a separate laboratory manual.

In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity and an unscheduled PK sample will be collected. In case of positive ADA, back-up of previous PK samples could be used to better characterize the onset of ADA response.

The detailed methods and analysis will be described in the Bioanalytical Data Report.

8.5.5 Target engagement - Soluble CD40 in plasma (Cohort A only)

In Cohort A (iscalimab), blood samples will be collected for soluble CD40 concentrations in plasma (before and during treatment and follow-up) in order to assess the rate, extent and duration of target engagement in WB.

Blood samples will be obtained from all subjects to protect blinding, but analysis may be performed only for subjects receiving active treatment.

Blood samples will be collected at the timepoints defined in the Assessment schedule (Table 8-2).

The SOM provides operational details including subject numbering, blood log with sample numbers. Further details on sample collection, processing and shipment will be provided in the Central Lab Manual. The detailed methods and analysis will be described in the Bioanalytical Data Report.

8.5.6 Target engagement - IL-1β, IL-18, and IL-18BP in serum (Cohort C only)

Serum samples for the exploratory measurement of total IL-1β, IL-18 and IL-18BP will be collected from all subjects at all dose levels as described in the Assessment schedule (Table 8-4). The number of blood draws and total blood volume collected will not exceed those stated in the protocol. Total IL-1β, IL-18 and IL-18BP will be measured using validated assays. The anticipated lower limit of quantification (LLOQ) is [redacted] pg/mL for IL-1β, ca. [redacted] pg/mL for IL-18 (total IL18) and ca. [redacted] ng/mL for IL-18BP. A detailed description of the will be included in the bioanalytical data report.

9 Study discontinuation and completion

9.1 Discontinuation

Subjects may voluntarily discontinue the study for any reason at any time. The investigator must discontinue study treatment for a given subject, if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

9.1.1 Discontinuation of study treatment

Study treatment must be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Following emergency unblinding
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation
- Emergence of the following adverse events related to study drug:
  - Grade 3 or higher allergic or hypersensitivity reaction (CTCAE, version 5.0 or higher)
  - Acute infection, grade 3 or higher (CTCAE, version 5.0 or higher) in particular infections that resist short term antibiotic therapy
  - Neutropenia grade 3 or higher (CTCAE, version 5.0 or higher)
- If a liver or renal event occurs, follow guidelines outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment.
- Clinical worsening of hidradenitis suppurativa as per investigator judgement
- Any other protocol deviation that results in a significant risk to the subject's safety

For Cohort A (iscalimab) (in addition to the above):

- Severe injection-related reactions. Immediate interruption of the study drug administration is required where possible in such case.
- Subject received a live vaccine
- Any acute infections with clinical signs and symptoms such as fever, rash, etc. which at the discretion of the investigator jeopardizes the safety or impact negatively on risk/benefit of the subject.
- Confirmed active CMV infection (presence of IgM or PCR)
- Significant changes in standard coagulation parameters, including prothrombin time (PT) and activated partial prothrombin time (aPTT) suggesting an increased risk for hypercoagulability or any sign or symptom of a thromboembolic event.

For Cohort C (MAS825) (in addition to the above):

- Severe injection-related reactions. Immediate interruption of the study drug administration is required where possible in such case.
- Subject received a live vaccine
- Any acute infections with clinical signs and symptoms such as fever, rash, etc. which at the discretion of the investigator jeopardizes the safety or impact negatively on risk/benefit of the subject.

For Cohort D (remibrutinib) (in addition to the above):

- Clinically significant spontaneous bleeding events
- New confirmed diagnosis of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer)

- Platelets <75 x 10^9L
- Any acute infections with clinical signs and symptoms such as fever, rash, etc. which at the discretion of the investigator jeopardizes the safety or impact negatively on risk/benefit of the subject.
- Subject received a live virus vaccination during the study

For Cohort E (ianalumab) (in addition to the above):

- Subject received a live virus vaccinee.

In addition, in case of emergence of the following adverse events discontinuation must be considered jointly by the Investigator and Novartis:

- Persistent neutropenia ≤ 1,000 / µL that may preclude further administration of a B cell depleting agent

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments as defined in the applicable Assessment schedules (Table 8-2 for Cohort A, Table 8-3 for Cohort B, Table 8-4 for Cohort C, Table 8-5 for Cohort D and Table 8-6 and Table 8-7 for Cohort E). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 9.1.3. Cohort E only: Patients who discontinue after having received at least one ianalumab administration and who do not complete the visits in the respective treatment period will be asked to remain in the study, and continue the assessments as per treatment visit schedule until EOT or, if they do not agree they will enter the mandatory Safety Follow up period.

This contact should preferably be done according to the study visit schedule. If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be made according to the study visit schedule.

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

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code Section 6.6.3.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

Does not want to participate in the study anymore, and

Does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the Table 8-2, Table 8-3, Table 8-4, Table 8-5 or Table 8-6 and Table 8-7.

Novartis will continue to keep, and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

9.1.4 Study stopping rules

The study, or any of its individual respective cohorts, will be paused for further enrollment: pending full safety data review if one or more of the following criteria are met:

- Any death or life-threatening event suspected to be related to study treatment
- Two or more subjects per cohort presenting with the same SAE related to the investigational drug.
- Two or more subjects per cohort presenting with active treatment-suspected severe systemic infection or opportunistic infection that requires treatment, e.g., sepsis, urosepsis, mycoses, pneumonia
- Three or more subjects per cohort experience a similar AE which was assessed as severe in intensity, and are considered as potentially related to the study treatment as determined by the investigator and / or Novartis
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold

- Other clinically significant events that in the opinion of the investigator or sponsor preclude to continue dosing (especially events that are suspected to be drug related, such as severe infections or other non-serious renal events)

For Cohort A (iscalimab) only*:*

- One subject presenting with suspected iscalimab-related thromboembolic event that is at least of moderate severity and is unrelated to pre-existing co-morbidities

For Cohort B (LYS006) only:

- One serious renal and/or pancreatitis adverse event causally related to LYS006

For Cohort C (MAS825) only*:*

- No additional criteria are necessary for MAS825

For Cohort D (remibrutinib) only*:*

- Two subjects presenting with clinically significant bleeding events, that are considered drug related

For Cohort E (ianalumab) only:

- More than one injection-related reaction of severe intensity within the first five (5) treated subjects or an incidence of >20% thereafter

In these cases, ad hoc internal experts will carefully evaluate the safety data of the entire study. The experts will recommend whether the study can be continued, should be stopped or if other safety measures need to be taken. The findings and recommendations of the internal experts will be documented and will be made available to the respective Ethics Committees/Review Boards.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed, and according to local regulations.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Should this be necessary, Subjects must be seen as soon as possible and treated as a prematurely discontinued subject.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject

completes his/her Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

For Cohort E (ianalumab) only:

The end-of-study will be performed at Visit 299, and EOS may be initiated within 4 weeks following confirmation of B cell count recovery (defined as ≥80 % of baseline or ≥50 cells/µL).

Subjects who discontinue during the follow up period will be asked to complete the end of study (EoS) visit.

Subjects must be monitored for AEs and SAEs for the durations outlined in Section 10.1. Documentation of attempts to contact the subject should be recorded in the source documentation. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them, unless required by local regulations.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 10.1 for an overview of the reporting requirements.

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

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

- the Common Toxicity Criteria (CTC) AE grade: Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher
- the causality: the investigator is obligated to assess the relationship between any treatment used in the study (study treatment, AxMP) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
  For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
  The causality assessment is one of the criteria used when determining regulatory reporting requirements.

  If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
- its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
- whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn
- its outcome

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

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

Adverse event monitoring should be continued for at least 30 days or 5 half-lives following the last dose of study treatment, or end of study visit, whichever is longer.

- Cohort A (iscalimab): EOS or 14 weeks (5 half-lives) following the last dose, whichever is longer
- Cohort B (LYS006): EOS or 30 days following the last dose, whichever is longer

- Cohort C (MAS825): EOS or [redacted] weeks [redacted] half-lives) following the last dose, whichever is longer.
- Cohort D (remibrutinib): EOS or 30 days following the last dose, whichever is longer
- Cohort E (ianalumab): EOS

In the event of a subject discontinuing study participation early, at minimum, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject at the end of the adverse event monitoring period listed above, to record any AEs or SAEs.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be nontypical in Subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Section 16.1 and Section 16.2, respectively.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

Reporting of AEs related to AxMP(s)

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply as well.

10.1.2 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH E2D Guideline 2003).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH E2D Guideline 2003).

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

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and subject Safety (CMO & PS) as per Section 10.1.3.

10.1.3 SAE reporting

10.1.3.1 Screen Failures

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

10.1.3.2 Randomized/ Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the end of the adverse event monitoring period listed in Section 10.1, must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

Reporting of SAEs related to AxMP(s)

All SAEs related to any auxiliary medicinal product (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it.

In assessing causality, the investigators will use the points in Section 10.1.1.

If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply as well.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Newborns will be followed up (monitored) up to 12 months post-birth.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO&

PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 10-1 summarizes the reporting requirements.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see Section 10.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

Refer to the Site Operations Manual for additional details.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Section 16.2 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.2.

Refer to the Site Operations Manual for additional details.

10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data, and critical efficacy variables and make recommendations to the sponsor whether to continue, modify or terminate the trial.

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

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate.

After database lock, the investigator will receive copies of the subject data for archiving at the investigational site. Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred to the CRO working on behalf of Novartis or to Novartis. This, and any additional data treated in this manner, will be source data verified by the study monitor per the monitoring plan and the location of source data (i.e., Source, paper or a local electronic system) will be documented prior to study start in the Data Handling Plan. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application; rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into the eCRF are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedules (Table 8-1, Table 8-2, Table 8-3, Table 8-4, Table 8-5, Table 8-6 and Table 8-7) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis staff and the CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or to the CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

11.2.1 CCI

CCI

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends. Unless otherwise specified, placebo data from each cohort will be pooled. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The main rationale for pooling the placebo data is to reduce the number of subjects exposed to placebo. The difference in the inclusion criterion on the baseline lesion count, minimum 3 inflammatory lesions for the oral compound versus minimum 5, for the injectable, is expected to have little impact on the key efficacy endpoints in HS patients (Kimball et al 2012 and Kimball et al 2016). In Cohort E, prednisone and prednisolone are classified as intermediate half-life corticosteroids with half-lives between 12-36 hours. Administration of a single oral dose 50 mg prednisolone at baseline is unlikely to affect the primary-endpoint simplified HiSCR 16 weeks later.

The final results of each cohort will be described in the relevant Investigators Brochure when they become available. For completeness, primary CSR will be submitted to all participating Health Authorities. Any relevant safety signal and/or safety findings interfering with the benefit/risk profile of the drug in this or other indications will also be reported. In case additional sub-protocols/arms (cohorts) are included, the protocol will be modified to ensure data transparency in the trial of these additional arms.

The two remibrutinib doses will be considered as two different treatment groups and the outputs will therefore be reported by the remibrutinib dose. The possibility of pooling the two remibrutinib doses will be investigated.

Baseline values, if not specified otherwise, refer to the values taken on Day 1, prior to the first dosing.

12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects who received any study drug and had no protocol deviations with relevant impact on PD data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the safety analysis set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group.

12.3 Treatments

The safety analysis set will be used for the analyses described in this section. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure in weeks to placebo, Iscalimab, LYS006, MAS825, remibrutinib and ianalumab will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

Use of pain medications as rescue medication will be explored across cohorts and treatment groups to assess the balances of the usage between treatment groups and cohorts where necessary.

12.4 Analysis of the primary endpoint(s)

The primary analysis to compare either iscalimab, LYS006, MAS825, each remibrutinib regimen or ianalumab against placebo will use the pooled placebo data from all cohorts. The primary objective of this Proof of concept platform study is to compare each compound to the pooled placebo and not to compare compounds with each other.

PD analysis set will be used for the analyses.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of this study is the proportion of subjects who have achieved a clinical response, as defined by simplified HiSCR, after 16 weeks of treatment. The simplified HiSCR is defined as

- a reduction of at least 50% in abscess and inflammatory nodule counts and
- no increase in draining fistula count related to baseline.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary variable will be modeled with the binomial distribution. A neutral non-informative Beta (1/3, 1/3) distribution will be used as the prior for the response rate for all treatment groups. Based on the priors and the observed primary outcome, posterior distributions for the response rate for the investigational treatment and pooled placebo groups will be computed respectively. The posterior distribution of the difference of response rates, investigational treatment (iscalimab/LYS006/MAS825/each remibrutinib regimen/ianalumab) minus placebo, will be obtained by simulations, i.e. sampling from the posterior distributions of the corresponding treatment groups. The posterior probabilities for the difference of response rates will be assessed according to the following dual criteria as a guide to decision making. Each investigational treatment will be assessed separately in comparison to the pooled placebo group.

The efficacy criteria are predefined as:

1. Better than placebo with high confidence (at least 90% probability that the simplified HiSCR rate at week 16 for an investigational treatment is better than placebo, i.e., Prob (delta >= 0) > 90%), AND
2. Simplified HiSCR rate 15% above placebo (at least 50% probability that the simplified HiSCR rate at week 16 for an investigational treatment is 15 percentage points above that of placebo, i.e., Prob (delta >= 0.15) > 50%.),

where delta is the difference in percentage points for investigational treatment versus placebo for simplified HiSCR rate.

12.4.3 Handling of missing values/censoring/discontinuations

Intercurrent events (IE) that may affect the assessment of the simplified HiSCR are discontinuations from study treatment before week 16. For the purpose of primary endpoint

analysis, a composite strategy will be used to take account of such discontinuations whereby subjects who discontinue study treatment before 16 weeks will be considered as follows:

- Subjects who do not complete the 16 week treatment due to lack of efficacy or adverse events due to worsening of disease, will be considered as non-responders and treated like completers.
- For subjects who discontinue for other reasons prior to 16 weeks of treatment, the following method will be used:
  - If among these subjects, those that discontinue before 12 weeks of treatment constitute <= 10% of the PD analysis set population, then such patients will be considered as non-responders and those who have had at least 12 weeks of treatment will have their simplified HiSCR taken to be their response after 16 weeks of treatment. The primary analysis will be pursued as described in Section 12.4.2 with the imputed responses as described above.
  - However, if such non-completers (< 12 weeks of treatment) constitute > 10% of the PD analysis set, multiple imputation methods will be used to impute missing abscess, inflammatory nodule and draining fistula counts while accounting for baseline covariates such as baseline disease characteristics and/or other demographic factors believed to affect HS. More details on the imputation model will be specified in the Statistical Analysis Plan.

    The primary response, simplified HiSCR, will be derived for each of the imputed dataset, which will be merged with data on subjects with IE for whom non-response is imputed in a composite strategy. Primary analysis will then be run on each imputed dataset, resulting in posterior distribution of the estimand and corresponding averages. Comparison of the primary response estimates based on data with and without MI will allow assessing the level of effect of treatment withdrawals.
- Any encounters of surgical incisions and excisions affecting the lesion counts will be handled in the following ways:
  - Excised lesions will be considered to be permanently present and included in the overall lesion counts and lesion counts by type at all the time points following the excision.
  - The lesions that experienced any incisions will be analyzed as the type observed at any given time or as not present (if not present) at any given time.

12.4.4 Sensitivity and Supportive analyses

12.4.4.1 Sensitivity analyses

The planned Bayesian analysis uses a non-informative prior for the response rate in each treatment group. Should additional data on placebo response rates for other trials become available, sensitivity analyses may be performed using alternative prior response rate distributions derived from these trials.

An additional sensitivity analysis will be conducted for the primary endpoint where the lesions that experienced any incisions will be included with Last Observation Carried Forward (LOCF),

with the type of lesion prior to the incision being used for the type of lesion at any time point after the incision, in order to assess the impact of surgical incisions on efficacy.

12.4.4.2 Supportive analyses

Supportive Bayesian analysis will be performed where the placebo subjects will not be pooled. Each investigational treatment will be compared to its respective placebo.

Supportive Bayesian analysis will be performed on placebo subjects to assess differences in the response rate across multiple cohorts. This is to address the assumption of nearly equal response among placebo arms of different cohorts, which may vary due to the route of administration (oral vs. iv) or differences in their eligibility criteria.

Supportive logistic regression analysis will be performed to investigate cohort-specific influence of baseline disease characteristics and other demographic factors believed to affect HS (such as weight and smoking status) on the treatment effect.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Not applicable.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of LYS006 and remibrutinib or 3 months after the last actual treatment of iscalimab, MAS825 and ianalumab.

12.5.2.1 Adverse events

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

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries may be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation if the number of events warrants such further detail.

The number (and proportion) of subjects with adverse events of infections (all cohorts) and renal events (for LYS006) will be summarized by treatment.

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

12.5.2.2 Vital signs

All vital signs data will be displayed graphically showing data over time.

12.5.2.3 12-lead ECG

All ECG data will be displayed graphically showing data over time.

12.5.2.4 Clinical laboratory evaluations

All laboratory data may be listed by treatment group, subject, and time and if normal ranges are available abnormalities will be flagged. Graphical displays of data over time will be provided. Shift tables using the low/normal/high classification will be used to compare pre-treatment to the worst on-treatment value.

12.5.2.5 Immunogenicity

Please refer to Section 12.6.4.

12.6 Analysis of exploratory endpoints

12.6.1 Exploratory efficacy endpoints

The PD analysis set will be used for analysis of exploratory efficacy objectives. The relevant data mainly include:

- Proportion of subjects meeting the simplified HiSCR over time (as defined in Section 8.3.2)
- Proportion of subjects meeting the simplified HiSCR75, original HiSCR50, HiSCR75, and HiSCR90 over time (as defined in Section 8.3.2) if applicable
- Proportion of CCI responders over time, CCI responder defined as an CCI score of clear, minimal, or mild with at least a 2-grade improvement relative to baseline
- CCI score over time
- Different types of HS inflammatory lesion counts over time
- New or flared existing boils
- CCI score over time
- CCI score over time
- NRS pain score over time
- CCI score over time
- CCI over time
- CCI over time

- Proportion of subjects who experience at least one flare over 16 weeks of treatment. Flare is defined as an at least 25% increase in total abscess and inflammatory nodule counts (AN counts) with a minimum increase of 2 AN relative to baseline.
- Proportion of subjects achieving NRS30 CCI [redacted] NRS30 is defined as at least 30% reduction and at least 1 unit reduction from baseline in Skin Pain NRS scale
- Proportion of patients achieving 50%, 75%, 90% and 100% reduction from baseline in sum of abscesses and nodules
- Change in anatomical HS regions involved over time
- CCI [redacted] (for Cohorts D and E only)
- CCI [redacted] (for Cohorts D and E only)

In general the variables will be presented graphically and/or summarized via descriptive statistics. For continuous/binary endpoints over time, mixed models for repeated measures (MMRM) may be used to estimate the values for each treatment at each time point and perform group comparisons over 16 weeks of treatment. Model-based estimates may be used for the visualizations. Data collected after a subject has discontinued treatment will not be used in these summaries and analyses.

12.6.2 Exploratory safety

For subjects in Cohort B, the proportion of subjects with CCI [redacted] and other exploratory markers in CCI [redacted] (such as, but not limited to, CCI [redacted]) will be summarised by treatment group. Safety analysis set will be used for this analysis.

12.6.3 Pharmacokinetics

PK analysis set will be used for analyses in this section.

12.6.3.1 Cohort A (iscalimab)

Iscalimab plasma concentrations will be listed by subject, and visit/sampling time point and displayed graphically. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics, and will be treated as missing in geometric mean calculation.

Pharmacokinetic parameters for iscalimab (Ctrough's; observed analyte concentration at the end of a dosing interval) will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

12.6.3.2 Cohort B (LYS006)

LYS006 concentrations in plasma, blood and CCI [redacted] over time will be listed, summarized and displayed graphically. Where steady state concentrations profiles are recorded, the PK parameters (max,ss, Cmax,ss. AUCtau,ss) derived from this will be summarized.

12.6.3.3 Cohort C (MAS825)

MAS825 serum concentrations will be listed by subject, and visit/sampling time point and displayed graphically. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics, and will be treated as missing in geometric mean calculation.

Pharmacokinetic parameters for MAS825 (Ctroughs; observed analyte concentration at the end of a dosing interval) will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

12.6.3.4 Cohort D (Remibrutinib)

Remibrutinib whole blood concentrations will be listed by subject, and visit/sampling time point and displayed graphically. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics, and will be treated as missing in geometric mean calculation.

Pharmacokinetic parameters for remibrutinib (Ctroughs; observed analyte concentration at the end of a dosing interval and apparent Cmax at CCI and CCI hrs) will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

12.6.3.5 Cohort E (Ianalumab)

Ianalumab serum concentrations will be listed by subject, and visit/sampling time point and displayed graphically. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics, and will be treated as missing in geometric mean calculation.

Pharmacokinetic parameter for ianalumab (Ctroughs; observed analyte concentration at the end of a dosing interval) will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

12.6.4 Pharmacodynamics

PD analysis set will be used for the analyses.

12.6.4.1 Cohort A (iscalimab)

Soluble CD40 in plasma will be presented with descriptive summary statistics by visit/sampling timepoint. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

12.6.4.2 Cohort B (LYS006)

LTB4 levels in ex vivo stimulated and non-stimulated whole blood and in non-stimulated plasma over time will be summarized and displayed graphically.

12.6.4.3 Cohort C (MAS825)

Target engagement biomarker (IL-18, IL-1ß, IL-18BP) in serum will be presented with descriptive summary statistics by visit/sampling timepoint. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

12.6.4.4 Cohort D (Remibrutinib)

BTK occupancy in stimulated whole blood will be presented with descriptive summary statistics by visit/sampling timepoint. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

12.6.4.5 Cohort E (Ianalumab)

CCI [redacted] in serum will be presented with descriptive summary statistics by visit/sampling timepoint. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

12.6.5 Exposure-response relationship

Graphical methods will be used to investigate the relationships between concentrations of the investigational treatments and HS lesion counts, for each investigational drug separately.

12.6.6 Immunogenicity (Cohort A, C and E)

Immunogenicity results may be listed by subject and visit/time (no descriptive statistics) in the CSR or a separate standalone document. The proportion/incidence of ADA-positive subjects will be summarized. An integrated PK/PD/Immunogenicity approach, focusing on the clinical and functional consequences of ADAs will be applied to allow an appropriate clinical management of subjects developing an ADA response to iscalimab, MAS825 and ianalumab. An immune response to iscalimab, MAS825 and ianaluamb may be correlated with a loss of efficacy, a loss of exposure (PK), a loss of target engagement and/or the appearance of immune related adverse events.

12.6.7 Exploratory biomarkers

Exploratory biomarker data may be reported in the CSR or a separate standalone document. The exploratory biomarkers include PD biomarkers in blood described in Section 12.6.4 and:

- Disease-related markers such as CCI [redacted]
- CCI [redacted]

- Cohort B: Levels of soluble biomarkers related to state of inflammation, cell infiltrates and activation, such as, but not limited to CCI measured from skin tape strip.
- Protein levels of exploratory CCI may be assessed if warranted by observation of clinical signs of CCI formation.
- CCI
- For subjects in Cohort B, LYS006 soluble biomarkers in CCI to explore inflammation markers (e.g. LTB4 and MPO) and neutrophil chemokines (e.g. GROα, IL-8)
- For subjects in Cohort C, soluble circulating target engagement biomarkers (e.g. IL1β, total/free IL-18, IL18-BP and downstream pathway biomarkers e.g. CXCL9, IP-10/CXCL10, IL-6 and markers of immune activation such as sIL2R)
- For subjects in Cohort D, BTK occupancy in stimulated whole blood. Additional assessments may include the analysis of certain CCI and occurrence of CCI over time for a subset of patients
- For subjects in Cohort E, B cell subsets and CCI

These variables may be displayed graphically over time for raw values and/or percentage change from baseline. Graphical methods and inferential models may be used to investigate whether some selected biomarkers (details to be specified in statistical analysis plan) associated with efficacy measures such as HS lesion counts or clinical response. PD analysis set will be used for these analyses. Additionally, hypothesis-free analysis methods may be applied to data from biomarker profiling in relation to disease severity, disease-endotypes and clinical efficacy.

12.6.8 Other optional exploratory endpoints

PD analysis set will be used for this analysis.

12.6.8.1 CCI

Exploratory CCI

CCI [redacted]

12.7 Interim analyses

Interim analyses for assessing efficacy and safety may be conducted during the study. These will be conducted when approximately half the planned subjects have completed the respective treatment period of the concerned cohort (16 weeks of treatment). Such early IAs, if conducted, are to ensure no safety issues with investigational drug treatment and also gain preliminary understanding of efficacy throughout a panel of efficacy endpoints.

If one cohort were to stop at an early IA (early signs of efficacy would not lead to the interruption of that cohort), all ongoing subjects in all treatment arms in this cohort would be discontinued and not be replaced. In this case for the final analysis of binary response rates, subjects who were discontinued only due to the stopping of a cohort will be excluded from the analysis.

Different cohorts may complete enrolment at different times and so interim analyses are also planned when all subjects in a cohort have completed the respective treatment period of the concerned cohort (16 weeks of treatment). These end-of-cohort interim analyses are intended to help with the planning of later steps in the development program of each treatment. Additional interim analyses may be conducted to support decision making, concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

In general the analyses will follow the methods described above. For the assessment of binary response rate efficacy data, only data from subjects who have either completed the treatment period or who have discontinued treatment will be included. For subjects who were still ongoing in the treatment period at the time of the IA, will not be included in the efficacy analysis.

For interim analyses, conducted after approximately half the planned subjects in a cohort have reached 16 weeks of treatment, all available data from all cohorts at the time of the analysis will be used, i.e. including placebo data from other cohorts. These results will not be communicated with individuals directly involved in treating the study's subjects or assessing clinical data.

For interim analyses conducted after the completion of one cohort, only the data relative to that specific cohort will be communicated externally. However, for the purpose of internal decision making, all available data from all cohorts at the time of the analysis will be used. For example, for an end-of-cohort analysis of Cohort B, all data including valid placebo data from Cohort A, C and D will be used for the purpose of internal decision making. The results of these analyses will not be communicated with individuals directly involved in treating the study's subjects or assessing clinical data.

Unblinded interim analysis results will be reviewed by the clinical team, following the blinding requirement in Section 6.4.

12.8 Sample size calculation

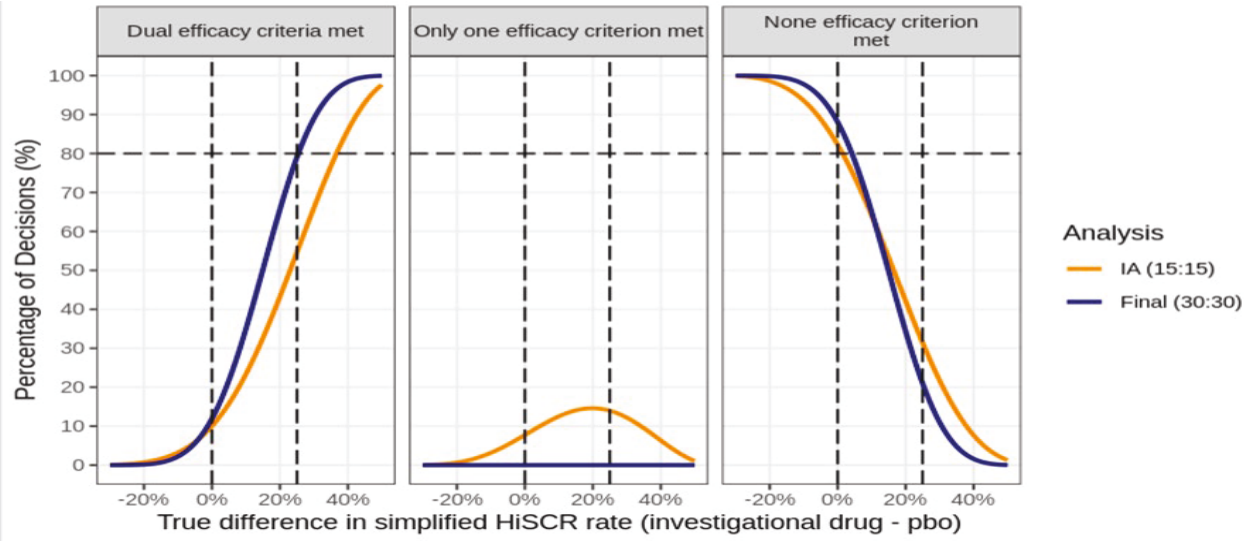
12.8.1 Primary endpoint(s)

Approximately 240 subjects are to be recruited, with approximately 40-45 in each of Cohort A and B, approximately CCI in Cohort C, approximately 70 in Cohort D (approximately 30 subjects will receive remibrutinib CCI mg CCI., approximately 30 subjects will receive remibrutinib CCI mg CCI and approximately 10 subjects corresponding placebo), and approximately 40 in Cohort E. Within the analysis set of the primary endpoint, if more than 10% treatment withdrawals/discontinuations are observed before completion of 12 weeks of treatment, the discontinued subjects may be replaced to ensure enough data are available to effectively assess the treatment effect. Subjects will be randomized in a 2:1 ratio to the investigational treatment or placebo within Cohorts A and B, 3:1 ratio for Cohorts C and E, and 3:3:1 ratio for Cohort D.

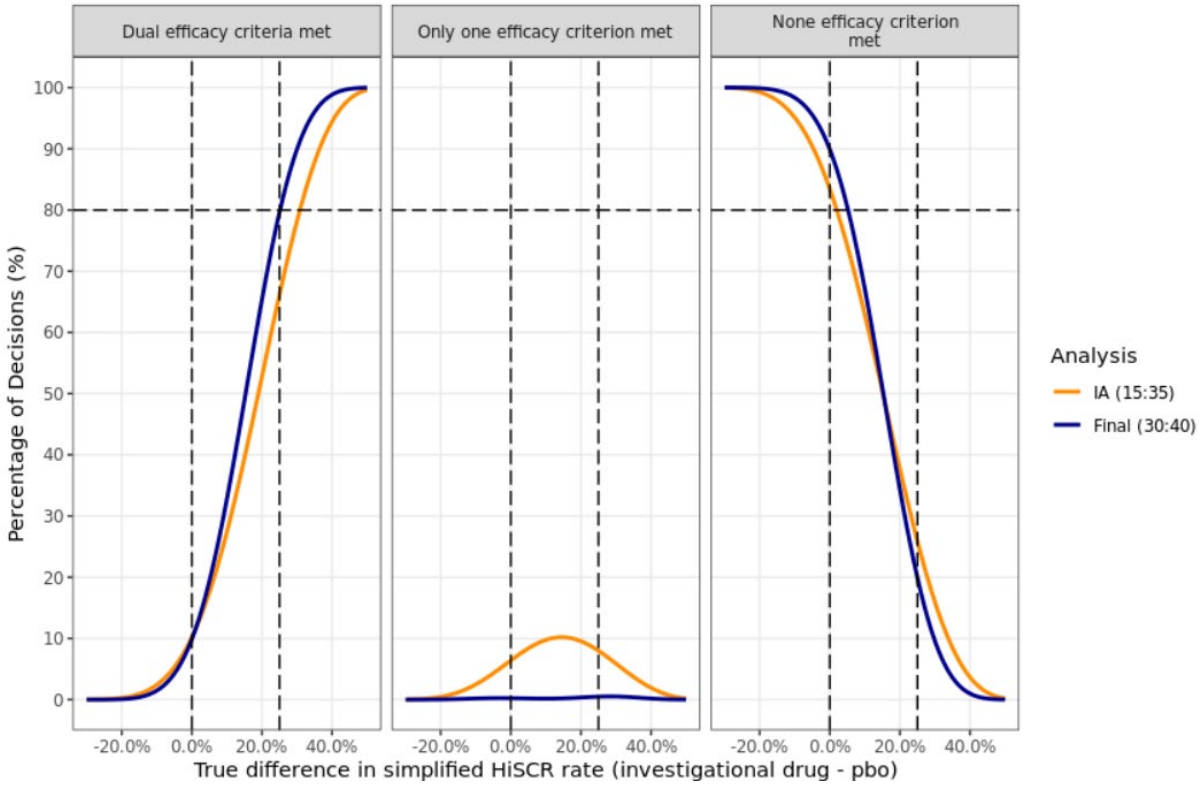
Based on 30 subjects for a given investigational treatment and 60 for placebo (pooled), it is estimated that this study will have approximately 80.5% probability of meeting the success criteria (as outlined in Section 12.4.2), if the true difference between an investigational treatment and placebo in the simplified HiSCR rate is 25% (25 percentage points). Conversely there is a low (7.6%) probability of meeting the success criteria when there is no difference between the investigational treatment and placebo. The outcome of the operating characteristics is presented in Figure 12-1. These results come from simulations of the trial outcomes and assume a placebo response rate of 42% (estimated from a previous study CCJM112X2202). For a range of placebo response rates (20% to 60%), the design of 30 versus 60 is able to provide a consistent power around 80.5%, i.e. 80.5% chance to meet the dual efficacy criteria with a true effect of 25%.

Figure 12-1 Operating characteristics for simplified HiSCR at interim and final analysis

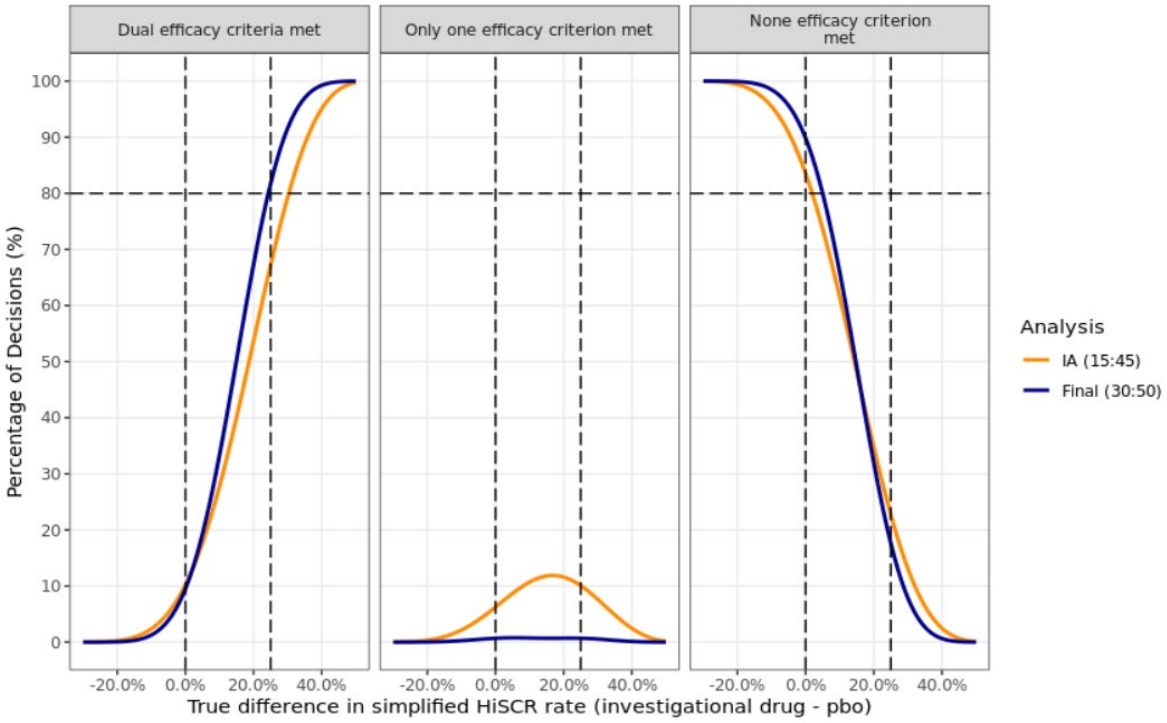
For the iscalimab and LYS006 cohort:



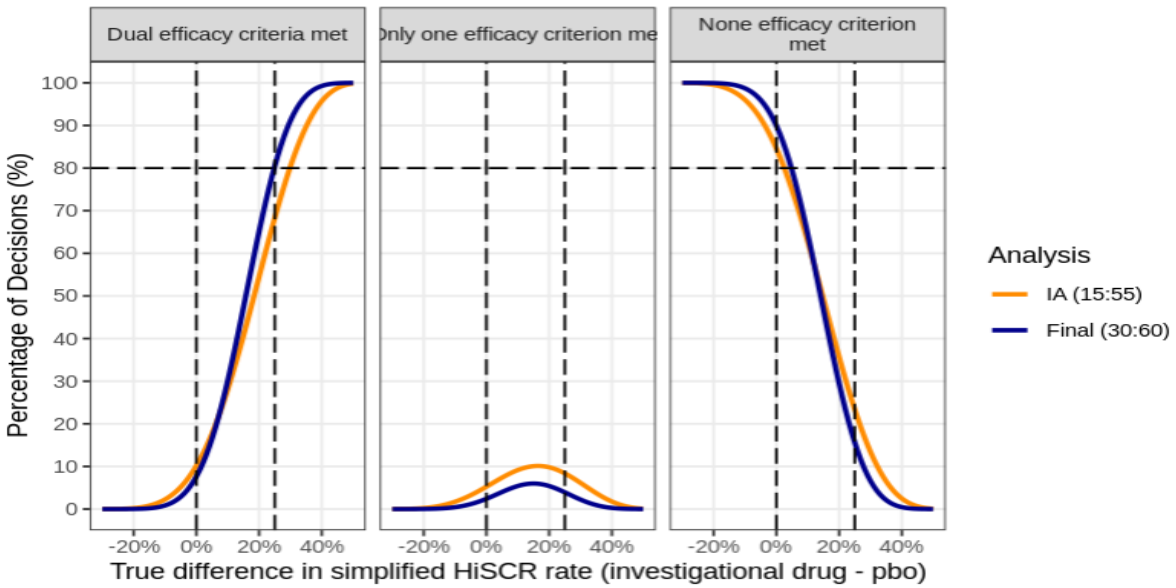
For the MAS825 cohort:



For the remibrutinib cohort:



For the ianalumab cohort:



Note: placebo sHiSCR assumed in this figure is 42%, based on the internal study CCJM112X2202.

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last subject Last Visit to be a reviewer and signatory for the clinical study report.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (***defined as last subject last visit***) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 10 (Safety Monitoring) must be followed and the Study Lead informed.

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16 Appendices

16.1 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≥ 5 x ULN 1.5 x ULN < TBL ≥ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF • Must be reported as an SAE even before all other causes of liver injury have been excluded.	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory assessments) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	Actions
eGFR decrease 25-49% compared to baseline	• Consider causes and possible interventions Repeat test after ≥24 hours but ≤ 5 days after assessment of the first abnormal lab values. Assess patient for signs and symptoms of illness and acute kidney injury
eGFR decrease > 50% compared to baseline	• Consider causes and possible interventions • Repeat test within 48 hours after receipt of abnormal lab values. Assess patient for signs and symptoms of illness and acute kidney injury • Consider study treatment interruption unless other causes are identified and corrected • Consider referral to nephrologist for diagnosis and management • Consider subject hospitalization/ specialized treatment
Urine Event	**Actions**
New onset dipstick proteinuria ≥3+, OR Protein-creatinine ratio (PCR)>1g/g or >100 mg/mmol	• Repeat test after ≥24 hours but ≤ 5 days after assessment of the first abnormal lab values. Ideally confirm presence of true proteinuria by quantification: PCR on first morning void • Consider causes and possible interventions • Assess serum albumin and total serum protein
New dipstick hematuria ≥1+ not due to trauma	• Consider drug interruption or discontinuation unless other causes are identified and corrected • Consider referral to a nephrologist • Repeat test after ≥24 hours but ≤ 5 days after assessment of the first abnormal lab values. • Assess serum creatinine • Exclude other causes (infection, trauma, menstruation, bleeding from urinary tract/bladder, bleeding disorder)

Follow-up for all renal events:
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed
Monitor subject regularly (frequency at investigator's discretion) until either:
Event resolution: sCr within 10% of baseline or protein-creatinine ratio, 1g/g creatinine or
Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.