CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED, MULTICENTER, 2-PART PHASE II STUDY ON REPLACEMENT OF STEROIDS BY IFX-1 IN ACTIVE GRANULOMATOSIS WITH POLYANGIITIS (GPA) AND MICROSCOPIC POLYANGIITIS (MPA)

Study Number: IFX-1-P2.5

Study Product: IFX-1

EudraCT Number: 2018-000768-27

Sponsor: InflaRx GmbH
Winzerlaer Strasse 2
07745 Jena
Germany

Sponsor's Responsible Medical Officer: [redacted], MD, MSc

[redacted]
[redacted] InflaRx GmbH

Coordinating Investigator: [redacted] MD, MPH

[redacted]

Version and Date of Protocol: Version 5.0, Final, 07 October 2020

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LIST OF ABBREVIATIONS

AAV	anti-neutrophil cytoplasmic antibody-associated vasculitis
AC	Adjudication Committee
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ANCA	anti-neutrophil cytoplasmic antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AxMP	Auxiliary Medicinal Product
AZA	azathioprine
BVASv3	Birmingham Vasculitis Activity Score (Version 3)
CH50	50% hemolytic complement
CHCC	Chapel Hill Consensus Conference
CMO	Contract Manufacturing Organization
CRO	Contract Research Organization
CRP	C-reactive protein
CYC	cyclophosphamide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
EOS	end of study
EQ-5D-5L	EuroQol-5 Dimensions 5-Levels survey
EU	European Union
FAS	full analysis set
GBM	glomerular basement membrane
GC	glucocorticoid
GCP	Good Clinical Practice

GDPR	General Data Protection Regulation
GPA	granulomatosis with polyangiitis
GTI	glucocorticoid toxicity index
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IWRS	Interactive Web Response System
MAC	membrane attack complex
MCP	monocyte chemoattractant protein
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MPS	mycophenolate sodium
MTX	methotrexate
NGC	No glucocorticoids
PCP	Pneumocystis carinii pneumonia
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
PPS	per protocol set
PR3	proteinase 3
PRO	patient-reported outcome
RDGC	reduced-dose glucocorticoids
RTX	rituximab
SAE	serious adverse event
SAF	safety analysis set
SDGC	Standard-dose glucocorticoids

SF-36v2	36-item Short Form survey version 2
SFU	safety follow-up
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UACR	urinary albumin:creatinine ratio
ULN	upper limit of normal range
USV	unscheduled visit
V	visit
VDI	Vasculitis Damage Index
W	week

DEFINITION OF TERMS

Auxiliary Medicinal Product (AxMP)	Medicinal product used as rescue medication, challenge agent, to assess endpoints in the clinical study, or background treatment. The AxMP should be related to and be relevant for the design of the clinical study.
Baseline	A value or quantity that serves as a reference for comparisons over time.
Central laboratory	A laboratory where subject-derived samples (e.g., serum, plasma) are centrally analyzed and if necessary, distributed for analysis to specialized laboratories.
Clinical remission	Birmingham Vasculitis Activity Score (Version 3 [BVASv3]) = 0.
Clinical response	Reduction in BVASv3 of ≥ 50% from baseline (=screening assessment) and no worsening in any body system.
Compliance	Adherence to all the study-related, Good Clinical Practice (GCP), and the applicable regulatory requirements.
Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed eligible or potentially eligible to participate in the clinical study.
Electronic case report form (eCRF)	An electronic form for recording subject's data during the study, as required by the protocol.

End of Study	Overall study completion: the day of the last visit of the last subject in the study. Individual subject: the time point after which no further study-related procedures are performed.
Endpoint	Key measurement or observation used to measure the effect of experimental variables in a study.
Enrolment	The time point at which a subject formally starts to participate in the study by signing an informed consent form.
Follow-up Period	After IFX-Investigational Medicinal Product (IMP) administration in Week 16 to Week 24, during which no IFX-IMP is given.
IFX-IMP	IFX-1 or Placebo-IFX-1.
Immunosuppressive therapy	Either Rituximab (RTX) or cyclophosphamide (CYC) administration in the Remission-Induction Phase. CYC, RTX, azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or mycophenolate sodium (MPS) administration in the Remission-Maintenance Phase.

Investigational medicinal product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in the current study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form.
Major relapse	Either BVASv3 > 3 minor items or 1 major BVASv3 item (listed in Appendix 18.2) after clinical remission (BVASv3 = 0).
Minor relapse	Any new occurrence of 1, 2 or 3 minor BVASv3 items listed in Appendix 18.2 (BVASv3 = 1, 2, 3) after clinical remission (BVASv3 = 0).
Pharmacy Manual	Manual provided to the study sites with detailed information on the composition of active and inactive ingredients of the IMP as well as details on shipment to site, site receipt, handling, storage, and administration.
Remission-Induction Phase	The time from the start of remission-induction therapy until clinical remission (BVASv3 = 0).
Remission-Maintenance Phase	The time from clinical remission until Week 24.
Safety follow-up (SFU) visit	To be performed for any subject who discontinues from the study during the Treatment Period (i.e., up to and including Week 16) at 1 month (±3 days) after the last IMP administration.

Screening	The predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for randomization into the study.
Study Drug Instructions for the Patient	Manual provided to subjects with details on the active and inactive ingredients of the glucocorticoid (GC)-IMPs including instructions on storage, handling, and intake.
Study start	The time point at which the first subject gives written informed consent; equivalent to first subject's first visit at the first study site that has enrolled a subject into the study.
Treatment Period	Week 0 to Week 16, during which IFX-IMP is given.

STUDY SYNOPSIS

Title of Study:

A randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study on replacement of steroids by IFX-1 in active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Protocol/Study Number: IFX-1-P2.5

EudraCT Number: 2018-000768-27

Type of Study:	**Indication:**
Proof of Concept Study	Induction of remission in adult subjects with active granulomatosis with GPA and MPA indicated for therapy with cyclophosphamide (CYC) or rituximab (RTX)

Sponsor: InflaRx GmbH, Winzerlaer Strasse 2, 07745 Jena, Germany

Coordinating Investigator: [redacted] **MD, MPH**

Study Site(s):

Approximately 87 sites in approximately 13 countries

Phase of Development: II

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of IFX-1 treatment as replacement for glucocorticoid (GC) therapy in subjects with GPA and MPA.

Secondary Objectives:

- To assess the safety and tolerability of IFX-1
- To compare GC-induced toxicity of standard-dose GC and reduced-dose GC with IFX-1 treatment
- To generate data for pharmacokinetic (PK) and pharmacodynamic (PD) modelling of IFX-1 treatment.

Methodology:

This is a prospective, randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study. A total of 3 treatment groups will be investigated:

Group A:	IFX-1 + reduced-dose GC (RDGC)	= IFX-1 + RDGC
Group B:	Placebo-IFX-1 + standard-dose GC (SDGC)	= Placebo-IFX-1 + SDGC
Group C:	IFX-1 + no GC (NGC)	= IFX-1 + Placebo-GC

In Study Part 1 subjects will be randomized in a 1:1 ratio to either Group A or Group B. The response to treatment will be evaluated under blinded conditions by an Adjudication Committee (AC). An unblinded Independent Data Monitoring Committee (IDMC) will then evaluate whether the data show efficacy signals in Group A and give a recommendation to continue with Study Part 2. In case more data are needed to give a recommendation, the IDMC can propose to prolong the Study Period 1 by recruiting additional subjects.

There will be a recruitment stop for IDMC evaluation after a maximum of 30 subjects have been enrolled in Study Part 1. In Study Part 2 subjects will be randomized to either Group B or Group C. Study Part 2 aims to investigate the efficacy of IFX-1 (Group C) compared to SDGC (Group B).

All subjects may receive RTX or CYC from up to 2 weeks prior to screening up to clinical remission (Remission-Induction Phase). Following clinical remission and up to Week 24 (Remission-Maintenance Phase), subjects can switch to another immunosuppressive therapy (azathioprine [AZA], methotrexate [MTX], mycophenolate mofetil [MMF], or mycophenolate sodium [MPS]), to use throughout the remainder of the study at the discretion of the investigator, or can stay on RTX or CYC.

Number of Subjects:

In Study Part 1, 20 subjects will be randomized to either Group A or Group B in a ratio of 1:1.

[redacted]

In Study Part 2, approximately 25 additional subjects will be randomized to Group B and Group C in an unchanged ratio compared to the previous protocol version. It will result in an unbalanced distribution of patients in Group B and C for the final analysis, i.e. about 24 treated in Group B (15 from Part 1 and 9 from Part 2) and about 16 in Group C (all enrolled in Part 2).

[redacted]

It is planned to not exceed 55 subjects in total.

Study Population:

Subjects must meet all the following criteria at screening and at inclusion to be randomized into the study:

1. Male or female, ≥ 18 years of age.
2. Written informed consent obtained from subject.

3. Diagnosis of GPA or MPA according to the definitions of the Chapel Hill Consensus Conference (CHCC).
4. History of positive antigen-specific anti-neutrophil cytoplasmic antibody (ANCA) testing since the time of diagnosis or at screening, or documented evidence of either anti-proteinase 3 (anti-PR3) or anti--myeloperoxidase (anti-MPO) (for newly diagnosed subjects a recent positive antigen-specific ANCA testing or documented positive anti-PR3 or anti-MPO is mandatory for inclusion).
5. Have ≥ 1 major item, or ≥ 3 minor items, or ≥ 2 renal items on the Birmingham Vasculitis Activity Score Version 3 (BVASv3).
6. Newly diagnosed or relapsed GPA or MPA that requires treatment with CYC or RTX plus GCs.
7. Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m².

Subjects who fulfil any of the following criteria at screening are not eligible to participate in the study:

1. Any other multi-system autoimmune disease as listed in Appendix 18.4.
2. Require mechanical ventilation because of alveolar hemorrhage at screening.
3. Known hypersensitivity to any investigational medicinal product (IMP) (i.e. GC, IFX-1) and/or any excipients.
4. Subject with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
5. Have required management of infections, as follows:
    a. Chronic infection requiring anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) within 3 months before screening.
    b. Use of intravenous antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 30 days of screening.
6. Current and/or history (within the previous 5 years) of drug and/or alcohol abuse and/or dependence.
7. Evidence of Hepatitis B virus (HBV), Hepatitis C virus (HCV) and/ or human immunodeficiency virus (HIV) infection. Only subjects with documented negative historical results (within 4 weeks before Screening) for HBV, HCV and HIV or a negative test by Screening can be included into the study.
8. Any of the following abnormal laboratory findings at screening:
    a. White blood cells < 3,500/mm^3
    b. Platelet count < 100,000/mm^3

c. Transaminase values (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) ≥ 2.5 times the upper limit of normal range (ULN)

d. Total bilirubin ≥ 1.5 times ULN

e. Alkaline Phosphatase (ALP) > 3 times ULN

9. Current or history of malignancy, lymphoproliferative, or myeloproliferative disorder except squamous cell or basal cell carcinomas of the skin and cervical carcinoma in situ with curative surgical treatment.
10. Received CYC or RTX within 12 weeks before screening or within 12 weeks before CYC or RTX is started for remission induction within 2 weeks before screening.
    If subject is on AZA, MMF or MPS or MTX, these drugs must be discontinued prior to receiving the first dose of CYC or RTX.
11. Received > 3 g cumulative intravenous GCs within 4 weeks before screening (RTX intravenous GC premedication is separate and does not count to the 3 g).
12. a) Received an oral daily dose of a GC of > 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening.
    b) Received an oral daily dose of a GC of > 80 mg prednisone-equivalent within 2 weeks before screening.
13. Received a CD20 inhibitor, anti-tumor necrosis factor treatment, abatacept, alemtuzumab, any other experimental or biological therapy, intravenous immunoglobulin or plasma exchange, antithymocyte globulin, or required renal dialysis within 12 weeks before screening.
14. Received a live vaccination within 4 weeks before screening or planned between screening and Week 24.
15. Either active or latent tuberculosis treatment is ongoing.
16. Pregnant or lactating.
17. Clinically significant abnormal electrocardiogram (ECG) during screening.
18. Female subjects of childbearing potential unwilling or unable to use a highly effective method of contraception (pearl index < 1) during treatment and for at least 3 months after last administration of IFX-1/Placebo-IFX-1 (or up to 12 months, the timeframes for Standard of Care agents have to be considered as described in the respective Prescribing Information/Summary of Product Characteristics [SmPC]). Contraception methods regarded as highly effective methods and the duration of contraception are further described in Section 7.7.
19. Evidence or suspicion that the subject might not comply with the requirements of the study protocol.
20. The subject is an employee or direct relative of an employee of the sponsor (InflaRx GmbH).
21. The subject is imprisoned or lawfully kept in an institution.

22. The subject has participated in an investigational clinical study during the 12 weeks (or 5 times the half-life of the previous IMP, whichever is longer) before screening, or plans to participate in another investigational clinical study during their participation in this study.
23. Male subjects with female partners of childbearing potential unwilling to use contraception (condoms) during treatment and for at least 3 months after last administration of IFX-1/Placebo-IFX-1.

Test Product, Dose, and Mode of Administration:

IFX-1 is provided in 10 mL vials containing 100 mg IFX-1 and will be infused over a period of 30 to 60 min via an intravenous line.

Placebo-GC are capsules for oral administration filled with an excipient only, they will have the same appearance as the GC capsules.

Reference Therapy, Dose, and Mode of Administration:

GC are provided in capsules for oral administration. Different numbers and strengths of tablets per capsule will be combined in order to have several GC doses available per dosing.

Placebo-IFX-1 is provided in 10 mL vials. The placebo vials and content have the same appearance as the IFX-1 vials and will be administered in the same manner as IFX-1.

Study Duration:

The study duration for an individual subject will be up to 26 weeks: a 2-week Screening Period, a 16-week Treatment Period, and an 8-week Follow-up Period.

Criteria for Evaluation

Primary Endpoint:

- The proportion of subjects achieving clinical response defined as reduction in BVASv3 $\geq$ 50% at Week 16 compared to baseline (=screening assessment) and no worsening in any body system. Subjects who receive rescue therapy up to Week 16 will be considered as not having achieved clinical response.

Secondary Endpoints:

Efficacy

- Proportion of subjects with a clinical response, defined as a reduction in BVASv3 $\geq$ 50% and no worsening in any body system at each measurement time point except Week 16
- Proportion of subjects with a clinical remission defined as having a BVASv3 = 0 at Week 16
- Change from baseline (=screening assessment) in BVASv3 total score at Week 16
- Absolute values and absolute and relative change from Day 1 in the Vasculitis Damage Index (VDI) at Week 16

- Absolute values and absolute and relative change from Day 1 in the Physician Global Assessment (PGA) at Week 16
- Absolute values and absolute and relative change from Day 1 in eGFR in mL/min/1.73 m² at Week 16

Pharmacokinetic/Pharmacodynamic

- Plasma concentration of IFX-1 at each sample time point
- Absolute values and absolute and relative changes from Day 1 in the PD parameters at each sample time point.

Safety

- Number and percentages of subjects with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)
- Absolute values of the glucocorticoid toxicity index (GTI) at each time point
- Absolute values and changes from Day 1 (baseline) by visit for safety laboratory and vital sign parameters.
- Immunogenicity will be assessed by determining the number and percentage of subjects with detection of anti-drug antibodies (ADAs).

Statistical Methods:

Efficacy:

For Study Part 1 only a descriptive efficacy analysis is planned.

The primary efficacy variable is the percentage of subjects with a clinical response defined as a reduction in BVASv3 ≥ 50% at Week 16 compared to baseline, and no worsening in any body system, and not having received rescue therapy. Missing primary endpoint data will be imputed.

The experimental arm (Group C) and the Standard of Care arm (Group B) will be compared using the risk difference and its 90% confidence interval based on the Farrington-Manning score.

As a secondary efficacy analysis, a logistic regression model will be fit for the binary response at Week 16 including relevant baseline characteristics (such as the baseline BVASv3) as covariates to further investigate the effect of subjects' baseline characteristics.

Further secondary and exploratory efficacy endpoints will be evaluated with appropriate statistical methods and will be described in detail in the statistical analysis plan.

Model based analyses (e.g., analysis of covariance, Poisson, and logistic regression models) for continuous, count, and binary endpoints will be defined in the statistical analysis plan as deemed necessary and possible.

Safety:

TEAEs will be analyzed according to the number and percentage of subjects who had a TEAE, as well as the number of TEAEs with the respective Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. Additionally, the number and percentage of subjects with TEAEs will be grouped by severity and causal relationship. The number and percentage of subjects with SAEs and AESIs and the number of SAEs and AESIs will be analyzed. Where AEs are grouped by severity or relationship, the maximum severity/relationship per subject and class of adverse event (AE) will be considered. If the number of subjects discontinuing treatment or discontinuing the study is substantial, further analyses taking into account the time of AE onset and cumulative dose may be considered.

Summary statistics will be presented for the absolute values of the GTI at each time point.

Safety laboratory and vital signs parameters will be analyzed by summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from Day 1 by visit.

Categorical safety parameters like ECG findings will be summarized by absolute and relative frequencies by time point.

Pharmacokinetics and pharmacodynamics:

Actual PK sampling times will be determined, and the plasma concentration of IFX-1 will be assessed by time point.

Where applicable, the absolute values and changes from baseline of PD endpoints will be summarized using descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, geometric mean) by time point.

SPONSOR SIGNATURE PAGE

Protocol/Study Number: IFX-1-P2.5

Study Title: A randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study on replacement of steroids by IFX-1 in active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Sponsor's Responsible Medical Officer:

_____ _____

Date [redacted] MD, MSc

[redacted]

COORDINATING INVESTIGATOR SIGNATURE PAGE

Protocol/Study Number: IFX-1-P2.5

Study Title: A randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study on replacement of steroids by IFX-1 in active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

Coordinating Investigator:

_____ _____

Date [redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE(S)

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Study Title: A randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study on replacement of steroids by IFX-1 in active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

I have read this study protocol, including the appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee/ Institutional Review Board, in accordance with the protocol, ICH-GCP, the Declaration of Helsinki, and applicable national regulatory requirements. As required by applicable regulatory requirements, changes to the protocol will only be implemented after written approval is received from the sponsor and the Independent Ethics Committee/Institutional Review Board, with the exception of medical emergencies. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this protocol and will receive all necessary instructions for performing the study according to the protocol.

A separate signature page should be created for each principal investigator.

Names and affiliations to be filled out by the investigators.

Principal Investigator:

Name and affiliation: _____

_____

_____ _____

Date Signature

1 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is applicable to all subjects in Study Parts 1 and 2.

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU [c]	USV [n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
Informed consent	X																
Inclusion/exclusion criteria	X																
Pregnancy test [d]	X [i]		X				X		X		X		X	X	X	X	
Demographics and baseline characteristics	X																
Body weight	X		X				X		X		X		X	X	X	X	X
Medical history	X																
SF-36v2, EQ-5D-5L [e]			X				X		X		X		X	X	X	X	
BVASv3	X		X				X		X		X		X	X	X		X
VDI			X										X		X		X
PGA			X				X		X		X		X	X	X		X
GTI [f]			X										X		X	X	X

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU [c]	USV [n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
Vital signs [g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X												X		X	X	
Physical examination	X												X		X	X	X
IFX-IMP administration: IFX-1 or Placebo-IFX-1			X	X	X	X	X	X	X	X	X	X	X				
Daily GC-IMP intake: RDGC/SDGC/NGC			←										→				X
Serum sample total protein	X [i]		X		X	X	X		X		X		X	X	X	X	X
Safety laboratory measurements	X [i]		X				X		X		X		X	X	X	X	X
Serology: HIV/hepatitis B/hepatitis C virus	X [i,l]																
[redacted]	[redacted]					[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
Anti-GBM	X																
Urinalysis	X [i]		X		X	X	X		X		X		X	X	X	X	X
IFX-1 level [h]			X	X	X[h*]	X	X[h*]	X	X	X	X	X	X[h*]	X	X		

	Screening	Randomization [a]	Treatment Period											Follow-Up Period		SFU [c]	USV [n]
Visit	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EOS [b]**		
Week	**W -2 to -1**		**W0**		**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W20**	**W24**		
Day	**-14 to -1**		**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**		
Accepted Time Window (in days)				**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**		
Sampling for:																	
[redacted] C5a			X	X	X	X	X		X		X		X	X	X		
CH50, CRP			X		X	X	X		X		X		X	X	X		
IFX-1 blocking activity						X							X	X	X		
[redacted]			X				X		X		X		X	X	X		
Samples for future research			X				X		X		X		X	X	X		
Anti-drug antibodies			X			X	X		X		X		X	X	X		
Adverse events	X		←										→			X	X
AxMP administration [m]	←												→				X
Prior and concomitant therapy	X		←										→			X	X

a Randomization can be performed at any time between completion of the screening assessments and the first IMP administration on Day 1.

b These assessments should be performed at:
- Week 24 for subjects who complete the study.
- The time when a subject's participation in the study is prematurely discontinued from the study (end of study [EOS] visit).

c Safety follow-up visit (SFU): 1 month (±3 days) after the last IMP administration for any subject who discontinues from the study up to and including Week 16 (i.e., during the Treatment Period).

d Only in women of childbearing potential: Serum pregnancy test (beta-human chorionic gonadotropin) at screening and Visit 14/EOS. Also at discontinuation and safety follow-up. Urine pregnancy test (dipstick) at Visits 2, 6, 8, 10, 12 and 13.

e The questionnaires should be completed at the study site before any other assessments are performed.

f Only baseline laboratory parameters and specific list items will be assessed for the GTI.

g Vital signs include: systolic and diastolic blood pressure, pulse rate (after 5 min in a sitting position), respiratory rate, and body temperature.

h [redacted]

i Only the screening laboratory testing for serology, safety laboratory (including serum total protein), serum pregnancy test, and urinalysis, including BVAS-relevant laboratory value assessments, for screening and inclusion into the study can be done either in a capable local laboratory or the central laboratory. If screening testing is done in a local laboratory, no respective blood samples are shipped to the central laboratory.
Blood samples for laboratory measurements taken from Visit 2 onwards always have to be sent to and analyzed by the central laboratory.

k [redacted]

l At screening, serology viral tests for HIV, HBV, and HCV are to be done for evidence of active or chronic viral infection, or a documented history (viral test results) done within 4 weeks before screening is available for HIV, HBV, and HCV viral testing.

m RTX (with intravenous GC premedication) or CYC as remission-induction treatments are allowed to be started up to 2 weeks prior to screening and are to be continued until clinical remission. Any other immunosuppressive therapy has to be stopped when RTX or CYC starts. After clinical remission, subject can stay on RTX or CYC, or can be switched to AZA, MTX, MMF, or MPS as remission-maintenance treatment at the discretion of the investigator until Week 24.

n For subjects with suspect of major or minor relapse visiting the center between 2 scheduled visits. If subject with suspect of minor or major relapse will visit the study center at a scheduled visit, the assessments and procedures of this respective scheduled visit have to be done.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION ON THE INDICATION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are related systemic vasculitides that, along with eosinophilic granulomatosis with polyangiitis (EGPA), are grouped under the term anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Both GPA and MPA are associated with ANCA, have many identical clinical manifestations, many similar histologic features, and similar outcomes. GPA and MPA predominantly affect small vessels and are associated with myeloperoxidase-ANCA (MPO-ANCA) or proteinase 3-ANCA (PR3-ANCA). Although neither sensitive nor specific, common complaints and signs of GPA and MPA include fatigue, fever, weight loss, arthralgia, rhinosinusitis, cough and dyspnea, urinary abnormalities (an active urine sediment) with or without renal insufficiency, purpura, and neurologic dysfunction. These forms of vasculitis can manifest themselves and progress slowly over months or explosively over days. If untreated, GPA and MPA progress from a limited disease process (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase, characterized by multiple complications of small-vessel vasculitis (i.e., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) [Reinhold-Keller et al.,2000].

GPA and MPA most commonly occur in older adults, although these diseases have been reported at all ages [Jennette et al.,1997, Seo et al.,2004]. Men and women are equally affected, and the diseases are far more common among white individuals than those of other races/ethnicities [Falk et al.,1990].

The incidence of these conditions in the United States of America is approximately 6,000 new cases per year, and the estimated prevalence is 25,000 to 30,000 cases. The overall incidence rates of AAV in Europe are reported to be in the range of 13 to approximately 20 per million [Watts et al.,2015]. The prevalence of AAV is estimated to be 46 to 184 per million [Ormerod et al.,2008, Reinhold-Keller et al.,2000]. The prevalence of AAV has generally increased over the last 20 years, this could reflect improved patient survival and case identification, e.g., by using multiple retrieval sources [Watts et al.,2015].

The Standard of Care as recommended in the guideline for AAV [Yates et al.,2016] usually consists of rituximab (RTX) or cyclophosphamide (CYC) administration for remission-induction, with glucocorticoid (GC) tapering followed by azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or mycophenolate sodium (MPS) for remission-maintenance. Alternatively, a second cycle of RTX can be given.

Although treatment failures and disease relapses decreased due to the improvement of remission-induction regimens during recent years, patients with MPA and GPA treated with conventional regimens have a 9-fold increased mortality risk in the first year

attributed to infection, cardiovascular disease, malignancies, vasculitis activity, and renal disease [Luqmani et al.,2011 a, Flossmann et al., 2011]. It is proven that current therapies contribute to more than half of this increased risk rather than the underlying disease itself [Little et al.,2010]. Most of the side effects are attributed to the high-dose of GCs, which are still part of Standard of Care for MPA and GPA. GCs have long-term side effects such as osteoporosis, Cushing's syndrome, increased infection risk and risk of diabetes mellitus [Goupil et al.,2013, Moghadam-Kia et al.,2010, Charlier et al.,2009, McGregor et al.,2012], and progressive organ damage [Robson et al.,2015]. Therefore, the replacement of GCs by IFX-1 may improve the short- and long-term safety of the treatment of MPA and GPA for the induction of remission.

2.2 BACKGROUND INFORMATION ON IFX-1

IFX-1 is a monoclonal antibody which specifically binds to the soluble human complement split product C5a. Nonclinical studies have demonstrated that IFX-1 binds to its target rapidly and is capable of a nearly complete blockade of C5a-induced biological effects, while not affecting cleavage of C5 or formation of the complement membrane attack complex (MAC).

[redacted]

Various nonclinical studies have been conducted to assess pharmacological and toxicological aspects of IFX-1, none of which revealed any obvious toxicological or safety concerns for IFX-1. IFX-1 was well tolerated and did not show any toxicity with any of the doses tested.

IFX-1 is an investigational medicinal product (IMP) and is not approved in any country worldwide. To date, IFX-1 has been investigated in 1 Phase I study in healthy subjects and in 3 Phase II studies: in subjects with early septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with moderate to severe hidradenitis suppurativa (HS).

[redacted] Based on the study data available, IFX-1 was safe and well tolerated when administered to healthy volunteers and subjects. In addition to GPA and MPA, IFX-1 is also in clinical development for moderate to severe HS and pyoderma gangrenosum.

[redacted]

2.3 RATIONALE FOR THE STUDY

AAV is a group of potentially life-threatening autoimmune diseases. Experimental data from animal models and in vitro experiments demonstrate that primed neutrophils are activated by ANCA and generate C5a that engages C5a receptors on neutrophils. As expected, patients with ANCA-related disease have elevated plasma and urine levels of C5a in active disease and not in remission [Chen et al.,2017]. Given the mode of action of IFX-1 as a monoclonal antibody specifically binding to the soluble human complement split product C5a and the resulting nearly complete blockade of C5a-induced biological effects, it may be effective in the treatment of subjects with AAV.

IFX-1 was safe and well tolerated in other life-threatening indications like sepsis and cardiac surgery, and long-term data are available from a clinical study in HS. Even though IFX-1 has not yet been investigated in AAV, no unexpected safety issues are anticipated.

The aim of this study is to investigate the efficacy and safety of IFX-1 in the replacement of GCs used for remission-induction in addition to immunosuppressive therapy. High-dose GCs are an important part of Standard of Care in AAV and are associated with several toxicities.

As demonstrated in a series of studies on Avacopan, a drug which blocks the effects of C5a by targeting its receptor C5aR, the reduction of C5a effects can replace high-dose GCs [Jayne et al.,2017]. The current study will investigate the efficacy and safety of IFX-1 in the replacement of GCs using a stepwise approach to reduce the amount of GC.

The study will also collect data on patient-reported outcomes (PROs) and clinical parameters that could be positively affected by a C5a blocking therapy instead of treatment with GC.

2.3.1 Study Population

Subjects with newly diagnosed or relapsed GPA or MPA who require treatment with RTX or CYC plus SDGCs will be randomized in this study. These subjects are considered to have a sufficiently severe disease, whereas subjects with life-threatening symptoms will not be enrolled since IFX-1 has not been investigated in this indication before.

The exclusion criteria (Section 5.3) will ensure that the study population is as homogenous as possible.

2.3.2 Dosing Regimen

The aim of treatment with IFX-1 is to achieve an almost complete blockade of the overall available C5a (existing and newly produced) in human whole blood during the entire treatment period.

[redacted] According to available data and derived estimates, dosing with 800 mg every 2 weeks will result in mean IFX-1 trough levels in the range of 10 to 20 µg/mL, which should result in a situation where C5a is almost completely blocked over the entire treatment period.

The toxicological profile of IFX-1 is considered adequate to support the planned Phase II clinical study in subjects who will be treated at doses of 800 mg IFX-1 for a period of 16 weeks. There were no relevant findings in the toxicology studies which would preclude the continued clinical development of IFX-1.

2.3.3 Study Design

This is a prospective, randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study evaluating the efficacy of IFX-1 treatment in the replacement of GCs in subjects with GPA or MPA. The primary objective is to evaluate the efficacy of IFX-1 treatment as a replacement for GC therapy in subjects with GPA and MPA. A design with 2 study parts was chosen, since the safety and efficacy of IFX-1 have not been investigated in GPA or MPA subjects to date. In Study Part 1, subjects will be randomized to either Placebo-IFX-1 with SDGC or to IFX-1 with a reduced-dose glucocorticoid (RDGC) treatment tapering regimen. After a blinded adjudication committee (AC) and an unblinded IDMC have concluded that subjects treated with IFX-1 and RDGC have shown an equivalent treatment response as compared to subjects treated with conventional SDGC, Study Part 2 will start with a comparison of Placebo-IFX-1 with SDGC and IFX-1 with placebo-glucocorticoids (Placebo-GC). This stepwise design is deemed appropriate for investigating the efficacy and safety of IFX-1 treatment in subjects with GPA or MPA without increasing the harm, since continuous monitoring of the subjects is guaranteed, and Study Part 2 can only start after such a recommendation by the IDMC.

The study will be conducted in compliance with this study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), and the applicable regulatory requirements.

2.3.4 Expected Benefits

The subjects who will be treated with IFX-1 or placebo in this study will benefit from an improvement in GPA and MPA-related symptoms since all subjects will receive background standard immunosuppressive therapy as detailed in Section 6.2. Since more than half of the subjects will additionally receive IFX- 1, they may experience a faster

response to treatment. Half of the subjects in Study Part 1 will receive reduced dose GC, and about 2/3 of the subjects enrolled in Study Part 2 will not be administered GC at all. These subjects are expected to have less or will not experience GC adverse effects at all, meaning a decreased risk of the above described and well-known high mortality during the first year of treatment.

2.4 RISK-BENEFIT ASSESSMENT

Considerations on risk-benefit-related aspects are derived from nonclinical data and clinical Phase I data in healthy subjects, as well as from clinical data from 3 other Phase II studies conducted in subjects with early, newly developing abdominal or pulmonary-derived septic organ dysfunction, in subjects undergoing complex cardiac surgery, and in subjects with HS. In addition, the mode of action of IFX-1 is clearly supported in subjects with GPA and MPA [Van Timmeren et al.,2012].

2.4.1 Potential Risks

No subject with GPA or MPA has been treated with IFX-1 to date, but IFX-1 was generally well tolerated in other studies and no new risks are anticipated. However, potential and theoretical risks associated with administration of IFX-1 may include infections, meningitis/meningococcal sepsis, and anaphylactic reactions/acute allergic hypersensitivity (Section 10.3).

Since no subject with GPA or MPA has been treated with IFX-1 in combination with immunosuppressive therapy, the drug-drug interactions, safety, tolerability, and efficacy of IFX-1 have not yet been investigated.

Subjects in Group A and B will receive GCs which may have adverse effects on many organ systems and range from those that are not necessarily serious, but are displeasing to patients, to those that are life-threatening. In addition, in several countries RTX and CYC are not licensed for all treatment periods. However, there are international treatment standards and/or local treatment guidelines that must be adhered to by the investigators.

2.4.2 Risk Associated with Lack of Efficacy

RTX or CYC will be administered as immunosuppressive therapy until clinical remission (i.e., during the Remission-Induction Phase) and can be given after clinical remission at the discretion of the investigator. Due to the treatment response rate of up to 90% for this established remission-induction therapy, the risk of lack of efficacy is deemed to be very low in this study. In accordance with the current guidelines for AAV [Yates et al.,2016], subjects can receive AZA, MTX, MMF, or MPS after clinical remission is reached (i.e., during the Remission-Maintenance Phase) as deemed appropriate by the investigator. In case of a lack of efficacy with IMP treatment (no effect of IFX-1 or too low dose of GC) or in case of any relapses, subjects can receive

rescue therapy with GCs as described in Section 5.4.1 and Section 7.5 to avoid harm to the subjects.

With the administration of IFX-1 or Placebo-IFX-1, no deterioration in health status is expected with respect to GPA and MPA [redacted]

In addition, during the Study Part 1 an AC will continuously evaluate the clinical response and remission status of each subject (Section 14.3).

In case of insufficient treatment response, the Independent Data Monitoring Committee (IDMC) can recommend stopping the study at any time. Similarly, the principal investigator can stop the study at his/her site at any time. The subject can also choose to discontinue the study at any time (Section 5.4).

2.4.3 Conclusion

GPA and MPA are the 2 major forms of systemic vasculitis associated with ANCA [Hoffman,1998]. If untreated, they progress from limited disease processes (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase, characterized by multiple complications of small-vessel vasculitis (i.e., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) [Reinhold-Keller 2000]. The outcome of untreated severe disease is death.

Although treatment failures and disease relapses have decreased due to improvement of remission-induction regimens during recent years, patients with MPA and GPA treated with conventional regimens have a 9-fold increased mortality risk in the first year. This is attributed to infection, cardiovascular disease, malignancies, vasculitis activity, and renal disease [Flossmann et al.,2011, Luqmani et al.,2011 a]. Current therapies contribute to more than half of this increased risk, rather than the underlying disease itself [Little et al.,2010]. Most of the side effects are attributed to the high dose of GCs, which are still part of Standard of Care for MPA and GPA. GCs have long-term side effects such as osteoporosis, Cushing's syndrome, increased infection risk, risk of diabetes [Moghadam-Kia et al.,2010, Charlier et al.,2009, McGregor et al.,2012, Goupil et al.,2013], and progressive organ damage [Robson et al.,2015].

It was demonstrated that C5a and C5b receptors are involved in the pathogenesis of AAV and that C5a levels are increased in patients with AAV [Chen et al.,2017, Furuta et al.,2013, Halbwachs et al.,2012, Kettritz,2014]. Since IFX-1 is a monoclonal antibody, which specifically binds to the soluble human complement split product C5a, it is capable of a nearly complete blockade of C5a-induced biological effects, while not affecting cleavage of C5 and formation of the complement MAC. Therefore, IFX-1 could be effective in the treatment of subjects with GPA and MPA and will be administered as add-on to immunosuppressive therapy for GPA and MPA to improve the time to clinical remission.

Subjects in Group B will receive Standard of Care and are not at a higher risk. Since in Study Part 1 subjects randomized to Group A will receive a lower GC regimen, these subjects will be at risk for too low levels of GC therapy if IFX-1 is not effective in this condition. Other studies are currently ongoing that are investigating GC tapering with lower GC doses in AAV [Furuta et al.,2017, Walsh et al.,2013], and it was recently shown that a low-dose tapering was non-inferior to standard high-dose GC [Walsh et al.,2018]. Group C will only receive Placebo-GCs if a comparable treatment response of Group B to Group A was seen by the IDMC in Study Part 1.

In case of a lack of efficacy or relapse after IMP treatment, subjects will receive adequate rescue medication as described in Section 7.5. Risk-limiting procedures have been put in place and therefore the hypothesized benefit of treatment with IFX-1 outweighs the potential risks for subjects participating in this study.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of IFX-1 treatment as replacement for GC therapy in subjects with GPA and MPA.

3.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To assess safety and tolerability of IFX-1
- To compare GC-induced toxicity of standard-dose GC and reduced-dose GC with IFX-1 treatment
- To generate data for pharmacokinetic (PK) and pharmacodynamic (PD) modelling of IFX-1 treatment.

All study endpoints are listed in Section 11.4.

4 STUDY DESIGN

4.1 OVERALL STUDY DESIGN AND PLAN

This is a prospective, randomized, double-blind, double-dummy, active-controlled, multicenter, 2-part Phase II study.

After a Screening Period of up to 14 days, 20 to 55 subjects are planned to be enrolled into the study (see Table 6 for further details).

This is a double-dummy study; Placebo-IFX-1 and Placebo-GC will be administered in different treatment groups. To investigate the efficacy of IFX-1 in the replacement of GC during the study, 2 different GCdose regimens, standard (SDGC), and reduced (RDGC) and a Placebo-GC will be investigated. The treatment groups receiving IFX-1 will receive RDGC or Placebo-GC, and the group with SDGC will receive Placebo-IFX.

The 3 treatment groups investigated in this study will receive the following IMP combinations:

Group A: IFX-1 + reduced-dose GC (RDGC) = IFX-1 + RDGC

Group B: Placebo-IFX-1 + standard-dose GC (SDGC) = Placebo-IFX-1 + SDGC

Group C: IFX-1 + no GC (NGC) = IFX-1 + Placebo-GC

Subjects in all 3 treatment groups will receive either RTX or CYC (for details, see Section 6.2.1). RTX or CYC can be started within 2 weeks prior to the screening or at any time during the screening period, independently from the planned date of randomization. Treatment with RDGC, SDGC, and Placebo-GC (no glucocorticoids [NGC]) will start at Day 1 and the SDGC and RDGC will be tapered down according to a predefined schedule within 24 weeks (Section 6.1.2.5, Table 2).

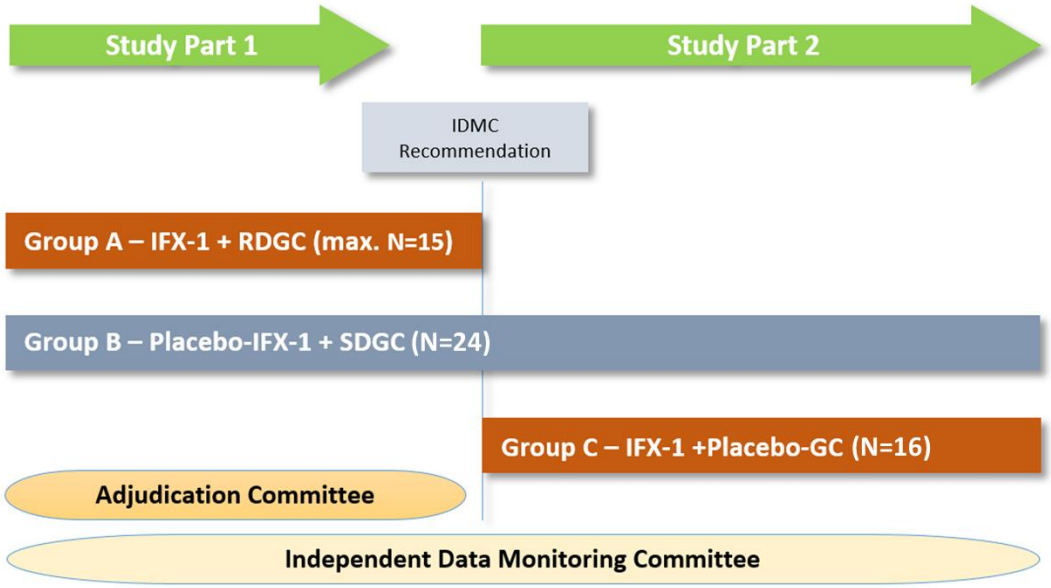
The study will consist of 2 parts:

Study Part 1 aims to mitigate subjects' risk by randomizing subjects to either Group A or Group B in a 1:1 distribution. Subjects will take either SDGC (Group B) or RDGC with IFX-1 (Group A), because there is no clinical data available regarding the efficacy of IFX-1 to replace GC treatment.

In Study Part 2, subjects will be randomized to either Group B or Group C in a ratio that yields about 9 subjects in Group B and about 16 subjects in Group C. Subjects who have been randomized into Group B in Study Part 1 will contribute to the set of subjects analyzed in Study Part 2 resulting in about 24 subjects in Group B vs about 16 subjects in Group C for the primary comparison.

An overview of the overall study design is shown in Figure 1.

Figure 1 Overall Study Design



Adjudication Committee
An AC will be set up before study start. The AC will continuously evaluate the treatment response of each subject for each study visit under blinded conditions throughout Study Part 1. (Sections 11.11 and 14.3). The organization and roles of the AC, and the individual efficacy data needed for their analysis will be defined and provided in a separate charter (Adjudication Committee Charter).

Independent Data Monitoring Committee
An IDMC will be set up and will be responsible for (1) a continuous review of subject safety data under unblinded conditions throughout the study, and (2) a recommendation to continue the study with Part 2 (Section 14.4). Details on the role and organization of the IDMC will be provided in a separate charter (Independent Data Monitoring Committee Charter).

The reports of the AC will be continuously provided to the IDMC. On the basis of the AC reports and further unblinded safety data analysis (provided by an unblinded statistician) the IDMC will make a recommendation without predefined statistical criteria at the latest at the end of Study Part 1, after 20 subjects have reached the Week 16 timepoint. The recommendation will be:

- If the study must be prematurely terminated
- If a second evaluation needs to be done after enrolment of 10 further subjects
- If a further evaluation needs to be done after 30 subjects, additional subjects should be included
- If the study can continue with an amended protocol

- If the study can continue with Study Part 2 and open Group C for enrolment.

There will be a recruitment stop after a maximum of 30 subjects have been enrolled in Study Part 1 for IDMC evaluation.

In both study parts, the study schedule for each participating subject comprises a Screening, a Treatment, and a Follow-up Period.

Screening period
The screening procedures will be conducted between Day -14 and Day -1 before the first administration of IMP. Randomization of eligible subjects will be performed during the Screening Period and needs to be done at Day 1 (Visit 2) at the latest and prior to Day 1 specific assessments.

Treatment Period
For each subject, the Treatment Period starts with Visit 2 in Week 0 (Day 1, immediately before first administration of IMP) and ends in Week 16 (Visit 12) immediately after administration of IFX-IMP.

Follow-up Period
After the Treatment Period, subjects will enter the Follow-up Period, which will last until Week 24. In this Follow-up Period, no IFX-IMP treatment will be administered but the subjects will finalize their GC tapering schedule and can receive standard maintenance therapy for GPA/MPA, as described in Section 6.2.2.

A final visit at the study site for efficacy and safety assessments (end of study visit) will occur in Week 24.

4.2 NUMBER OF SUBJECTS AND STUDY SITES

This multicenter study is planned to be conducted at approximately 87 sites in approximately 13 countries.

It is planned to randomize 55 subjects (Section 11.2).

4.3 STUDY DURATION

The study start is defined as the date of the first screening visit of the first subject who signs informed consent, and the end of the study is defined as the date of the last visit of the last subject, as recorded in the electronic case report form (eCRF).

The study duration for an individual subject will be up to 26 weeks.

The duration of the study periods is as follows:

- Screening Period: up to 14 days before randomization (Week -2 to Week -1 [Day -14 to Day -1])

- Treatment Period: starts in Week 0 (Day 1) and ends in Week 16 (Day 113)
- Follow-up Period: starts after administration of IFX-IMP in Week 16 and ends in Week 24 (Day 169).

Subjects, who discontinue the study during the treatment period up to and including Week 16, will have a safety follow-up visit (SFU) 1 month (±3 days) after the last IMP administration.

IFX-1 or Placebo-IFX-1 will be administered starting in Week 0 through Week 16, with a total of 11 infusions.

4.4 PREMATURE TERMINATION OF THE STUDY

The entire study can be prematurely discontinued at all sites by the sponsor at any time for any reason (e.g., medical, ethical, or if the IDMC recommends not to start Part 2).

The investigator(s) will be notified in writing, outlining the reasons for discontinuation, and the investigator(s) must promptly inform all participating subjects. Detailed instructions on further assessments will be provided.

All study materials, except documents needed for archiving requirements, will be returned to the sponsor, including all records regarding the IMP. The clinical monitor will ensure that any outstanding data clarification issues and queries are resolved and that all study records at the study site are completed.

In accordance with applicable regulatory requirements, the sponsor will promptly inform the competent regulatory authorities of the discontinuation and its reason(s), and the investigator or sponsor will promptly inform the Ethics Committee.

Furthermore, the approval of the study can be rescinded, or the study can be discontinued by a competent authority or a responsible Ethics Committee.

5 STUDY POPULATION

5.1 SCREEN FAILURES

Screen failures are defined as study subjects who consent to participate in the study but are not subsequently randomized to a treatment group. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Screen failure information includes demographics, AAV-related and general medical history, AAV-related prior and concomitant medication, screen failure details, eligibility criteria, and any (serious) adverse event ([S]AE).

Rescreening of subjects who do not meet the criteria for participation in this study is not allowed.

5.2 INCLUSION CRITERIA

Subjects must meet all of the following criteria at screening and at inclusion to be randomized into the study:

Inclusion Criteria	**Rationale**
1. Male or female, ≥ 18 years of age.	Safety concern
2. Written informed consent obtained from subject.	Administrative
3. Diagnosis of GPA or MPA according to the definitions of the Chapel Hill Consensus Conference (CHCC).	Effectiveness
4. History of positive antigen-specific ANCA testing since the time of diagnosis or at screening, or documented evidence of either anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) (for newly diagnosed subjects a recent positive antigen-specific ANCA testing or documented positive anti-PR3 or anti-MPO is mandatory for inclusion).	Effectiveness
5. Have ≥ 1 major item, or ≥ 3 minor items, or ≥ 2 renal items on the BVASv3.	Effectiveness
6. Newly diagnosed or relapsed GPA or MPA that requires treatment with CYC or RTX plus GCs.	Effectiveness
7. Estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m².	Effectiveness / Safety concern

5.3 EXCLUSION CRITERIA

Subjects who fulfil any of the following criteria at screening are not eligible to participate in the study:

Exclusion Criteria	**Rationale**
1. Any other multi-system autoimmune disease as listed in Appendix 18.4.	Safety concern
2. Requires mechanical ventilation because of alveolar hemorrhage at screening.	Safety concern
3. Known hypersensitivity to any IMP (i.e. GC, IFX-1) and/or any excipients.	Safety concern
4. Subject with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.	Safety concern
5. Have required management of infections, as follows: a. Chronic infection requiring anti-infective therapy (such as latent tuberculosis, pneumocystis, aspergillosis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) within 3 months before screening. b. Use of intravenous antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 30 days of screening.	Safety concern
6. Current and/or history (within the previous 5 years) of drug and/or alcohol abuse and/or dependence.	Safety concern
7. Evidence of Hepatitis B virus (HBV), Hepatitis C virus (HCV) and/ or human immunodeficiency virus (HIV) infection. Only subjects with documented negative historical results (within 4 weeks before Screening) for HBV, HCV and HIV or a negative test by Screening can be included into the study.	Safety concern
8. Any of the following abnormal laboratory findings at screening: • White blood cells < 3,500/mm^3 • Platelet count < 100,000/mm^3 • Transaminase values (AST and/or ALT) ≥ 2.5 times the ULN • Total bilirubin ≥ 1.5 times ULN • ALP > 3 times ULN.	Safety concern

Exclusion Criteria	Rationale
9. Current or history of, malignancy, lymphoproliferative or myeloproliferative disorder except squamous cell or basal cell carcinomas of the skin and cervical carcinoma in situ with curative surgical treatment.	Safety concern
10. Received CYC or RTX within 12 weeks before screening or within 12 weeks before CYC or RTX is started for remission induction within 2 weeks before screening. If subject is on AZA, MMF or MPS or MTX, these drugs must be discontinued prior to receiving the first dose of CYC or RTX.	Safety concern
11. Received > 3 g cumulative intravenous GCs within 4 weeks before screening (RTX intravenous GC premedication is separate and does not count to the 3 g).	Effectiveness
12. a) Received an oral daily dose of a GC of > 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening. b) Received an oral daily dose of a GC of > 80 mg prednisone-equivalent within 2 weeks before screening.	Effectiveness
13. Received a CD20 inhibitor, anti-tumor necrosis factor treatment, abatacept, alemtuzumab, any other experimental or biological therapy, intravenous immunoglobulin (Ig) or plasma exchange, antithymocyte globulin, or required renal dialysis within 12 weeks before screening.	Safety concern
14. Received a live vaccination within 4 weeks before screening or planned between screening and Week 24.	Safety concern
15. Either active or latent tuberculosis treatment is ongoing.	Safety concern
16. Pregnant or lactating.	Safety concern
17. Clinically significant abnormal electrocardiogram (ECG) during screening.	Safety concern
18. Female subjects of childbearing potential unwilling or unable to use a highly effective method of contraception (pearl index < 1) during treatment, and for at least 3 months after last administration of IFX-1/Placebo-IFX-1 (or up to 12 months, the timeframes for Standard of Care agents have to be considered as described in the respective Prescribing Information/SmPC). Contraception methods regarded as highly effective methods and the duration of contraception are further described in Section 7.7.	Safety concern

Exclusion Criteria	Rationale
19. Evidence or suspicion that the subject might not comply with the requirements of the study protocol.	Safety concern
20. The subject is an employee or direct relative of an employee of the sponsor (InflaRx GmbH).	Administrative
21. The subject is imprisoned or lawfully kept in an institution.	Administrative
22. The subject has participated in an investigational clinical study during the 12 weeks (or 5 times the half-life of the previous IMP, whichever is longer) before screening, or plans to participate in another investigational clinical study during their participation in this study.	Administrative
23. Male subjects with female partners of childbearing potential unwilling to use contraception (condoms) during treatment and for at least 3 months after last administration of IFX-1/Placebo-IFX-1.	Safety

5.4 DISCONTINUATION OF INDIVIDUAL SUBJECT PARTICIPATION

Each early discontinuation of individual subject participation, irrespective of the reason for discontinuation, must be documented by the investigator. If possible, the date, circumstances, and reason for discontinuation should be documented.

The investigator will complete all procedures usually required at the end of the study (EOS, i.e., Week 24) visit at the time when the subject's participation in the study is discontinued. Subjects who discontinue until, and including, Week 16 will have a safety follow-up visit at 1 month (±3 days) after the last IMP administration.

5.4.1 Lack of Efficacy

In case of lack of efficacy (for example: no improvement or deterioration in the BVASv3, lack of efficacy according to the clinical judgement of the investigator), it is at the discretion of the investigator to administer rescue medication (see Section 7.5), to keep the subject in the study and continue with IMP (IFX-IMP and GC-IMP) administrations, AxMP intake and study procedures/ assessments as scheduled, to discontinue IMPs (IFX-IMP and GC-IMP), or to withdraw the subject from further study participation (refer also to Section 7.5)

If the investigator unblinds the subject to allow for an appropriate treatment, the subject must be discontinued from further study participation (see Section 6.3, Emergency Identification of Investigational Medicinal Product). Whenever possible, the investigator should contact the medical monitor before breaking the blind.

5.4.2 Withdrawal of Informed Consent

Subjects may discontinue their participation in the study by withdrawing their consent at any time without giving reasons. Nevertheless, they should be asked about the reason(s) for discontinuation after being informed that they do not need to do so. Information as to when they withdrew consent must be documented.

Subjects are to be informed that when consent is withdrawn, the stored and captured data as well as blood samples taken up until the time of termination may be used in the future to:

- Assess effects of the IMP being tested
- Guarantee that the subject's personal interests are not adversely affected
- Comply with the requirement to provide complete documentation when seeking marketing authorization.

5.4.3 Discontinuation of the Investigational Medicinal Products

Subjects' treatment with IMPs (IFX-IMP and GC-IMP) must be discontinued under any of the following circumstances:

- Unacceptable toxicity or treatment-emergent adverse event (TEAE) related to the IMP, as determined by the investigator
- Subjects unblinded for IMP administration due to safety concerns or emergency treatments. Subjects must be discontinued from further study participation (see Section 6.3, Emergency Identification of Investigational Medicinal Product)
- Anaphylactic or other serious allergic reaction
- Serious infection, including meningitis or sepsis
- If, in the investigator's or sponsor's opinion, continued administration of IMP could be detrimental to the subject's well-being
- Use of prohibited treatment that in the investigator's or sponsor's opinion necessitates the subject being removed
- Biopsy confirmation of any malignancy
- Pregnancy.

Discontinuation of IMPs does not necessarily discontinue the subject from study participation and he/she can continue study procedures/assessments as scheduled.

Lost to follow-up is defined as an unsuccessful attempt at contacting a subject.

At least 3 attempts, e.g. letter to the subject, phone calls, etc., at 3 different times should be performed. In case all attempts are unsuccessful in contacting the subject, a certified letter will be issued to the subject. If the attempts and the letter remain unanswered after approximately 1 month, the subject is to be declared as lost to follow-up. All the attempts at contacting the subject should be documented in the subject's records.

The date of being lost to follow-up is defined as the last date with any assessment of the subject.

6 STUDY TREATMENTS

6.1 DETAILS OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

In this double-blind, double-dummy study, the drugs IFX-1 and Placebo-IFX-1, as well as GCs (RDGC, SDGC) and Placebo-GC (NGC) are considered IMP and will be supplied by the sponsor's designated Contract Manufacturing Organization (CMO). All IMP must be kept strictly blinded to subjects, investigators, and other site personnel and will be labelled, handled, and administered accordingly.

All IMP supplied for use in this study will be manufactured, tested, and released according to the standards of Good Manufacturing Practice.

6.1.1 Description of IFX-1 and Placebo-IFX-1 (IFX-IMP)

The active pharmaceutical ingredient of IFX-1 is a monoclonal anti-human C5a Ig.

IFX-1 will be supplied in 10 mL glass vials at a concentration of 10 mg/mL (i.e., 100 mg per vial) for intravenous administration. [redacted]

Placebo-IFX-1 will be supplied in 10 mL glass vials for intravenous administration. [redacted].

The Placebo-IFX-1 vials and content will have the same appearance as the IFX-1 vials.

6.1.1.1 Packaging and Labelling of IFX-IMP

IFX-1 and Placebo-IFX-1 will be packaged in cartons and labeled in accordance with all legal requirements.

Each carton will contain 4 vials of IFX-1 or Placebo-IFX-1.

The cartons will be labeled with a unique number ("medication number"). The glass vials containing IFX-1 or Placebo-IFX-1 will be labeled with the same medication number as the cartons in which they are packed.

Each carton and each vial will be labeled with a multilingual booklet label or a country specific single panel label.

6.1.1.2 Shipment of IFX-IMP

The initial, and all subsequent supplies of IFX-IMP required, will be supplied to study sites by the sponsor's designated CMO.

The IFX-IMP must be shipped at a temperature of 2°C to 8°C and should not be frozen. Each shipment will be controlled by a temperature logger, of which a read-out must be obtained by the site personnel upon receipt of the shipment.

The initial shipment of IFX-IMP to the sites will be automatically triggered by the Interactive Web Response System (IWRS). IFX-IMP shipments will be initiated, maintained and controlled by the IWRS.

The site personnel will be responsible for the correct receipt, storage handling, and accountability of the IFX-IMP at the study site. Further details on shipment procedures, process for receipt, storage and handling of the IFX-IMP is provided in the Pharmacy Manual.

6.1.1.3 Storage of IFX-IMP

IFX-IMP must be stored at 2°C to 8°C and must not be frozen. All supplies of IFX-IMP must be stored separately from other study supplies and site stock in a dedicated locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled and monitored and compliant with applicable regulatory requirements.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization (CRO) and the site personnel will maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported to the CMO as soon as possible. Further instruction on the management and reporting of temperature deviations is provided in the Pharmacy Manual.

6.1.1.4 Drug Accountability of IFX-IMP

During the study, all vials of IFX-IMP will be reconciled against the current inventory and the dispensing records as a component of the monitoring visits.

Data on the administration of IFX-IMP kept at the site will be monitored throughout the study by the study monitor. Used vials of IFX-IMP can be destroyed at the site after IFX-IMP accountability has been assessed by the study monitor unless there is a different procedure agreed to with the site.

After completion of the study, copies of all IFX-IMP accountability records will be provided to the CRO. Unused vials of IFX-IMP will either be returned to the CMO or destroyed at the study site according to institutional policy and in compliance with the current applicable regulatory requirements. The destruction of any unused vials of

IFX-IMP at the study site must be documented on a form provided by the CRO. Further details on the monitoring procedures will be provided in the Clinical Monitoring Plan.

6.1.1.5 Reconstitution of IFX-IMP

The IFX-IMP for infusion will be reconstituted (prepared) in a controlled area at the study site or at the study site's pharmacy in accordance with local regulations/requirements for reconstitution of products for intravenous administration.

The reconstituted IFX-IMP should be used within 4 hours after dilution if stored at room temperature. Otherwise, the reconstituted IFX-IMP has to be stored at 2°C to 8°C and used within 24 hours. Details on reconstituting the IFX-IMP will be provided in the Pharmacy Manual.

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept, in general, at the site until the drug accountability documentation has been checked by the study monitor (see Section 6.1.1.4).

6.1.1.6 Administration of IFX-IMP

After screening, in Study Part 1, subjects will be randomized into Group A (IFX-1 + RDGC) or Group B (Placebo-IFX-1 + SDGC) in a ratio of 1:1.

IFX-1 and Placebo-IFX-1 will be administered during the Treatment Period up to Week 16. Group A will receive 800 mg IFX-1 on Days 1, 4, and 8, and then every other week from Week 2 (Day 15) to Week 16; Group B will receive Placebo-IFX-1 infusions at the same timepoints as the IFX-1 infusions for Group A (Table 1).

In Study Part 2, the IMP for subjects in Group C (800 mg IFX-1+ Placebo-GC) will be administered at the same time points as the IMP for Group B (Table 1).

Table 1 Dosing Schedule for IFX-1 and Placebo-IFX-1

Visit	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Week	0	0	1	2	4	6	8	10	12	14	16
Day	1	4	8	15	29	43	57	71	85	99	113
Group A (IFX-1 800 mg + RDGC)	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg
Group B (Placebo-IFX-1 + SDGC)	P	P	P	P	P	P	P	P	P	P	P
Group C (IFX-1 800 mg + Placebo-GC)	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg	800 mg

RDGC = reduced-dose glucocorticoids; P = infusion of placebo; SDGC = standard-dose glucocorticoids; V = scheduled visit for all subjects.

The IFX-IMP will be administered by the responsible personnel at the site as follows:

- The reconstituted IFX-IMP will be infused over a period of 30 to 60 min, as described in the Pharmacy Manual
- At the end of the infusion, the intravenous line will be briefly flushed with 10-15 mL of sterile sodium chloride to ensure that any IFX-IMP remaining in the intravenous line is administered.

Subjects should remain at the study site for at least 30 min after the end of the IFX-IMP administration. Appropriate treatment for potential infusion-related reactions must be available during this time.

Each administration of IFX-IMP will be recorded in detail in the source data and in the eCRF.

If the scheduled infusion cannot be administered at the scheduled time of infusion (also considering an acceptable time window of ± 1 day at the respective visit), then the medical monitor from the CRO should be contacted to decide on a case by case basis whether the infusion can be administered later or whether it should be omitted.

Further details on the IFX-IMP administration will be outlined in the Pharmacy Manual.

6.1.2 Description of Glucocorticoids and Placebo-Glucocorticoids (GC-IMP)

The replacement of steroid tapering is an essential part of the study design. For this purpose, prednisone, the GC used in this study, is considered as an IMP.

Prednisone is a synthetic derivative of cortisone with widespread effects on metabolism and organ function. Desirable effects in vasculitis relate to the suppression of acute and chronic inflammatory processes and immune cell function.

Commercially available prednisone tablets with a strength of 5 mg or 10 mg sourced from either the United States of America or countries in the European Union will be used. The exact composition of the active and inactive ingredients in the tablets will be provided in the Pharmacy Manual. Details are also provided in the ‘Study Drug Instructions for the Patient’ document that is issued to the subjects.

To maintain blinding, the prednisone tablets will be over-encapsulated in hard gelatin capsule shells. Different numbers and strengths of tablets per capsule will be combined to provide the different doses required. The capsules will also be filled with an inactive filling excipient (lactose). The amount of lactose per capsule will be less than 1 g. The appearance of the capsules will be identical for each dose.

Placebo-GC capsules will be filled only with lactose. Placebo-GC capsules will be identical in appearance to the corresponding GC capsules.

6.1.2.1 Packaging and Labeling of GC-IMP

GC and Placebo-GC capsules will be supplied as blister packs in wallets. Each wallet will contain 24 capsules to supply the medication required for 1 week, plus reserve capsules for 1 additional day. The subjects will take 3 capsules once per day (i.e., 3 capsules for each of the 7 days per week). An exception is Week 1, when subjects will take 6 capsules per day, and therefore 2 wallets will be provided for Week 1. In total, 8 different GC wallets and 1 Placebo-GC wallet will be provided to account for the different dosages needed for the tapering process (see Table 2).

Each wallet will be labeled in accordance with local legal requirements (a multilingual booklet label or a specific single panel label) and will indicate the number of capsules to be taken per day. The GC-IMP capsules, blister packs, and wallets will be identical in appearance to maintain the blind.

6.1.2.2 Shipment of GC-IMP

The GC-IMP will be supplied to study sites by the sponsor's designated CMO and must be shipped protected from light at a temperature of 15°C to 25°C. Each shipment will be controlled by a temperature logger, of which a read-out must be obtained by the site personnel upon receipt of the shipment.

The initial shipment of GC-IMP to the sites will be automatically triggered according to the settings in the IWRS. All subsequent shipments of GC-IMP will be initiated, maintained, and controlled by the IWRS. During all visits to the site, subjects will receive a sufficient number of blinded wallets to cover their requirements until the next visit.

The site personnel will be responsible for the correct receipt, storage, handling, and accountability of the GC-IMP at the study site. Further details regarding shipment, process for receipt, storage, and dispensing of the wallets to the subjects will be provided in the Pharmacy Manual. Subjects will receive "Study Drug Instructions for the Patient", providing details on the correct use of the wallets.

6.1.2.3 Storage of GC-IMP

The GC-IMP must be stored protected from light at 15°C to 25°C. All GC-IMP supplies must be stored separately from other study supplies and site stock, in a dedicated locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled and monitored and compliant with applicable regulatory requirements.

Detailed information about the storage after handout to the subjects will be provided in the "Study Drug Instructions for the Patient" provided to the subjects.

A validated temperature management system with temperature logs should be used to record the storage temperature at site. If this is not possible, the study site will be

provided with a temperature record form by the CRO and the site personnel will maintain temperature records for the duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported to the CMO as soon as possible. Further information on the management and reporting of temperature deviations is provided in the Pharmacy Manual.

6.1.2.4 Drug Accountability of GC-IMP

During the study, all GC-IMP will be reconciled against the current inventory and the dispensing records as a component of the monitoring visits.

To aid completion of drug accountability records, subjects must return all used and unused GC-IMP wallets to the site at the next visit.

The dates for issuing, administering, and returning the GC-IMP to the study site will be recorded and kept at the study site, and monitored throughout the study by the study monitor.

All returned used and unused GC-IMP wallets can be destroyed at the study site according to institutional policy and in compliance with the current applicable regulatory requirements or sent back to the CMO, in either case after the drug accountability has been assessed by the study monitor.

After completion of the study, certified copies of all GC-IMP accountability records will be provided to the CRO. Unused GC-IMP will either be returned to the CMO or destroyed at the study site according to institutional policy and in compliance with the current applicable regulatory requirements. The destruction of any unused GC-IMP at the study site must be documented on a form provided by the CRO. Further details on the monitoring procedures will be provided in the Clinical Monitoring Plan.

6.1.2.5 Administration of GC-IMP

GC-IMP will be administered once per day in the morning during the Treatment Period and up to Week 23 in the Follow-up Period. The GC tapering is an important part of the study design because it serves as an active control. An overview of the dosing schedule for the GC tapering in each treatment group is shown in Table 2.

Subjects randomized into Group B (Placebo-IFX-1 + SDGC) will start with a standard-dose of 60 mg GC daily and be tapered down as described in Table 2. On Day 1 of Week 0, subjects in Group A (IFX-1 + RDGC) will receive only half of the starting dose received by subjects in Group B (30 mg). In Group C all subjects will receive GC-IMP until Week 24.

The IWRS will ensure subjects are assigned with sufficient GC-IMP wallets containing capsules packaged in blister packs. Each wallet contains 24 capsules (GC and Placebo-

GC) in blister packs to supply the medication required for 1 week plus reserve medication for 1 additional day (i.e., 3 capsules x 8 days). An exception is Week 1, when subjects will take 6 capsules per day, and therefore 2 wallets will be provided for Week 1. Dosing details are provided in the Study Drug Instructions for the Patient document that is issued to the subjects.

Table 2 Dosing Schedule for Glucocorticoid Tapering (Daily Dose per Week)

Week	Number of Wallets per week	Group A: RDGC	Group B: SDGC	Group C: Placebo-GC
0	1	30 mg	60 mg	0 mg
1	2	20 mg	50 mg	0 mg
2, 3	1	15 mg	40 mg	0 mg
4, 5, 6, 7	1	10 mg	30 mg	0 mg
8, 9, 10, 11	1	5 mg	25 mg	0 mg
12, 13	1	5 mg	20 mg	0 mg
14, 15	1	0 mg	15 mg	0 mg
16, 17, 18, 19	1	0 mg	10 mg	0 mg
20, 21, 22, 23	1	0 mg	5 mg	0 mg
24	0	-	-	-

GC = glucocorticoids; RDGC = reduced-dose glucocorticoids; SDGC = standard-dose glucocorticoids.

To keep the blind and allow for GC tapering, all subjects will need to take GC-IMP capsules up to and including Week 23.

6.2 DETAILS OF THE AUXILIARY MEDICINAL PRODUCTS

An Auxiliary Medicinal Product (AxMP) is defined as immunosuppressive therapy administered during Remission-Induction Phase (RTX or CYC) or Remission-Maintenance Phase (RTX, CYC AZA, MTX, MMF, or MPS). AxMPs will not be supplied by the sponsor.

It is at the discretion of the investigator to choose an immunosuppressive therapy for the individual subject that theyconsider being most appropriate from a medical point of view, and also depending on international treatment guidelines [Merkel et al.,2017, Ntatsaki et al.,2014, Yates et al.,2016], the local Standard of Care, and/or guidelines at the study site. Furthermore, investigators must follow the current summaries of product characteristics and prescribe the administration and standard safety and laboratory procedures according to these summaries.

Further details and recommendations regarding immunosuppressive therapy administration will be provided in the separate "Recommendations for Standard of Care (SoC)" document.

If intravenous AxMP and IFX-IMP are administered on the same day, IFX-IMP is recommended to be administered before intravenous AxMP treatment.

Each administration of AxMP will be recorded in detail in the source data and in the eCRF.

6.2.1 Immunosuppressive Therapy During Remission-Induction Phase

6.2.1.1 Rituximab

RTX can be administered up to 2 weeks prior to screening and during the entire study. Administration of intravenous GCs as premedication for RTX is recommended (see also Section 7.4). Investigators must follow local guidelines and the current summaries of product characteristics and prescribe the administration and standard safety laboratory procedures accordingly.

6.2.1.2 Cyclophosphamide

CYC can be administered up to 2 weeks prior to screening and during the entire study. Investigators must follow local guidelines and the current summaries of product characteristics and prescribe the administration and standard safety lab procedures accordingly.

6.2.2 Immunosuppressive Therapy During Remission-Maintenance Phase

In the Remission-Maintenance Phase, all subjects will receive immunosuppressive therapy with either RTX or CYC, or subjects may be switched to immunosuppressive therapy with AZA, MTX, MMF, or MPS (following clinical remission and until Week 24) at the discretion of the investigator. Investigators should follow applicable treatment guidelines for AAV**.**

RTX has been shown to be effective and safe for use as maintenance therapy in AAV, both in recently diagnosed disease and in subjects with frequent relapses [Alba et al.,2016] Therefore, it is left to the investigator's discretion if RTX will be administered to subjects in the Remission-Maintenance Phase.

6.2.2.1 Azathioprine

Subjects may be switched from RTX or CYC to AZA, at the investigator's discretion, only during the Remission-Maintenance Phase.

6.2.2.2 Methotrexate

Subjects may be switched from RTX or CYC plus GCs to MTX, at the investigator's discretion, only during the Remission-Maintenance Phase.

6.2.2.3 Mycophenolate Mofetil and Mycophenolate Sodium

MMF and MPS are uncompetitive and reversible inhibitors of inosine monophosphate dehydrogenase. Subjects may be switched from RTX or CYC plus GCs to MMF or MPS at the investigator's discretion, only during the Remission-Maintenance Phase.

6.3 RANDOMIZATION AND BLINDING

Subjects will be assigned into treatment groups by means of a computer-generated randomization list implemented in the IWRS. At each study site, each new subject who qualifies for enrolment into the study according to the inclusion and exclusion criteria will be assigned a number in ascending order, beginning with the lowest number available at the study site.

Eligible subjects will be randomized to the treatment groups in each of the 2 Study Parts by means of a central IWRS. The IWRS will assign the appropriate IMPs to each subject. The CRO will supply the investigator with a user guide for the IWRS.

In Study Part 1, subjects will be randomized into Group A or B in a ratio of 1:1 stratified by diagnosis of AAV type (GPA or MPA).

In Study Part 2, subjects will be randomized into Group B or C in a ratio that yields about 9 subjects in Group B and about 16 subjects in Group C. Randomization will also be stratified by diagnosis of AAV type (GPA or MPA) as in Study Part 1.

There will be a recruitment stop after a maximum of 30 subjects have been enrolled in Study Part 1 for IDMC evaluation.

It is planned to randomize 55 subjects.

The double-blind will be maintained throughout the Treatment and Follow-up Period as applicable for all IMP administered or provided to the subjects, including the GC tapering process. Label, appearance, and handling of IMP will not compromise the blind.

Subject data for the IDMC will be handled and analyzed by an independent, unblinded statistician to maintain the blind for all site and sponsor personnel.

The randomization and blinding procedures are not applicable to the AxMP administered during the study.

Emergency Identification of Investigational Medicinal Product

Breaking of the treatment-assigned blind will be performed in the IWRS. Any premature breaking of the blind should be confined to emergency cases in which knowledge of the IMP received is necessary, e.g., to be able to provide appropriate emergency medical treatment. Whenever possible, the investigator should contact the medical monitor of the responsible CRO before breaking the blind, unless this would delay the emergency treatment. Subject safety must always be the primary consideration when determining whether to break the blind.

Investigators will be provided with the appropriate IWRS access to unblind the treatment assignment of an individual subject. Further information regarding randomization and assignment of IFX-IMP or GC-IMP to the individual visits will be provided in the Pharmacy Manual.

If a subject's treatment assignment is unblinded, the medical monitor will receive an alert from the IWRS. In addition, the investigator must inform the medical monitor within 24 hours of breaking the blind and the subject will be discontinued from further participation in the study. The date and reason why the blind was broken must be provided by the investigator and recorded in the source documentation and in the eCRF, as applicable.

7 PRIOR AND CONCOMITANT THERAPY

7.1 PRIOR THERAPY

All drugs taken by the subject within 3 months before enrolment into the study are regarded as prior therapy and must be documented as such in the source documentation and eCRF with details on the reason for use, date(s) of administration (with start and end dates), and dosing information, including dose, route, and frequency of administration.

Any AAV therapy that the subjects received 1 year prior to study enrolment will be documented in the source and in the eCRF by verbatim name with start and end dates.

7.2 CONCOMITANT THERAPY

All drugs currently being taken by a subject at enrolment into the study or after enrolment are regarded as concomitant therapy. All concomitant therapy must be documented in the source documentation and in the eCRF with details on the reason for use, administration start dates, and dosing information, including dose, route, and frequency of administration.

7.3 RECOMMENDED CONCOMITANT THERAPY

7.3.1 Pneumocystis Carinii Pneumonia (PCP) Prophylaxis

Participants treated with RTX or CYC should receive PCP prophylaxis during RTX or CYC and GC administration. For details, refer to the current SmPCs and relevant guidance documents (e.g. Park et al., 2018; Yates et al., 2016).

7.3.2 Osteoporosis Prophylaxis

Treatment measures to prevent osteoporosis should be administered at the discretion of the investigator.

7.4 PERMITTED GLUCOCORTICOID THERAPY

Inhaled and topical GCs can be used for subjects diagnosed with diseases other than AAV (for example: eczema, asthma, chronic obstructive pulmonary disease, eosinophilic esophagitis), or for subjects with large airway involvement of GPA as documented by bronchoscopy. All use of topical or inhaled GCs must be documented accurately in the source documentation and in the concomitant medication section of the eCRF.

Up to 80 mg daily dose of oral GCs (prednisone-equivalent) are allowed to be administered within two weeks prior to screening (see exclusion criterion 12b) and during screening. The dose should be tapered down to 0 mg/day as fast as possible but

the 0 mg/day dose must be achieved 4 weeks after start of IMP treatment (Day 1/Visit 2) at the latest.

Up to 3 g of intravenous GCs are allowed to be administered within 4 weeks prior to screening (see exclusion criterion 11) and during screening as maximum cumulative dose.

Intravenous GCs as premedication for RTX administration are permitted and are not included in the maximum cumulative dose of 3 g intravenous GCs.

If subjects have been on chronic treatment with oral GCs (prednisone-equivalent) at a dose of 10 mg/day or less at Screening, and are not given higher doses of non-study GCs, this dose should be tapered to 0 mg/day by 4 weeks after start of IMP treatment at Day 1/Visit 2. If the investigator feels it is necessary to continue low-dose daily GCs beyond this date to avoid adrenal insufficiency, then the investigator should discuss this situation with the medical monitor.

7.5 RESCUE THERAPY

The rescue therapy will not be provided by the sponsor. The administration or the receipt of rescue therapy for lack of efficacy or major or minor relapses do not necessarily discontinue the subject from further IMP administration or from study participation.

If the investigator unblinds the subject to allow for an appropriate treatment (see Section 6.3, Emergency Identification of Investigational Medicinal Product), the subject must be discontinued from further study participation. Whenever possible, the investigator should contact the medical monitor before breaking the blind.

Lack of efficacy

In case of lack of efficacy (for example: no improvement or deterioration in the BVASv3 or lack of efficacy according to the clinical judgement of the investigator), it is at the discretion of the investigator to administer rescue medication, to keep the subject in the study and continue with IMP (IFX-IMP and GC-IMP) administrations, AxMP intake and study procedures/assessments as scheduled, to discontinue IMPs (IFX-IMP and GC-IMP), or to withdraw the subject from further study participation (refer also to Section 5.4.1).

Major Relapse

A major relapse is defined as having a BVASv3 > 3 minor items or experiencing 1 of the major BVASv3 items listed in Appendix 18.3 after clinical remission (BVASv3 = 0). Up to 1 g/day of intravenous methylprednisolone or the equivalent dose of other intravenous GCs can be given. Depending on the severity of a participant’s presenting

symptoms, as well as the clinical picture, the investigator will be allowed to prescribe intravenous GC to a maximum of 3 g of methylprednisolone, or to an equivalent dose of other intravenous GCs, over 3 days. Subjects experiencing a major relapse can also receive up to 20 mg/day of oral GCs (prednisone-equivalent) in addition to the study-defined dose of GC-IMP for a maximum of 14 days at the discretion of the investigator.

The investigator, at their discretion, can decide if subjects with a major relapse:

i. can remain in the study and continue with further IMP (IFX-IMP and GC-IMP) administrations, AxMP intake, and study procedures/assessments as scheduled;

   OR

ii. can remain in the study but should discontinue IMPs (always both, IFX-IMP and GC-IMP), and continue with AxMP intake and study procedures/assessments as scheduled;

   OR

iii. should be withdrawn from the study (refer also to Sections 5.4 and 5.4.3). If the investigator considers that the relapse requires the early discontinuation or unblinding of the subject, they should contact the medical advisor of the sponsor's designated CRO or the sponsor to allow for case by case discussions before the subject may be withdrawn from the study.

At the time a major relapse is suspected by the subject, they have to visit the study center for an unscheduled visit (USV) (see Sections 8.5 and 1. Schedule of Assessments).

If withdrawal from the study occurs up to and including Week 16 due to a major relapse, the EOS visit (Visit 14) assessments and a safety follow-up visit (see Section 8.4) 1 month (±3 days) after the last IMP administration must be performed.

Minor Relapse

A minor relapse is defined as experiencing 1, 2, or 3 minor items as defined for the BVASv3 (BVASv3 = 1, 2, 3, see Appendix 18.2) after clinical remission (BVASv3 = 0) in the study. Subjects experiencing a minor relapse can receive up to 20 mg/day of oral GCs (prednisone-equivalent) in addition to the study-defined dose of GC-IMP for a maximum of 14 days at the discretion of the investigator.

The investigator, at their discretion, can decide if subjects with a minor relapse:

i. can remain in the study and continue with further IMP (IFX-IMP and GC-IMP) administrations, AxMP intake, and study procedures/assessments as scheduled;

   OR

ii. can remain in the study but should discontinue IMPs (always both, IFX-IMP and GC-IMP), and continue with AxMP intake and study procedures/assessments as scheduled;

OR

iii. should be withdrawn from the study (refer also to Sections 5.4 and 5.4.3). ~~and~~ If the investigator considers that the relapse requires the withdrawal or unblinding of the subject, they should contact the medical advisor of the sponsor's designated CRO or the sponsor to allow for case by case discussions before the subject may be withdrawn from the study.

At the time a minor relapse is suspected by the subject, they have to visit the study center for an USV (see Sections 8.5 and 1. Schedule of Assessments).

If withdrawal from the study occurs up to and including Week 16 due to a minor relapse, the EOS visit (Visit 14) assessments and a safety follow-up visit (see Section 8.4) 1 month(±3 days) after the last IMP administration must be performed .

7.6 PROHIBITED THERAPY DURING THE STUDY

The following therapies are prohibited for all subjects during the study:

- Tumor necrosis factor inhibitor treatment (e.g., etanercept)
- Anti-CD20 therapies other than RTX
- Abatacept
- Alemtuzumab
- Any other experimental or biologic therapies
- Intravenous, intramuscular, or sub-cutaneous immunoglobin
- Plasma exchange
- Antithymocyte globulin
- Live vaccines
- Renal dialysis
- Any other oral or intravenous GCs (than defined by the protocol).

If administration of any prohibited concomitant therapy becomes necessary during the study for medical reasons that in the investigator's or sponsor's opinion necessitates the subject being removed, the subject must be withdrawn from further study participation.

The investigator should contact the medical advisor of the sponsor's designated CRO or the sponsor if there are any questions regarding prior or concomitant therapy, and case by case discussions are recommended.

7.7 CONTRACEPTION IN WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential must use highly effective methods for contraception (pearl index < 1), which are the following:

- "Combined" (that is oestrogen and progesterone containing with oral, intravaginal or transdermal administration)
- Or "progesteron-only" (with oral, injectable, or implantable formulation) hormonal contraceptives
- Complete sexual abstinence
- Intrauterine device /Intrauterine system
- Bilateral tubal occlusion
- Vasectomized partner.

Contraception methods with a low user dependence (intrauterine device, intrauterine system, bilateral tubal occlusion, vasectomized partner, should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments: from screening up to the very last pregnancy test (3 months after the last IFX-1 /Placebo-IFX-1 administration).

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are **not** acceptable methods of contraception.

Based on the half-life of IFX-1, the duration of contraception in women of childbearing potential should last 3 months after the last IFX-1/Placebo-IFX-1 administration. As the choice of the standard of care is at the discretion of the investigator, further contraception periods should be taken into consideration by following the corresponding SmPC.

As outlined in the Schedule of Assessments and Section 8, pregnancy tests in women of childbearing potential will be performed at screening, Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24 and at SFU.

7.8 CONTRACEPTION FOR MALES WITH FEMALE PARTNERS OF CHILDBEARING POTENTIAL

Males subjects with female partners of childbearing potential must use condoms as a contraception method during the study.

8 STUDY PROCEDURES AND VISIT SCHEDULE

The following sections describe all study assessments and procedures that will be performed at screening, in the Treatment- and Follow-up Period.

The visit schedule is applicable to all subjects in Group A, B and C.

An overview of the visit schedule is available in the Schedule of Assessments.

8.1 SCREENING

Screening is the predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for enrolment into the study.

The screening procedures will be conducted between Day -14 and Day -1 before the first administration of IMP. However, the screening period should be as short as possible to allow for the enrollment of severely ill subjects.

The investigator may pre-screen subjects for study inclusion and exclusion criteria without first obtaining written informed consent for participation in the current study on the basis of 1 or both of the following situations:

- Pre-existing data (e.g., for study inclusion and exclusion criteria, as available in medical records held by the investigator)
- Initial contact (e.g., routine visit, phone call) where only routine and/or non-study-specific questions are allowed.

After subjects have provided written informed consent, potentially eligible subjects will be assessed at the screening visit to determine if all inclusion criteria and no exclusion criteria are met. All subjects must provide written informed consent before any study-specific assessments or procedures are performed. The following procedures will be conducted and documented at the screening visit:

- Initiate and complete informed consent procedure and document process
- Check all inclusion and exclusion criteria (see Sections 5.2 and 5.3)
- Serum pregnancy test, required for all women of childbearing potential
- Vital signs (systolic and diastolic blood pressure, pulse rate (after 5 minutes in a sitting position), respiratory rate, body temperature)
- Serum sample for total protein
- Blood sample for analysis of safety laboratory parameters
- Blood sample for serological testing for HIV, HBV, and HCV, if no test results for HIV, HBV, and HCV available from within 4 weeks before screening
- Document medical history prior to screening (Section 9.1.3)
- Record prior medication or therapy (Section 7)

- Demographics and baseline characteristics (age, gender, race and ethnicity, body weight, height)
- GPA/MPA medical history
- [redacted]
- Blood sample for anti-glomerular basement membrane (GBM) assessment
- 12-lead ECG
- Physical examination
- BVASv3 assessment
- Urine samples for analyses of creatinine, total protein, microalbumin, [redacted], and monocyte chemoattractant protein (MCP)-1
- Documentation of AEs.

Analyses for laboratory assessments at screening relevant for the inclusion of a subject, i.e. serum pregnancy test, safety laboratory measurements including serum total protein, serology, and urinalysis, can be done either in a local laboratory or the central laboratory. If screening testing is done in a local laboratory, no respective blood samples are shipped to the central laboratory. [redacted]

If the subject fulfils all the inclusion criteria, does not meet any of the exclusion criteria, and written informed consent is available, the subject will be randomized into one of the treatment groups. Randomization will be performed during the Screening Period, it must be done at Day 1 (Visit 2) at the latest, and prior to Day 1 specific assessments.

All randomized subjects will be issued with a subject card with relevant contact details, including emergency contact details. Subjects will be instructed on the completion of the PROs by the investigator at screening. If the subject meets an exclusion criterion or another reason for non-inclusion in the study is given after obtaining informed consent, the subject will not be randomized into any of the treatment groups and will be deemed a screen failure.

8.2 TREATMENT PERIOD

The Treatment Period will comprise Visits 2 to 12 (Weeks 0 to 16). All visits will have an accepted time window of ±1 day. Subjects will be provided with the GC wallets to comply with the GC dosing schedule (Table 2).

Before administration of IFX-IMP, the following assessments and procedures will be performed at the visits to the study site, as indicated:

- Documentation of PROs:
    - 36-item Short Form survey version 2 (SF-36v2) (*Weeks 0 [Day 1], 4, 8, 12, and 16*)

  - EuroQol-5 Dimensions 5-Levels survey (EQ-5D-5L) (*Weeks 0 [Day 1], 4, 8, 12, and 16*)

- Urine pregnancy test (dipstick), required for all women of childbearing potential (*Weeks 0 [Day 1], 4, 8, 12, and 16*)
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature) (*Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16*)
- Serum sample for total protein (*Weeks 0 [Day 1] 1, 2, 4, 8, 12, 16*)
- Blood sample for analysis of safety laboratory parameters (*Weeks 0 [Day 1], 4, 8, 12, 16*)
- Documentation of body weight (*Weeks 0 [Day 1], 4, 8, 12, 16*)
- [redacted] (*Weeks 2, 4, 8, 12, 16*)
- ECG (*Week 16*)
- Physical examination (*Week 16*)
- Glucocorticoid toxicity index (GTI) assessment (*Weeks 0 [Day 1], 16*)
- BVASv3 assessment (*Weeks 0 [Day 1], 4, 8, 12, 16*)
- Vasculitis Damage Index (VDI) assessment (*Weeks 0 [Day 1], 16*)
- Physician Global Assessment (PGA) assessment (*Weeks 0 [Day 1], 4, 8, 12, 16*)
- Urine samples for analyses of creatinine, total protein, microalbumin, [redacted] and MCP-1 (*Weeks 0 [Day 1], 1, 2, 4, 8, 12, 16*)
- [redacted] sample for analysis of:
  - IFX-1 level (*Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16*)
  - IFX-1 blocking activity (*Weeks 2 and 16*)
  - C5a (*Weeks 0 [Days 1 and 4], 1, 2, 4, 8, 12, 16*)
- [redacted] sample for analysis of:
  - [redacted] (*Weeks 0 [Days 1 and 4], 1, 2, 4, 8, 12, 16*)
- [redacted] sample for analysis of:
  - 50% hemolytic complement (CH50) (*Weeks 0 [Day 1], 1, 2, 4, 8, 12, 16*)
  - C-reactive protein (CRP) (*Weeks 0 [Day 1],1, 2, 4, 8, 12, 16*)
  - [redacted] (*Weeks 0 [Day 1], 4, 8, 12, 16*)
  - Anti-drug antibodies (ADAs) (*Weeks 0 [Day 1], 2, 4, 8, 12, 16*)
- Additional blood samples for further research, [redacted] (*Weeks 0 [Day 1], 4, 8, 12, 16*)
- Documentation of AEs (*Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16*)
- Documentation of concomitant therapy (*Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16*).

After the assessments and procedures listed above have been completed:

- Administration of IFX-IMP according to the dosing schedules shown in Table 1 (*Weeks 0 [Days 1 and 4], 1, 2, 4, 6, 8, 10, 12, 14, 16*).

After administration of IFX-IMP:

- [redacted] sample for analysis of IFX-1 peak levels, to be taken within 10 min after end of IFX-IMP administration ncluding brief flushing)[redacted] These samples must be taken from a vein, from a different sampling site to the IFX-IMP infusion, such as the other arm.

During the Treatment Period, subjects will take GC-IMP and AxMP as indicated in the Schedule of Assessments and Sections 6.1.2and 6.2.

For subjects who discontinue the study early during the Treatment Period (i.e., up to and including Week 16), all assessments scheduled for the EOS visit (Visit 14) should be performed. A safety follow-up visit will occur 1 month (±3 days) after the last IMP administration. For further details see Section 5.4.

8.3 FOLLOW-UP PERIOD

The Follow-up Period will run from after the IFX-IMP administration at Week 16, to Week 24 and it will include Visits 13 and 14 (EOS visit). All visits will have an accepted time window of ±3 days. Subjects will be provided with the GC wallets to comply with the GC dosing schedule (Table 2). The following assessments and procedures will be performed at the visits to the study site, as indicated:

- Continue documentation of PROs:
    - SF-36v2 (*Weeks 20 and 24*)
    - EQ-5D-5L (*Weeks 20 and 24*)
- Urine pregnancy test (*Week 20*) and serum pregnancy test (*Week 24*), required for all women of childbearing potential
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature) (*Weeks 20 and 24*)
- Serum sample for total protein (*Weeks 20 and 24*)
- Blood sample for analysis of safety laboratory parameters (*Weeks 20 and 24*)
- Documentation of body weight (*Weeks 20 and 24*)
- [redacted](*Week 24*)
- ECG (*Week 24*)
- Physical examination (*Week 24*)
- GTI assessment (*Week 24*)
- BVASv3 assessment (*Weeks 20 and 24*)

- VDI assessment (*Week 24*)
- PGA assessment (*Weeks 20 and 24*)
- Urine samples for analyses of creatinine, total protein, microalbumin, [redacted] and MCP-1, blood sample for analysis of serum protein (*Weeks 20 and 24*)
- [redacted] sample for analysis of:
    - IFX-1 level (*Weeks 20 and 24*)
    - IFX-1 blocking activity (*Weeks 20 and 24*)
    - C5a (*Weeks 20 and 24*)
- [redacted] sample for analysis of:
    - [redacted] (*Weeks 20 and 24*)
- [redacted] sample for analysis of:
    - CH50 (*Weeks 20 and 24*)
    - CRP (*Weeks 20 and 24*)
    - [redacted] (*Weeks 20 and 24*)
    - ADAs (*Weeks 20 and 24*)
- Additional blood samples for further research, [redacted] (*Weeks 20 and 24*)
- Documentation of AEs (*Weeks 20 and, 24*)
- Documentation of concomitant therapy (*Weeks 20 and 24*).

During the Follow-up Period, subjects will receive AxMP and GC-IMP as indicated in the Schedule of Assessments, Sections 6.2.2 and 6.1.2, and Table 2.

For subjects who discontinue the study early during the follow-up period (i.e., up to and including Week 24), all assessments scheduled for the EOS visit (Visit 14) should be performed.

8.4 SAFETY FOLLOW-UP VISIT

For subjects who discontinue the study during the Treatment Period (i.e., up to and including Week 16), a safety follow-up visit will occur 1 month (±3 days) after the last IMP administration. For further details see Section 5.4.

The following assessments and procedures will be performed at the study site as indicated:

- Documentation of PROs:
    - 36-item Short Form survey version 2 (SF-36v2) (Weeks 0 [Day 1], 4, 8, 12, and 16)

    - EuroQol-5 Dimensions 5-Levels survey (EQ-5D-5L) (Weeks 0 [Day 1], 4, 8, 12, and 16)
- Serum pregnancy test, required for all women of childbearing potential
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature)
- Serum sample for total protein
- Blood sample for analysis of safety laboratory parameters
- Documentation of body weight
- [redacted]
- ECG
- Physical examination
- GTI assessment
- Urine samples for analyses of creatinine, total protein, microalbumin, [redacted] and MCP-1
- Conclude documentation of AEs
- Conclude documentation of concomitant therapy.

8.5 UNSCHEDULED VISIT

An USV will be arranged for subjects with suspect of a major or minor relapse.

The following assessments and procedures will be performed during the USV to evaluate whether there is major or minor relapse:

- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature)
- Physical examination
- Documentation of body weight
- Serum sample for total protein
- Blood sample for analysis of safety laboratory parameters
- BVASv3 assessment
- VDI assessment
- PGA assessment
- GTI assessment
- Urine samples for analyses of creatinine, total protein, albumin, [redacted] MCP-1; blood sample for analysis of serum protein
- Documentation of AEs

- Documentation of concomitant medication.

If subject with suspect of minor or major relapse will visit the study center at a scheduled visit, the assessments and procedures of this respective scheduled visit have to be performed.

9 STUDY VARIABLES AND ASSESSMENT METHODS

9.1 STUDY SUBJECTS

9.1.1 Demographics and Baseline Characteristics

The following demographic data and baseline characteristics will be documented at screening:

- Age
- Gender
- Race
- Body weight
- Height.

9.1.2 GPA/MPA Medical History

Widely accepted diagnostic criteria, as opposed to classification criteria or definitions, have not yet been developed for GPA and MPA. In 1994, the CHCC developed definitions for these vasculitides and some of their mimickers with a revision issued in 2013 [Jennette et al.,2013]. These definitions are useful in formulating the diagnostic criteria that will be applied to determine a subject's eligibility for this study (see Appendix 18.1) [Fries et al.,1990].

The GPA/MPA medical history will be documented in terms of:

- Date of GPA/MPA diagnosis
- Positive antigen-specific ANCA titer prior to screening (including the type and last date of positive ANCA lab test result) or documented evidence for antibodies to proteinase 3 or antibodies to myeloperoxidase
- Number of major relapses since diagnosis
- Date of most recent major relapse
- Family history of GPA/MPA (first degree family pedigree).

9.1.3 Medical History

Medical history for the 12 months prior to screening will be obtained from each subject at screening.

9.1.4 Prior and Concomitant Therapy

All prior and concomitant therapy will be documented, as described in Section 7.

9.2 EFFICACY

9.2.1 Efficacy Variables

Efficacy will be assessed on the basis of the following variables:

- BVASv3
- VDI
- PGA
- SF-36v2
- EQ-5D-5L
- Renal variables including eGFR and all ratios (urinary MCP-1:creatinine; urinary albumin:creatinine ratio)
- [redacted]

9.2.2 Methods of Assessing Efficacy Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.2.2.1 Birmingham Vasculitis Activity Score Version 3.0

The BVASv3 is a validated instrument for the assessment of disease activity and response to treatment in AAV [Mukhtyar et al.,2009].

The BVASv3 form is a list of 56 items with a numerical weight attached to each item, and each organ system has a ceiling score. The form is divided into 9 organ-based systems (i.e., general symptoms such as arthralgia, arthritis, and fever, plus involvement of 8 major organ systems), with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis (Appendix 18.2). The ceiling scores reflect the proportional importance of each manifestation and each organ system. Completion of the form provides a numerical score by using the Glossary and Scoring for the BVASv3 (Appendix 18.3). Scoring ranges are higher when any of the features are new or worse. Creatinine levels can be scored at a subject's first assessment only. Higher scores indicate more severe disease.

To standardize the BVASv3 assessment in this study, the same investigator should score the subject at all visits, if possible.

In order to use and score the form properly, all investigators performing the BVASv3 assessment must be certified. Training and specific instructions on the use of BVASv3 for this study will be provided to sites.

9.2.2.2 Vasculitis Damage Index

The VDI will be used to assess damage induced by GPA or MPA and by the treatment applied during this study. The VDI is a validated assessment tool divided into 11 organ systems. The scoring sheet is divided into 10 systems plus an 11th section for other items, mainly related to the effects of drugs. The VDI is used to record any condition that has occurred and lasted for at least 3 months since the start of vasculitis and refers to chronic damage whether or not it is related to vasculitis. It consists of 64 items selected by expert consensus as representative of the forms of damage developed by subjects with systemic vasculitis [Exley et al.,1997]. Completion of the form provides a numerical score by summation of each damage (Appendix 18.5). Each item scores 1 point.

Three scores will be calculated for each subject:

- Total VDI score: the total number of items will be counted leading to a minimum score of 0 and a maximum score of 64
- System score: the extent of disease defined by the number of separate systems with at least 1 item score
- Critical damage score: the number of items of damage consistent with organ failure (as defined in the glossary).

To standardize the VDI assessment in this study, the same investigator should score the subject at all visits, if possible.

In order to use and score the form properly, all investigators performing the VDI scoring must be certified.

9.2.2.3 Physician Global Assessment

The PGA scale is an 11-point scale to record the assessment of the overall disease activity of GPA or MPA (not including longstanding damage) within the previous 28 days [Stone et al.,2001]. The rating ranges from 0 (remission) to 10 (maximum activity) (Appendix 18.7).

If possible, the same investigator should score the subject at all visits and when completing this assessment, the investigator should not be influenced by the presence of any accumulated damage, complication of treatment, social/emotional problems, or other issues not related to active GPA or MPA.

9.2.2.4 36-Item Short Form Survey Version 2

The SF-36v2 is a subject-reported generic measurement of health status that has proven useful in studies of both general and specific populations, comparing the relative burden of diseases and the health benefits produced by different treatments [Ware et al.,1998]. Inclusion of the SF-36 has become standard practice for almost all clinical studies and

observational studies for most rheumatic diseases, including vasculitis [Merkel et al.,2011].

The SF-36v2 consists of 36 questions from the following 8 domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Appendix 18.8).

Each domain is directly transformed into a scale from 0 to 100 on the assumption that each question carries equal weight. A lower score indicates a poorer health status; a higher score indicates a better health status (i.e., a score of zero is equal to maximum disability and a score of 100 is equal to no disability). The 8 domains are summarized to form 2 distinct higher-ordered clusters (physical health and mental health).

A paper version of the questionnaire will be provided and thoroughly explained to the subjects during their visits to the study site. To avoid bias in the subject's response, the subject has to complete the questionnaire at the study site before the study site personnel performs any other assessments.

The study site personnel will be responsible to enter the data from the completed SF--36v2 questionnaire into the eCRF in a timely manner; the original paper questionnaires will then be filed in the study records.

9.2.2.5 EuroQol-5L Dimensions Survey

The EQ-5D-5L is a standardized subject-reported measure of health status in terms of quality of life parameters, such as the subject's mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are 5 categorical response choices for each of the 5 measures. In addition, subjects are asked to indicate "the state of your health today" on a visual analog scale of 0 to 100 (0 = worst imaginable health state, 100 = best imaginable health state) [Rabin et al.,2001].

The EQ-5D-5L relates to the respondent's situation at the time the assessment is completed, therefore the subject does not need to recall their health status over the preceding days or weeks (Appendix 18.9).

A paper version of the questionnaire will be provided and thoroughly explained to the subjects during their visits at the study site. To avoid biasing the subject's response, the subject has to complete the questionnaire at the study site before study site personnel performs any other assessments.

The study site personnel will be responsible to enter the data from the completed EQ-5D-5L questionnaire into the eCRF in a timely manner; the original paper questionnaires will then be filed in the study records.

9.2.2.6 Urinalysis and Renal Variables

Renal variables will be analyzed for both safety and efficacy and will be used to adapt the different therapies during the course of the study.

The renal variables to be analyzed in this study are listed in Table 3.

Table 3 Renal Variables

Variable	Urine	Serum	Calculation	Laboratory*
Creatinine	X	X		Central
Total protein	X			Central
Microalbumin	X			Central
MCP-1	X			Central
[redacted]	[redacted]			[redacted]
Urinary MCP-1: creatinine ratio			X	
UACR			X	
eGFR			X	

*For screening assessment only, local or central laboratory can be used.
eGFR = estimated glomerular filtration rate; MCP-1 = monocyte chemoattractant protein-1;
UACR = urinary albumin:creatinine ratio

Instructions regarding the collection, processing, and shipping of samples for analysis of laboratory parameters (i.e., urinary and serum creatinine, [redacted] and urinary MCP-1) will be available in the Laboratory Manual provided by the responsible CRO. All samples will be analyzed in a central laboratory, or a local laboratory for screening assessments only, as indicated in Table 3 using validated assays.

All derived ratios and the eGFR will be calculated at the time points when the respective single serum or urinary parameters are planned to be assessed.

The eGFR will be calculated by the central laboratory according to the Modified Diet in Renal Disease equation:

$$eGFR = 175 \times (\text{serum creatinine, mg/dL})^{-1.154} \times (\text{age, years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$$ [Levey et al.,1999].

[redacted]

[redacted]

9.3 SAFETY

9.3.1 Safety Variables

Safety will be assessed based on the following variables:

- AEs
- GTI
- Physical examination
- Vital signs
- ECG
- Laboratory safety parameters
- Pregnancy test
- Serology: HIV-1, HIV-2, hepatitis B, and hepatitis C status at screening
- ADA status.

9.3.2 Methods of Assessing Safety Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.3.2.1 Adverse Events

The incidence, severity, and causality of AEs will be assessed at every visit from signature of the informed consent form at screening to the subject's last evaluation according to the procedures described in Section 10.

9.3.2.2 Glucocorticoid Toxicity Index

The GTI measures the change in glucocorticoid toxicity over time and has 2 components: the composite GTI and a specific list. In a first evaluation, excellent reliability and validity was shown [Miloslavsky et al.,2017]. The composite GTI serves as the primary instrument and is intended to capture common toxicities that are sensitive to differing cumulative GC doses over the period of a typical clinical study. Nine domains and 31 items are in the composite GTI and 11 domains and 23 items are included in the specific list. When a specific list item occurs, the most severe corresponding item in the composite GTI should also be scored (see Appendix 18.6).

The specific list items will be assessed at Day 1, Weeks 16, and 24. The composite GTI should be scored at least 2 times in this study (in Weeks 16 and 24), since it measures changes in GC toxicity. For the comparison of composite GTI domains with quantitative laboratory values to Day 1 (baseline), those laboratory values must be analysed at Day 1 as indicated in the Schedule of Assessment. The laboratory assessments required for this index are part of the safety laboratory variables. The bone domain is excluded since the study is shorter than 1 year in duration. Therefore, the total score can range from 35 to 410. Higher scores indicate greater GC toxicity, negative scores demonstrate improvement in GC toxicity. Further information will be provided in a specific manual.

9.3.2.3 Physical Examinations

Physical examination findings that are related to the medical history will be recorded in the source documentation and in the eCRF.

Any abnormality noted after the informed consent had been signed by the subject will be evaluated by the investigator for whether it constitutes an AE.

9.3.2.4 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate (after 5 min in a sitting position), respiratory rate, and body temperature will be obtained at each visit. Body weight will be recorded as specified in the Schedule of Assessments. Blood pressure and pulse rate should be measured before blood samples are taken.

9.3.2.5 Electrocardiogram

12-lead ECGs will be performed.

An appropriately certified physician will interpret, sign, and date each ECG. Results will be recorded in the source documentation and in the eCRF.

9.3.2.6 Safety Laboratory

Blood samples for safety laboratory analysis should be obtained after the subjects have provided responses to questionnaires and after vital signs assessments have been performed, but before administration of IFX-IMP.

Analyses will be conducted by a certified central laboratory, or a local laboratory for screening assessments only.

Instructions regarding the collection, processing, and shipping of samples for the analysis of laboratory safety parameters will be available in the Laboratory Manual provided by the responsible CRO. Instructions for urine pregnancy testing are also provided in the Laboratory Manual.

The following parameters will be assessed using standard validated methods:

Clinical chemistry:	serum creatinine, urea, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, total bilirubin, lactate dehydrogenase, alkaline phosphatase, sodium, potassium, calcium, total protein, and albumin
Hematology:	red blood cells (erythrocytes), platelets, hemoglobin, white blood cells (including differential blood count), and complete blood count
Coagulation:	partial thromboplastin time and international normalized rate
For GTI only:	glycosylated hemoglobin and low density lipoprotein

All abnormal laboratory values will require a comment in the eCRF according to the following classification:

- Not clinically significant
- Clinically significant
- Error (e.g., laboratory error, improper sample preparation, hemolysis, or delayed transit to laboratory).

At screening, any laboratory value that deviates from the reference range and is considered by the investigator to be clinically significant or considered to be a result of a disease noted in the medical history, must be documented on the medical history page of the eCRF. Any deviation from the reference range considered by the investigator as clinically significant at any later visit must be documented in the eCRF as an AE if not previously documented as an ongoing medical condition or as an ongoing AE. Follow-up laboratory investigations due to an AE will be performed at a local laboratory at the discretion of the investigator.

9.3.2.7 Pregnancy Test

Pregnancy testing will be conducted in all women of childbearing potential. A woman is considered to be of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

The pregnancy test is to be performed in serum at screening and in urine (using a dipstick) at the other visits indicated in the Schedule of Assessments.

If any pregnancy test is positive, the subject will not be eligible for participation, randomization, or continuation in the study.

Lactating women will not be eligible for participation or continuation in the study. Further detailed instructions will be provided in the Laboratory Manual provided by the responsible CRO.

9.3.2.8 Human Immunodeficiency Virus and Hepatitis Virus Testing

Analyses for HIV-1 and 2, HBV andHCV will be conducted at screening, if no corresponding historical test results from within 4 weeks before screening are available.

Analyses for HIV-1 and 2 antibodies will be conducted by the central laboratory or a local laboratory according to its standard testing. Subjects will not be eligible for participation in the study if they test positive for HIV infection.

Analyses for the presence of a hepatitis B infection will be conducted by the central laboratory using a hepatitis B DNA polymerase chain reaction test or a local laboratory according to its standard testing. If the result meets or exceeds detection sensitivity, the subjects will be excluded from participation in the study.

Analyses for the presence of anti-hepatitis C antibodies in serum will be conducted by a central laboratory via chemiluminescence or a local laboratory according to its standard testing.

Detailed instructions regarding collection, processing and shipment of samples will be provided in the Laboratory Manual provided by the responsible CRO.

9.3.2.9 Anti-Glomerular Basement Membrane Disease Assessment

Blood samples taken at screening will additionally be measured for anti-GBM using an immunoassay to assess the anti-GBM status.

Detailed instructions regarding the collection, processing, etc., of samples will be given in the Laboratory Manual provided by the responsible CRO.

9.3.2.10 Anti-Drug Antibodies

ADAs will be measured in serum samples at a specialized laboratory [redacted] Samples that are confirmed as ADA-positive will be semi-quantified by titration. [redacted]

Detailed instructions regarding the collection, processing, etc., of samples will be included in the Laboratory Manual provided by the responsible CRO.

At each sampling time point an additional serum retention sample will also be collected for possible future analysis.

9.4 PHARMACOKINETICS, PHARMACODYNAMICS, AND BIOMARKERS

9.4.1 Variables

PK will be assessed by measuring the IFX-1 concentration [redacted]

PD will be assessed by measuring: C5a and IFX-1 blocking activity (Table 4).

Biomarkers will be assessed by measuring: [redacted] CH50, CRP, and [redacted] (Table 5).

9.4.2 Methods of Assessing Variables

All assessments will be performed at the time points specified in the Schedule of Assessments.

9.4.2.1 Pharmacokinetics

IFX-1 concentrations will be measured for all subjects [redacted]

Detailed instructions regarding the collection, processing, etc., of samples will be provided in the Laboratory Manual provided by the responsible CRO.

9.4.2.2 Pharmacodynamics

Instructions regarding the collection, processing, and shipment of samples to the central laboratory will be available in the laboratory manual provided by responsible CRO. Central laboratory will further transfer samples to specialized laboratory for analysis.

Table 4 Pharmacodynamic Variables

Variable	[redacted]	Laboratory
C5a	[redacted]	Specialized
IFX-1 blocking activity	[redacted]	Specialized

9.4.2.3 Biomarkers

Instructions regarding the collection, processing, and shipping of samples to the central or specialized laboratory will be available in the Laboratory Manual provided by the responsible CRO.

Table 5 Biomarker Variables

Variable	Matrix	Laboratory
[redacted]	[redacted]	[redacted]
CH50	Serum	Central
CRP	Serum	Central
[redacted]	[redacted]	Central

[redacted] CH50 = 50% hemolytic complement; CRP = C-reactive protein

9.4.2.4 Samples for Future Research

Additional blood samples for [redacted] preparation will be taken to allow future research on certain parameters.

[redacted]

10 ADVERSE EVENT REPORTING

10.1 ADVERSE EVENTS

10.1.1 Definition

An AE is any untoward medical occurrence in a subject administered an IMP; an AE does not necessarily have to have a causal relationship with the treatment.

AEs encompass any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that arises or worsens after the inclusion of the subject into the study.

"Lack of efficacy" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE.

AEs may include:

- The significant worsening of the disease or symptoms of the disease under investigation following administration of an IMP
- Illnesses that coincide with an onset after administration of an IMP
- Exacerbation (i.e., increase in frequency or severity) of a pre-existing condition. Chronic illnesses present prior to study entry, other than the indication being investigated, should be recorded in the medical history page of the eCRF and only be reported as AEs if there is an increase in the frequency or severity of the condition during the study
- For laboratory safety parameters, any absolute values outside of the reference range or changes after initial administration of the IMP that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs if not previously documented as ongoing medical conditions or as ongoing AEs. Examples of laboratory abnormalities that should be considered as AEs include those that result in discontinuation of treatment with the IMP, withholding treatment with the IMP pending some investigational outcome, reduction of IMP dose, or additional concomitant therapy
- Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at baseline (unless considered as clinically significant)
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g., hemolysis) and flagged as such by the laboratory in the laboratory report

- Abnormal parameters that are obviously biologically implausible (e.g., values that are incompatible with life)
- An abnormal laboratory value that cannot be confirmed after repeated analysis, preferably in the same laboratory (i.e., the previous result could be marked as not valid and should not necessarily be reported as an AE).

In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs, if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

AEs do not include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE
- Untoward medical findings that occur before initial administration of the IMP if they occur in the scope of investigations that are performed for assessing inclusion and exclusion criteria (e.g., results of laboratory tests conducted at screening)
- Situations where an untoward medical occurrence has not occurred, e.g., planned hospitalization due to a pre-existing condition that has not worsened, hospitalization that occurs for a procedure not associated with an AE (e.g., elective surgery or social admission), or hospitalization for a diagnostic procedure that takes less than 24 hours
- Overdose of an IMP or any concomitant therapy that does not result in any adverse signs or symptoms. Details of the dosing (volume, location of infusion, and infusion rate) of the IMP will be recorded in the eCRF
- Anticipated day-to day fluctuations of pre-existing disease(s) or condition(s) present at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, sign, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

At each visit to the study site, the investigator will determine whether any AEs have occurred. If known, the medical diagnosis of an AE should be recorded according to the listing of individual signs and symptoms.

10.1.2 Documentation and Reporting

The observation and reporting period for AEs will start with a subject signing the informed consent form at screening (i.e., at Day -14 to Day -1) and ends at Week 24 (EOS).

All AEs will be collected and recorded in the eCRF, irrespective of whether they were solicited or reported spontaneously by the subject.

For subjects who discontinue the study up to and including Week 16, AEs will be observed and reported at a safety follow-up visit that will be performed 1 month (±3 days) after last IMP administration.

Investigators are not obligated to actively seek AEs after conclusion of the study participation. However, if the investigator learns of any AE at any time after a subject has been discontinued from the study, and theyconsider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Every attempt should be made to describe AEs in terms of a diagnosis. If appropriate, component symptoms should be listed in addition to the diagnosis. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses in the eCRF.

All subjects who experience AEs, irrespective of whether the AEsare considered by the investigator to be at least possibly related to treatment with the IMP, must be monitored to determine the outcome. The clinical course of each AE will be followed up according to accepted standards of medical practice, even after the subject has completed participation in the study, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate the follow-up. Should the AE result in death, a full pathologist's report should be provided, if possible.

AEs will be classified according to their severity, causal relationship to the IMPs, and seriousness.

If the severity of a recurrent AE changes from mild to moderate, from moderate to severe, or from mild to severe, this AE recurrence should be reported as a new AE.

If the AE is serious or of special interest, as defined in Sections 10.2.1 and 10.3, the investigator or other authorized medical personnel at the study site must be notified and complete the paper "SAE form" at the time the SAE is detected. SAE reporting should occur within 24 hours (Section 10.2.2).

Severity of Adverse Events

The severity of AEs will be assessed according to the following criteria:

Mild

- Transient or mild discomfort
- No limitation in activity
- No medical intervention or therapy required.

Moderate	• Marked limitation in activity • Some assistance usually required • Medical intervention or therapy required • Hospitalization possible.
Severe	• Extreme limitation in activity • Significant assistance required • Significant medical intervention or therapy required • Hospitalization or hospice care probable.

Causal Relationship of Adverse Events

The investigator must assess whether or not the AE is causally related to administration of the IMP. Even if the investigator considers that there is no causal relationship to the IMP, the AE must still be reported.

The causal relationship of AEs to administration of the IMP will be assessed according to the following criteria:

Not related	• Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship impossible • Is most likely explained by concurrent disease or other drugs or chemicals (either pathophysiologically or clinically) • Has occurred before administration of the IMP in comparable severity and/or frequency.
Unlikely related	• Event or laboratory test abnormality with a time to administration of the IMP that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations.
Possibly related	• Event or laboratory test abnormality with reasonable time relationship to administration of the IMP • Could also be explained by disease or other drugs • Information on IMP withdrawal may be lacking or unclear.
Probably related	• Event or laboratory test abnormality with reasonable time relationship to administration of the IMP • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required.

Certainly related	• Event or laboratory test abnormality with plausible time relationship to administration of the IMP • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically or pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary.

All AEs classified as "possibly", "probably", or "certainly" related will be considered as "at least possibly related to the IMP". All AEs classified as "not related" or "unlikely related" will be considered as "not related" to the IMP.

The degree of certainty with which an AE is attributed to administration of the IMP, or an alternative cause (e.g., natural history of the underlying disease, concomitant therapy, AxMP etc.) must be determined on the basis of how well the AE can be understood in terms of:

- Known pharmacology of the IMP
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product-related (e.g., headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (e.g., the event being related by time to administration or termination of treatment with the IMP, drug withdrawal, or reproduced on rechallenge).

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definition

An AE is defined as serious (i.e., as an SAE) according to the ICH E2A guideline if any of the following criteria are fulfilled:

- Results in death
- Is life-threatening

  NOTE: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed above.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalization for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed after administration of IMP).

10.2.2 Documentation and Reporting

The observation and reporting period for SAEs starts with a subject signing the informed consent form at screening (i.e., at Day -14 to Day -1) and ends at Week 24 (EOS).

Investigators are not obligated to actively seek SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discontinued from the study, and theyconsider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

SAEs have to be documented on "SAE forms" and the investigator must report them immediately to the CRO, or no later than 24 hours after becoming aware of the SAE. If more information about the SAE becomes available later, this must also be reported immediately or no later than 24 hours after becoming aware of the SAE.

In case of a subject's death, the investigator will provide the applicable Ethics Committee(s) and the applicable responsible authorities with any further information requested.

In all reports, personal data are to be pseudonymized by using the subject identification number. It must be possible to relate the initial and all follow-up reports to each other by means of the subject identification number, or name and address, or the like.

The investigator must report all SAEs to the following contact details:

Fax: [redacted]
[redacted]

10.3 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is an AE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it.

For this study, the following AEs are defined as AESIs:

- **Infusion-related reactions/anaphylactic reactions and acute systemic hypersensitivity reaction** during or shortly after IFX-IMP infusion:
  In case of any severe, acute systemic hypersensitivity reaction during or shortly after infusion of IFX-IMP, the infusion should be stopped immediately and the subject discontinued from further dosing with IFX-IMP (and GC-IMP) but can stay in the study and continue AxMP and study-related procedures/assessments as scheduled. It is at the discretion of the investigator to discontinue the subject from further study participation (refer also to Sections 5.4.3 and 8.4).
  In case of such a reaction, subjects should be closely monitored for any changes in blood pressure, heart rate, metabolic conditions, or organ function, and appropriate measures should be taken to stabilize all vital signs. Fluid resuscitation may be needed, as well as vasopressor therapy or other measures to treat changes in blood pressure, vital signs, or metabolic conditions in general. In cases of emergency with immediate life-threatening potential such as cardiac arrest or similar life-threatening changes, appropriate cardiopulmonary resuscitation should be started immediately according to applicable guidelines, or as established at the study sites through existing standard operating procedures or other algorithms for cardiopulmonary resuscitation according to current recommended resuscitation guidelines.

  For any potential infusion-related event, the investigator should check for a potentially developing or existing anaphylactic reaction. In case an anaphylactic reaction is anticipated, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction as recommended by existing guidelines for the treatment of anaphylactic reactions or, if established at the study sites, according to available standard operating procedures or other algorithms.

- **Meningitis** and **meningococcal sepsis**:
  In case of signs of meningitis at any time during the study, the IMPs should be discontinued for the rest of the study, if meningitis is confirmed, but the subject can stay in the study and continue AxMP and study-related procedures/assessments as scheduled. It is at the discretion of the investigator to discontinue the subject from further study participation (refer also to Sections 5.4.3 and 8.4).

In case of meningitis, the subject must be closely monitored and the guidelines for treatment of meningitis should be followed [Tunkel et al.,2017, Van de Beek et al.,2016]. This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search for the focus of the infection (e.g., computed tomography or magnetic resonance tomography).

- **Invasive infection:**
  In case of signs of invasive infection at any time during the study, IMPs should be discontinued for the rest of the study, if invasive infection is confirmed, but the subject can stay in the study and continue AxMP and study-related procedures/assessments as scheduled. It is at the discretion of the investigator to discontinue the subject from further study participation (refer also to Sections 5.4.3 and 8.4).
  In case of invasive infection, the subject must be closely monitored and the guidelines for treatment of invasive infection should be followed.

[redacted]

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

10.4.1 Definition

Suspected unexpected serious adverse reactions (SUSARs) are side effects whose nature or severity is inconsistent with the information available about the product in the Investigator's Brochure.

10.4.2 Documentation and Reporting

The sponsor or delegate will submit all available information on a SUSAR immediately to the applicable Ethics Committee, the applicable regulatory authority, and the investigators in this study, at the latest within 15 calendar days after the event becomes known.

For every SUSAR that results in death or a life-threatening condition, the responsible Ethics Committee, the applicable regulatory authority, and the investigators in this study must be informed by the sponsor within 7 calendar days after the event becomes known. Additional information has to be given within 8 further calendar days.

10.5 PREGNANCY

Pregnancy, by definition, is not considered as an AE unless it results in a complication that meets the definition of an AE or is associated with a congenital anomaly or birth defect in the fetus. Any such complication must then be reported accordingly as an SAE.

A female subject who becomes pregnant while participating in the study, or up to and including 28 days after the last dose of IMP, must notify the investigator immediately and must discontinue treatment with the IMPs. The subject may continue other study procedures at the discretion of the investigator.

The sponsor and the designee of the sponsor must be immediately notified by the investigator becoming aware of a pregnancy of a participating female subject or a female partner of a participating male subject, using the following contact details:

Fax: [redacted]

[redacted]

Whenever possible, a pregnancy in subjects exposed to IFX-IMP or female partners of participating male subjects exposed to IFX-IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator.

Severe side effects and complications during a pregnancy as well as congenital birth defects are SAEs per definition and, therefore, have to be reported additionally as SAEs according to the reporting procedures described above.

10.6 OVERDOSE

The consequences of an overdose with IFX-1 are not known.

In case of GC-IMP overdose, the investigator should contact the medical monitor to discuss further actions to be taken,

Overdoses accompanied by adverse outcomes must be recorded as AE.

AEs caused by overdose should be followed to ensure that the information is as complete as possible.

11 STATISTICS

11.1 GENERAL CONSIDERATIONS

A detailed statistical analysis plan will be developed and finalized prior to unblinding of the study database.

The statistical analysis plan will include the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report.

All endpoints and variables will be adequately evaluated. Individual data will be listed. Data will be summarized using suitable descriptive statistics; depending on the structure of the data, either sample statistics or frequency tables will be used. [redacted]

11.2 DETERMINATION OF SAMPLE SIZE

The study is divided into 2 parts:

Study Part 1:

A total of 20 subjects will be randomized 1:1 to either Group A (IFX-1 + RDGC) or Group B (IFX-1-Placebo + SDGC). [redacted]

Study Part 2:

This Study Part only starts if the IDMC recommends randomizing subjects to Group C (IFX-1 + Placebo-GC) at the end of Study Part 1. In Study Part 2, the efficacy of treatment with IFX-1 in the experimental treatment (Group C) compared to the control treatment (Group B) with respect to the primary efficacy endpoint will be investigated. Subjects who have been randomized in Study Part 1 into Group B will contribute to the set of subjects analyzed for Study Part 2. A total of approximately 25 additional subjects will be randomized to Group B and Group C. The randomization ratio was selected to yield an equal number of 33 subjects in Group B and Group C for the primary comparison. With the reduced number of subjects in Part 2, this randomization ratio remains unchanged. It will result in an unbalanced distribution of patients in Group B and C for the final analysis, i.e. about 24 treated in Group B (15 from Part 1 and 9 from Part 2) and about 16 in Group C (all enrolled in Part 2). [redacted]

In summary, the planned number of subjects are planned to be randomized in this study are shown in Table 6.

Table 6 Planned Sample Size in Study Parts

	Group A	Group B	Group C
Part 1	15	15	-
Part 2	-	9	16
Planned number of subjects per group	15	24	16

11.3 ANALYSIS SETS

Full analysis set (FAS): the FAS will consist of all subjects who receive at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs).

Per protocol set (PPS): the PPS will be a subset of the FAS and will exclude all subjects with major protocol violations that affect the evaluation of the primary endpoint of the study.

Safety analysis set (SAF): the SAF will consist of all subjects who receive at least 1 administration of study medication (1 infusion of IFX-1 or Placebo-IFX-1 and at least 1 dose of GCs or Placebo-GCs).

Safety analyses will be based on the SAF. Efficacy analyses will be provided for the FAS and the PPS for subjects in Group B and C. Descriptive analysis will be provided for Study Part 1.

More detailed specifications of the analysis sets and analyses will be provided in the statistical analysis plan.

11.4 ENDPOINTS

11.4.1 Efficacy

11.4.1.1 Primary

The primary efficacy endpoint is the proportion of subjects achieving clinical response defined as a reduction in BVASv3 ≥ 50% at Week 16 compared to baseline (=screening assessment) and no worsening in any body system. Subjects who receive rescue therapy up to Week 16 will be considered as not having achieved clinical response.

11.4.1.2 Secondary

Efficacy

- Proportion of subjects with a clinical response, defined as a reduction in BVASv3 ≥ 50% and no worsening in any body system at each measurement time point except Week 16. Subjects who receive rescue therapy will be considered as not having achieved a clinical response at each time point later than the first administration of rescue therapy
- Proportion of subjects with a clinical remission, defined as having a BVASv3 = 0 at Week 16
- Change from baseline (=screening assessment) in BVASv3 total score at Week 16
- Absolute values and absolute and relative change from Day 1 in the VDI at Week 16
- Absolute values and absolute and relative change from Day 1 in the PGA at Week 16
- Absolute values and absolute and relative change from Day 1 in eGFR in mL/min/1.73 m² at Week 16.

Pharmacokinetic/Pharmacodynamic

- Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point (see Section 11.4.4)
- Where applicable, absolute values and absolute and relative changes from Day 1 in the PD parameters at each measured time point (see Section 11.4.5).

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]t
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

11.4.2 Safety

The number and percentage of subjects who had a TEAE as well as the number of TEAEs will be assessed for all TEAEs and SAEs as secondary endpoint. Another secondary endpoint is the GTI per time point.

Furthermore, the number and percentage of subjects who have a TEAE as well as the number of TEAEs will be assessed for all causally related TEAEs, related SAEs, AESIs, TEAEs leading to study discontinuation, related TEAEs leading to study discontinuation, TEAEs leading to IMP discontinuation, and related TEAEs leading to IMP discontinuation. Causal relationship of AEs will be assessed with regard to IFX—1 and GC.

For the analysis of severity and causal relationship of AEs, the worst severity and the strongest relationship per subject and class of AE will be considered.

Laboratory safety parameters (blood and urine), especially the change in inflammatory markers and differential blood cell counts, will be described by time point and changes in routine laboratory parameters from baseline will be determined. Shifts in safety laboratory parameters outside of normal ranges compared with baseline will be investigated.

Immunogenicity will be assessed by determining the number and percentage of subjects with detection of ADAs (before administration of IFX-IMP).

Other safety endpoints will be exploratory, as defined in detail in the statistical analysis plan.

Non-treatment-emergent AEs will be listed.

11.4.3 Quality of Life

The SF-36v2 will be analyzed by time point and changes from baseline will be determined overall and per domain. The EQ-5D-5L will be analyzed by time point and changes from baseline will be determined.

11.4.4 Pharmacokinetics

The exposure to IFX-1 in all subjects will be measured as the plasma concentration of IFX-1 determined on Day 1 and at all subsequent scheduled visits to the study site through Week 24 before administration of IFX-IMP, and in Weeks 1 (Day 4), 4, and 16 after administration of IFX-IMP using a separate infusion line. Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point.

11.4.5 Pharmacodynamics

The PD of IFX-1 are primarily measured by plasma concentration of C5a, which is determined at pre-specified times after administration of IFX-1. Plasma concentrations of C5a and IFX-1 blocking activity will be summarized by time point and as absolute and relative changes from Day 1. [redacted]

11.4.6 Biomarkers

Serum concentrations of CRP, CH50 [redacted] will be summarized by time point and as absolute and relative changes from Day 1.

11.5 ANALYSES OF ENDPOINTS

11.5.1 Efficacy

Study Part 1

For Study Part 1 only a descriptive efficacy analysis is planned.

Study Part 2

The primary efficacy variable is the percentage of subjects with clinical response defined as a reduction in BVASv3 ≥ 50% at Week 16 compared to baseline (=screening assessment) and no worsening in any body system and not having received rescue therapy. Missing primary endpoint data will be imputed, as described in Section 11.10.

The experimental arm (Group C) and the Standard of Care arm (Group B) will be compared regarding the risk difference and its 90% confidence interval [redacted]

As a secondary efficacy analysis, a logistic regression model will be fit for the binary response at Week 16 including relevant baseline characteristics (such as the baseline BVASv3) as covariates to further investigate the effect of subjects' baseline characteristics.

Further secondary and exploratory efficacy endpoints will be evaluated with appropriate statistical methods and will be described in detail in the statistical analysis plan.

[redacted]

11.5.2 Safety

TEAEs will be analyzed according to the number and percentage of subjects who had a TEAE, as well as the number of TEAEs with the respective Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. Additionally, the number and percentage of subjects with TEAEs will be grouped by severity and causal relationship. The number and percentage of subjects with SAEs and AESIs and the number of SAEs and AESIs will be analyzed. Where AEs are grouped by severity or relationship, the maximum severity/relationship per subject and class of AE will be considered. If the number of subjects discontinuing treatment or discontinuing the study is substantial, further analyses taking into account the time of AE onset and cumulative dose may be considered.

Summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) will be presented for the absolute values of the GTI at each time point.

Safety laboratory and vital signs parameters will be analyzed by summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline by visit.

Immunogenicity will be assessed by determining the number and percentage of subjects with detection of ADAs.

Categorical safety parameters like ECG findings will be summarized by absolute and relative frequencies by time point.

11.5.3 Pharmacokinetics

Actual PK sampling times will be determined and the plasma concentration of IFX-1 will be assessed by time point.

11.5.4 Pharmacodynamics

Where applicable, the absolute values and changes from baseline of PD endpoints will be summarized using descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, geometric mean) by time point.

All PD parameters will be analyzed based on the FAS with all values and assessments available. Some analyses may be repeated for the PPS.

11.5.5 Quality of Life

Absolute values and changes from baseline in the overall SF-36v2 and per domain at Weeks 16 and 24 will be analyzed by descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) for absolute values and changes from baseline (absolute and relative) by time point and treatment group.

11.5.6 Biomarkers

Absolute values will be analyzed by time point and absolute and relative changes from baseline at each time point using descriptive statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile, and geometric mean) for each treatment group.

11.6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics and demographic information (including medical history and surgeries) will be summarized by treatment group and overall. If applicable, the baseline measurement will be defined as the latest measurement obtained prior to the first administration of IMP.

11.7 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant therapies will be summarized by absolute and relative frequencies by treatment group and overall. Therapies will be defined as concomitant if the start or end date is later than the date of first IMP administration, or if no end date is available (ongoing therapy).

In case of incomplete start and/or end dates, a therapy is considered as concomitant if it is possible that the therapy was administered after first dose of IMP (e.g., if only end year and month are provided and are equal to the month and year of the first IMP administration).

11.8 SUBJECT DISPOSITION

The disposition of subjects who were enrolled (i.e., signed the written informed consent form) in the study as well as reasons for discontinuation from study and treatment will be summarized for each group.

11.9 TREATMENT EXPOSURE

The administration of IMP will be summarized by time point and treatment group and will include the number and percentage of subjects completing each treatment visit and the mean dose per infusion at each visit. The actual received cumulative dose in mg and the dose relative to the planned cumulative dose will be calculated per subject and will be summarized for each treatment group.

11.10 HANDLING OF MISSING DATA

Data imputation rules are defined for missing values for the primary efficacy endpoint of achieving clinical response defined as reduction in BVASv3 ≥ 50% at Week 16 compared to baseline (=screening assessment) and no worsening in any body system. Subjects with missing baseline BVASv3 assessments (baseline assessments must be obtained at screening) will not be randomized (i.e., there shall be no missing baseline values for the primary endpoint). Missing values for assessments of the BVASv3 at Week 16 will be replaced by multiple imputation.

Multiple imputations will only be performed for subjects with a missing BVASv3 at Week 16 who did not discontinue before Week 16 because of one of the following reasons:

- AE (e.g., major relapse) or death caused by persistent disease activity
- Lack of efficacy.

Subjects who will discontinue before Week 16 because of 1 of the above-mentioned reasons will be treated as not having achieved clinical response at Week 16 (non-responders). Additionally, subjects receiving GC as rescue therapy will be considered as non-responders regardless of their BVASv3 at Week 16.

All further specifications for multiple imputations are based on the assumption that the number of subjects for whom the BVASv3 at Week 16 needs to be imputed, will be relatively small. Further, it is assumed that the BVASv3 assessment at Week 16 is missing at random, i.e., being missing will not depend on the BVASv3 at Week 16 itself but will only depend on the factors in the imputation model. The factors that will be used in the multiple imputation model for BVASv3 at Week 16 are BVASv3 at previous visits, treatment group, and GPA/MPA disease type. The multiple imputation model will be using fully conditional specification predictive mean matching. Twenty imputations will be performed using SAS PROC MI and using a random seed of 1,502. Subsequently, it will be determined for each subject within each of the imputed datasets whether clinical response is achieved (BVASv3 reduction of ≥ 50% compared to

baseline). The risk difference and the corresponding confidence interval will be calculated based on the binary response variable (clinical response vs. no clinical response at Week 16) for each imputed dataset. [redacted]

Additionally, sensitivity analyses will be conducted based on the PPS. Further sensitivity analyses (e.g., evaluating subjects with missing BVASv3 at Week 16 as non-responders) will be defined in the statistical analysis plan if deemed necessary.

All other missing data will not be replaced.

11.11 INTERIM ANALYSIS

No formal interim analysis will be performed.

There will be an IDMC recommendation point in Study Part 1 after a total of 20 subjects in Group A and B have completed the IFX-IMP administration (Week 16) and the corresponding assessments (see also Section 14.4 and 11.2 and IDMC charter).

12 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

12.1 GOOD CLINICAL PRACTICE

All persons participating in the conduct of the study (e.g., sponsor, investigators) commit themselves to observe the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) as well as all pertinent national laws and the ICH guidelines for GCP (June 2017) and CPMP/ICH/135/95 (September 1997).

12.2 ETHICS COMMITTEE AND RESPONSIBLE REGULATORY AUTHORITY

The protocol and other associated documents will be submitted to the applicable Ethics Committee for approval. The study documents will be submitted to the applicable regulatory authority.

The study can only start after obtaining a positive evaluation by the applicable Ethics Committee and approval from the applicable regulatory authority. The written approval of the applicable Ethics Committee and the applicable responsible regulatory authority must be filed in the trial master file. Additionally, each study site must receive a copy of these documents to be filed in the investigator site file.

12.3 SUBJECTS INFORMATION AND INFORMED CONSENT

The investigator must explain to each potential study subject the nature of the study, the objectives, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. The potential subjects must be informed that participation in the study is voluntary, that they may withdraw their consent to participate at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

The informed consent must be given by means of standard written statements, written in non-technical language. The subjects should read the informed consent form and consider their decision before signing and dating the document. A copy of the signed document must be given to the subject. No subject can be involved in the study if he/she is related to the investigator, any member of the team at the study site, or the sponsor.

The informed consent of the subject must also refer specifically to the assessment and processing of data on the subject's health. The subject is to be informed explicitly about the purpose and extent of the assessment and the use of their personal data, especially the health-related data. Informed consent will also be given for the storage and testing of samples for possible futureresearch, if legally allowed.

12.4 PROTOCOL AMENDMENTS

If modifications are made to the protocol, after it has been positively appraised by the Ethics Committee and approved by the responsible regulatory authority, these modifications must be reappraised and approved by the Ethics Committee and the responsible regulatory authority if the changes:

- Are such that they may affect the subjects' safety
- Are fundamental to the therapeutic procedures
- Result in further data collection that necessitates changes to the subject information and/or informed consent form
- Affect the interpretation of the scientific documents upon which the study is based or the significance of the results of the study
- Significantly affect the leadership or conduct of the study
- Concern the quality or the innocuousness of the investigational drug.

Protocol amendments need the authorization of the sponsor, the coordinating investigator, and the responsible biostatistician, if applicable. All protocol amendments will be:

- Submitted to the Ethics Committee and, where applicable, to the responsible regulatory authority
- Provided in written form to the responsible parties
- Filed in the trial master file.

13 DOCUMENTATION

13.1 ELECTRONIC CASE REPORT FORMS

All data assessments required by this clinical study protocol will be collected in an eCRF and entered into a database validated by the CRO for eCRFs.

The sponsor or its designee will supply the study site with access to eCRFs. The sponsor or its designee will make arrangements to train appropriate study site personnel in the use of the eCRF.

These eCRFs are used to transmit information collected on the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

Data will be entered directly into the eCRF by the investigator or study site personnel via a single data entry process. Study site personnel will be granted access to the eCRF system through a personal user identification and password assigned by the system administrator. In the eCRF, subjects will be identified by their subject numbers. The eCRF is to be dated and signed by the investigator or a qualified person who has been delegated by the investigator to do so on his/her behalf, as documented on a signature delegation log filed in the investigator site file. Data entered in the eCRF will be stored in a centralized database on a remote server.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by designees of the sponsor and will be answered by the site.

Corrections to the eCRF database are recorded in an audit trail that captures a complete record of all information. The new information, identification of the person making the correction, the date the correction was made, and the reason for change are captured in a new record.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered into the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the clinical monitor. The sponsor and/or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Further information on handling of the eCRF data (e.g., data entry, clarification, and validation) will be defined in the data management plan.

13.2 ARCHIVING

Because the study is being conducted to obtain marketing authorization, the requirements of ICH Guideline E6 sections 5.5.11 and 5.5.12 shall be taken into account.

The investigator is responsible for archiving the investigator site file, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 15 years after completion or discontinuation of the trial or at least two years after the granting of the last marketing authorisation in the European Union (when there are no pending or contemplated marketing applications in the EU) or for at least two years after formal discontinuation of clinical development of the investigational product, whatever is the longest.

If the investigator can no longer maintain the archive of study records (e.g., due to retirement or relocation), the sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records must not be destroyed without prior written consent from the sponsor.

14 SUPERVISION OF THE CLINICAL STUDY

14.1 ACCESS TO SOURCE DATA

According to ICH guidelines for GCP and the applicable laws, the investigator must permit all authorized third parties access to the study site and the medical records of the study subjects (source data). These include the clinical monitors, auditors, and other authorized employees of the sponsor as well as members of the local or federal authorities. All these persons are bound to strict confidentiality.

14.2 MONITORING

Monitoring of the study sites will be performed by a CRO designated by the sponsor and will be based on the CRO's monitoring standard operating procedures as well as the study-specific Monitoring Manual.

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. The monitor will visit the study site at periodic intervals and, in addition, the monitor will be adequately trained and maintain contact with the study site via telephone calls as well as in written form, as appropriate. The monitor will be adequately trained and maintain a working knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and study site personnel. Source data review and verification of the most important parameters will be performed for all subjects as described in the Monitoring Manual. The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The clinical monitor will report via the project manager of the sponsor-designated CRO to the sponsor who carefully monitors all aspects of the study for compliance with applicable government regulations, with respect to current ICH guidelines for GCP and current standard operating procedures.

Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will need to have eCRFs and source documents available on request.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify the appointed CRO/clinical monitor of any inspections that will be scheduled with any regulatory authority.

The clinical monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the clinical monitor to ensure that corrective and preventative action is taken to resolve any

problems noted in the course of the monitoring, and that the preventative measures are put in place to prevent recurrence of issues.

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., correspondence, clinical study materials, supply shipping manifests, or monitoring logs). An investigator site file will be provided with instructions for the maintenance of study records.

14.3 ADJUDICATION COMMITTEE

A blinded AC with expertise in vasculitis, will be assembled. The AC will adjudicate the response to therapy in a blinded manner in Study Part 1 for all randomized subjects, taking all predefined efficacy data into consideration. The responsible CRO will provide predefined data for the committee review. Further details on the AC membership, roles, timing of the reviews, details of the data and outputs to be provided to the AC, and the procedures for ensuring the blinded conditions, with all the operational details, will be provided in the AC Charter.

14.4 INDEPENDENT DATA MONITORING COMMITTEE

The safety of the subjects will be monitored by an unblinded IDMC. The IDMC will receive data for regular safety reviews at pre-specified time points in order to detect and report early evidence of unanticipated harm to subjects. To maintain the blind, the data for the safety reviews will be delivered by an unblinded CRO biostatistics team different from the blinded CRO biostatistics personnel involved in the study. Further details on the provided outputs and the time points of the reviews will be specified in the IDMC charter. In addition, further ad hoc reviews on safety data may be arranged and conducted if deemed necessary.

Furthermore, [redacted]

[redacted]

If the IDMC recommends enrolling further subjects, the AC will review, under blinded conditions, the response to therapy of these additional subjects, up to the last additional subject completing Week 16. The outcome of this review will be provided to the IDMC, who will also review these new data under unblinded conditions, together with the unblinded safety outputs, and make the recommendation about opening Group C or stopping the study.

Further details on the IDMC membership, the responsibilities of the IDMC, the purpose and timing of the reviews, details of the data and outputs to be provided to the IDMC and the procedures for ensuring confidentiality and proper communication will also be provided in the IDMC charter. The charter will also outline the required content of the written report to be provided by the IDMC after each safety review, including their recommendations for the future conduct of the study.

14.5 AUDITS

In order to guarantee that the conduct of the study is in accordance with ICH guidelines for GCP and the national laws, audits may be performed at the study sites to be carried out by an independent auditor. In addition, for-cause audits may be scheduled.

The investigator agrees to give the auditor access to all relevant documents for review.

14.6 INSPECTIONS

According to the corresponding ICH guidelines for GCP, inspections of the study sites may be performed by the local or regulatory authorities at any time during or after completion of the study. The investigator will contact the sponsor or designated CRO immediately upon knowledge of a planned inspection.

The investigator agrees to give the inspectors access to all relevant documents for review.

15 DATA PROTECTION AND CONFIDENTIALITY

Within this study, personal data from the study subjects and data regarding the treatment and the course of subject's welfare will be collected.

The data will be stored and processed in pseudonymized form (i.e., without reference to the subject's name) with the aid of a unique subject identification number.

Data will be managed by a sponsor-designated CRO (data entry, data cleaning, and data exports). The safety concept ensures among other things that data access is limited to authorized persons, that measures are taken to prevent loss of data, and that the applicable laws pertaining to data protection are observed. The data are protected from third party access and only members of the study team are permitted access. These members are bound to strict confidentiality.

Personal data will be stored in an pseudonymous manner after reaching finishing completion status of all concomitant scientific projects for at least 15 years, if no other or new regulatory requirements come into effect warranting different time periods for archiving.

15.1 DECLARATION REGARDING DATA PROTECTION

During data entry, processing, and analysis by a sponsor-designated CRO, all requirements of the data protection act will be taken into account. Access to data is strictly limited to authorized persons. Data are protected against unauthorized access according to current federal legislation and regulations.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches, and complies otherwise with the requirements of European Union General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). The sponsor will regularly check all procedures relevant to the processing of personal data, as to ensure privacy by design and compliance with GDPR.

15.2 DECLARATION REGARDING THE PSEUDONYMIZED TRANSFER OF PERSONAL DATA

The sponsor certifies herewith that the transfer of pseudonymized personal data will take place according to the applicable local laws. Moreover, the sponsor certifies that study subjects who do not permit the transfer of data will not be admitted to the study.

16 ADMINISTRATIVE AGREEMENTS

16.1 ADHERENCE TO THE PROTOCOL/PROTOCOL DEVIATIONS

The clinical study described here will be conducted and analyzed in accordance with local laws and ICH guidelines for GCP.

After a subject has been enrolled, it is the investigator's responsibility to avoid protocol deviations in order to obtain unbiased data for the analysis of the study.

All protocol deviations will be documented and discussed with the responsible biostatistician before closing the database and carrying out the statistical analyses.

16.2 FINANCING AND INSURANCE

The study is financed by the sponsor.

The subjects are covered by an applicable insurance policy for participation in a clinical study. One copy of the insurance certificate and the insurance conditions will be handed out to the subject and 1 will be filed in the investigator site file.

16.3 NOTIFICATION OF THE LOCAL AUTHORITIES

The sponsor, their contractors, and all investigators and their deputies are responsible for notifying the local regulatory authority of their participation in the study prior to enrolment of the first subject in the study. Responsibility for notification to the local authorities has been delegated to a sponsor-designated CRO.

This extends also to amendments, discontinuation of study arms or of the entire study, and the regular conclusion of the study.

16.4 PUBLICATION POLICY AND REGISTRATION

16.4.1 Publication Policy

The rights and obligations of investigators and the sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Study Agreement for the study.

The first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol.

The sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not

inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include investigators from study sites that contributed data as well as relevant personnel from the sponsor. Ownership of all data will remain with the sponsor.

Furthermore, the publication policy will follow the recommendations of Good Scientific Practice of the Deutsche Forschungsgemeinschaft (www.dfg.de) and will meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org).

16.4.2 Registration

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/; EU Clinical Trials Register, https://www.clinicaltrialsregister.eu) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for randomization into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

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18 APPENDICES

18.1 CHAPEL HILL CONSENSUS CONFERENCE

DIAGNOSTIC CRITERIA

Widely accepted diagnostic criteria, as opposed to classification criteria or definitions, have not yet been developed for GPA and MPA. In 1994, the CHCC developed definitions for these vasculitides and some of their mimickers, that were revised in 2012 [Jennette 1997, Jennette 2013]. These definitions will be applied to determine a participant's eligibility for this clinical study [Fries 1990].

Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis

- Necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles)
- Necrotizing arteritis involving small and medium arteries may be present
- Necrotizing glomerulonephritis is very common
- Pulmonary capillaritis often occurs
- Granulomatous inflammation is absent.

Chapel Hill Consensus Conference Definitions GPA

- Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract
- Necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins)
- Necrotizing glomerulonephritis is common.

18.2 BIRMINGHAM VASCULITIS ACTIVITY SCORE VERSION 3.0

Birmingham Vasculitis Activity Score (version 3)

Case Number:

Name: **Date of assessment:**

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.

If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner

Is this the patient's first assessment? **Yes** ☐ **No** ☐

	None	Active disease
1. General	☐	
Myalgia		☐
Arthralgia / arthritis		☐
Fever ≥38° C		☐
Weight loss ≥2 kg		☐
2. Cutaneous	☐	
Infarct		☐
Purpura		☐
Ulcer		☐
♦**Gangrene**		☐
Other skin vasculitis		☐
3. Mucous membranes / eyes	☐	
Mouth ulcers		☐
Genital ulcers		☐
Adnexal inflammation		☐
Significant proptosis		☐
Scleritis / Episcleritis		☐
Conjunctivitis / Blepharitis / Keratitis		☐
Blurred vision		☐
Sudden visual loss		☐
Uveitis		☐
♦**Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)**		☐
4. ENT	☐	
Bloody nasal discharge / crusts / ulcers / granulomata		☐
Paranasal sinus involvement		☐
Subglottic stenosis		☐
Conductive hearing loss		☐
♦**Sensorineural hearing loss**		☐
5. Chest	☐	
Wheeze		☐
Nodules or cavities		☐
Pleural effusion / pleurisy		☐
Infiltrate		☐
Endobronchial involvement		☐
♦**Massive haemoptysis / alveolar haemorrhage**		☐
♦**Respiratory failure**		☐

	None	Active disease
6. Cardiovascular	☐	
Loss of pulses		☐
Valvular heart disease		☐
Pericarditis		☐
♦**Ischaemic cardiac pain**		☐
♦**Cardiomyopathy**		☐
♦**Congestive cardiac failure**		☐
7. Abdominal	☐	
Peritonitis		☐
Bloody diarrhoea		☐
♦**Ischaemic abdominal pain**		☐
8. Renal	☐	
Hypertension		☐
Proteinuria >1+		☐
♦**Haematuria ≥10 RBCs/hpf**		☐
Creatinine 125-249 µmol/L (1.41-2.82 mg/dl)*		☐
Creatinine 250-499 µmol/L (2.83-5.64 mg/dl)*		☐
♦**Creatinine ≥500 µmol/L (≥5.66 mg/dl)***		☐
♦**Rise in serum creatinine >30% or fall in creatinine clearance >25%**		☐
***Can only be scored on the first assessment**		
9. Nervous system	☐	
Headache		☐
Meningitis		☐
Organic confusion		☐
Seizures (not hypertensive)		☐
♦**Cerebrovascular accident**		☐
♦**Spinal cord lesion**		☐
♦**Cranial nerve palsy**		☐
Sensory peripheral neuropathy		☐
♦**Mononeuritis multiplex**		☐
10. Other	☐	
a.		☐
b.		☐
c.		☐
d.		☐
PERSISTENT DISEASE ONLY: (Tick here if **all** the abnormalities are due to persistent disease)		☐

♦ **Major items highlighted**

References: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM 87(11):671-8; Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Baillieres Clin Rheumatol 11(2): 423-46; Mukhtyar C. et al (2009). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3) ARD 2009 68:1827

modified for 'µmol/L' for creatinine values by InflaRx; 19 July 2019

18.3 GLOSSARY AND SCORING FOR BVAS VERSION 3.0

GLOSSARY AND SCORING FOR BVAS version 3

Rules for scoring BVAS

1. Disease manifestations are scored **only when they are attributable to active vasculitis**. The manifestation should not be scored if there is reasonable evidence of another aetiology for the symptoms e.g. infection, drug reaction, other co-morbidity.
2. Tick "Persistent Disease" box if **all** the abnormalities are due to active (but not new or worse) vasculitis.
3. Specialist opinion, or the results of laboratory or imaging investigations will be required for some items. Excepting those circumstances, the whole form should be completed at the time of the consultation.
4. The bands of serum creatinine should be scored **only** on the first visit.
5. Items marked with an asterisk (*) are not compatible with 'persistent' disease. These manifestations always suggest new or worse disease when due to active vasculitis.

Manifestation	Definition	Persistent	New / Worse
1. General	**Maximum scores**	**2**	**3**
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥38° C	Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5° C	2	2
Weight Loss ≥2 kg	Loss of dry body weight without dieting	2	2
2. Cutaneous	**Maximum scores**	**3**	**6**
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer	A disruption in the continuity of the skin	1	4
Gangrene	Extensive tissue necrosis	2	6
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2
3. Mucous Membranes / eyes	**Maximum scores**	**3**	**6**
Mouth ulcers / granulomata	Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers	Ulcers on the genitalia or perineum	1	1
Adnexal inflammation	Salivary or lacrimal gland inflammation.	2	4
Significant proptosis	>2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis	Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis	Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1
Blurred vision	Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss*	Acute loss of vision	*	6
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage)	Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate (exclude hard exudates) / retinal haemorrhage	2	6
4. ENT	**Maximum scores**	**3**	**6**
Bloody nasal discharge / crusts / ulcers / granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis	Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss	Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6

5. Chest	Maximum scores	3	6
Wheeze	Wheeze on clinical examination	1	2
Nodules or cavities*	New lesions detected on imaging	*	3
Pleural effusion / pleurisy	Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate	Detected on chest X-ray or CT scan	2	4
Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure	The need for artificial ventilation	4	6

6. Cardiovascular	Maximum scores	3	6
Loss of pulses	Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease	Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis	Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina.	2	4
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure	Heart failure by history or clinical examination	3	6

7. Abdominal	Maximum scores	4	9
Peritonitis	Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea	Of recent onset	3	9
Ischaemic abdominal pain	Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6

8. Renal	Maximum scores	6	12
Hypertension	Diastolic >95 mm Hg	1	4
Proteinuria	>1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria	'Moderate' on urinalysis or ≥10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 µmol/L	At first assessment only	2	4
Serum creatinine 250-499 µmol/L		3	6
Serum creatinine ≥500 µmol/L		4	8
>30% rise in creatinine or >25% fall in creatinine clearance *	Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	*	6

9. Nervous system	Maximum scores	6	9
Headache	Unaccustomed & persistent headache	1	1
Meningitis	Clinical evidence of meningism	1	3
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke	Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion	Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy	Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy	Objective sensory deficit in a non-dermatomal distribution	3	6
Mononeuritis multiplex	Single or multiple specific motor nerve palsies	3	9

18.4 OTHER MULTI-SYSTEM AUTOIMMUNE DISEASES

Prohibited Diseases	**Permitted Diseases**
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) according to the definitions of the CHCC	Rheumatoid arthritis without non-articular manifestations (1)
Systemic lupus erythematosus	Ankylosing spondylitis without systemic and non-articular manifestations (2)
IgA vasculitis (Henoch-Schönlein)	Autoimmune thyroiditis (Hashimoto)
Rheumatoid vasculitis	Diabetes mellitus type 1
Primary and secondary Sjögren's syndrome	
Cryoglobulinemic vasculitis	
Autoimmune hemolytic anemia	
Mixed connective tissue disease	
Autoimmune lymphoproliferative syndrome	

If any other multi-system autoimmune disease is not listed, please contact the responsible medical monitor for further decisions.

(1) Including, but not limited to: gastrointestinal, pulmonary, cardiac, renal, neurological, skin and ocular manifestations due to RA.

(2) Spine and joints may be affected.

18.5 VASCULITIS DAMAGE INDEX

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***usually have a VDI score of zero,*** unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse since the onset of vasculitis

	No	Yes
1. Musculoskeletal		
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertention		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericaritis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name
Trial Number
Date
Centre

	No	Yes
7. Peripheral vascular disease		
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

VDI Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI … Arthritis Rheum 40: 371-380

18.6 GLUCOCORTICOID TOXICITY INDEX

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	–8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	–8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	–10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	–9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	

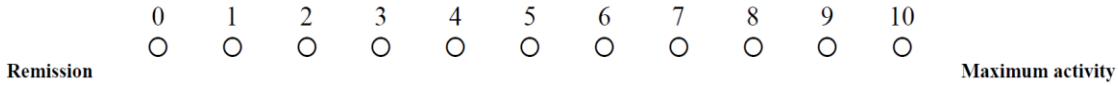
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		Perforation
		Peptic ulcer disease
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	35-410	

BMI, body mass index; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index.

18.7 PHYSICIAN GLOBAL ASSESSMENT

The Physician Global Assessment scale is an 11-point scale to record the assessment of the overall disease activity of the subject. The investigator should not be influenced by the presence of any accumulated damage, complication of treatment, social/emotional problems, or other issues not related to GPA or MPA.

Mark to indicate the amount of GPA or MPA disease activity (not including longstanding damage) within the previous 28 days:



18.8 36-ITEM SHORT FORM SURVEY

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

18.9 THE EUROQOL-5 DIMENSIONS SURVEY

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

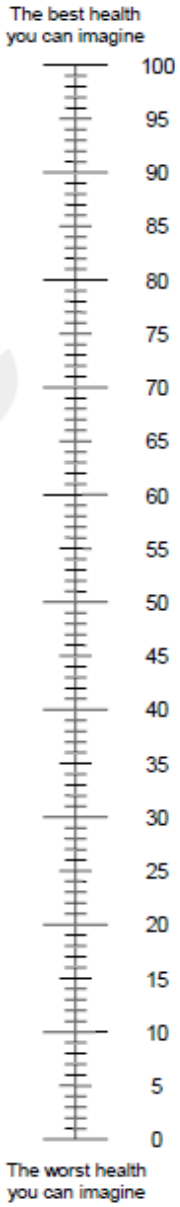
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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