PROTOCOL SYNOPSIS

Study Title	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Intravenous Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Immunogenicity of ARGX-113 in Healthy Males and Female Subjects of Non-Child Bearing Potential		
Product	ARGX-113	**Clinical Phase**	I
Protocol Number	ARGX-113-1501	**Indication**	Autoimmune Disorders
Eudract Number	2015-003549-24		

Sponsor	arGEN-X
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Objectives:

The primary objectives of this study are:

- To evaluate the safety and tolerability of a single ascending intravenous doses of ARGX-113 in healthy male subjects and female subjects of non-child bearing potential, compared to placebo (Part 1).
- To evaluate the safety and tolerability of multiple ascending intravenous doses of ARGX-113 in healthy male subjects and female subjects of non-child bearing potential, compared to placebo (Part 2).

The secondary objectives are:

- To determine the pharmacokinetics (PK) of single and multiple ascending doses of ARGX-113 given intravenously to healthy subjects.
- To determine the pharmacodynamic (PD) and immunogenicity effects of single and multiple ascending intravenous doses of ARGX-113.

Overview of Study Design:

This study is a First-in-Human, Phase I, randomized, double-blind, placebo-controlled, single-center study evaluating single (SAD) and multiple (MAD) ascending intravenous (IV) doses of ARGX-113 in healthy subjects. The study will consist of 2 parts.

Up to 68 healthy male subjects or healthy female subjects of non-childbearing potential will be selected according to the inclusion and exclusion criteria, i.e., up to 36 subjects in the SAD study (Part 1) and up to 32 subjects in the MAD study (Part 2). The SAD study will contain up to 6 cohorts of 6 subjects each, with the 6th cohort being optional (to be added if no plateau in IgG reduction is reached and if there are no safety issues with the prior dose level). The MAD study will contain up to 4 cohorts of 8 subjects each.

ARGX-113 or placebo will be administered intravenously by an infusion over 2h. A staggered approach will be observed within all dose levels. For the SAD study, for each cohort, 2 sentinel subjects will be dosed followed by 4 subjects 24h later. For the MAD study, dosing will be done in 2 subgroups, 4 subjects in each subgroup. This will apply to all MAD cohorts (8 subgroups in total). An interval of at least 14 days between dosing of the first subject of each SAD and MAD dose level will be observed.

A schematic overview of the study design for Part 1 and Part 2 is presented below:

Part 1: SAD

Cohort[1]	N[2]	Dose[3]	Drug administration
1a	1:1	0.2 mg/kg	ARGX-113 or placebo x 1 day
1b	3:1	0.2 mg/kg	ARGX-113 or placebo x 1 day
2a	1:1	2.0 mg/kg	ARGX-113 or placebo x 1 day
2b	3:1	2.0 mg/kg	ARGX-113 or placebo x 1 day
3a	1:1	10 mg/kg	ARGX-113 or placebo x 1 day
3b	3:1	10 mg/kg	ARGX-113 or placebo x 1 day
4a	1:1	25 mg/kg	ARGX-113 or placebo x 1 day
4b	3:1	25 mg/kg	ARGX-113 or placebo x 1 day
5a	1:1	50 mg/kg	ARGX-113 or placebo x 1 day
5b	3:1	50 mg/kg	ARGX-113 or placebo x 1 day
6a[4]	*1:1*	*TBD*	*ARGX-113 or placebo x 1 day*
6b[4]	*3:1*	*TBD*	*ARGX-113 or placebo x 1 day*

[1]The a-group refers to the sentinel subjects and the b-group refers to the remainder of the subjects in the cohort. Two sentinel subjects will be dosed, followed by 4 subjects 24h later. An interval of at least 14 days between dosing of the first subject of each SAD dose level will be observed.
[2]active:placebo
[3]Doses are based on weight at Day -1. These doses may be adapted according to the safety, PK and PD data obtained during the study.
[4]Optional cohort, to be conducted as needed. Dose level to be determined (TBD).

Part 2: MAD

Cohort[1]	N[2]	Dose[3]	Drug administration
7	6:2	10 mg/kg	ARGX-113 or placebo every 4 days on 6 occasions
8	6:2	25 mg/kg	ARGX-113 or placebo every 7 days on 4 occasions
9	6:2	Either 10 mg/kg[4]	ARGX-113 or placebo every 7 days on 4 occasions
		Or 25 mg/kg[4]	ARGX-113 or placebo every 4 days on 6 occasions
10	6:2	25 mg/kg	ARGX-113 or placebo every 7 days on 4 occasions

[1]An interval of at least 14 days between dosing of the first subject of each MAD dose level will be observed.
[2]active:placebo
[3]Doses are based on weight at Day -1. Starting dose and dosing interval to be confirmed following SAD study. The doses administered for the Part 2 MAD study were determined following review of the blinded safety, PK and PD data (as available) from the Part 1 SAD study and are based on the lowest observed IgG measurement (IgG nadir) and time to IgG nadir (IgG t_{nadir}).
[4]Dose and dosing schedule will be chosen based on blinded results obtained from Cohorts 7 and 8. After dosing was stopped in Cohort 8, it was decided to dose 10 mg/kg every 7 days in Cohort 9. Per amendment 4, an additional Cohort 10 was added.

Study Population:

Healthy male subjects and healthy female subjects of non-child bearing potential.
In total up to 68 subjects are planned to be enrolled.
Part 1 (SAD):
Up to 30 subjects, with the potential for 6 additional subjects.
Part 2 (MAD):
Up to 32 subjects.

Eligibility Criteria:

Inclusion Criteria:
Subjects meeting all of the following criteria are eligible to participate in this study:

1. Willingness and ability to understand the purpose and risks of the study and provide signed and dated informed consent prior to any procedures and be available for all study visits.
2. Male or female of non-child bearing potential, between 18-55 years of age, inclusive, on the day of signing the Informed Consent Form (ICF).
3. Body mass index (BMI) between 18-30 kg/m^2, inclusive with a weight of at least 50 kg and no more than 100 kg.

4. Female subjects must have a negative blood pregnancy test at screening and a negative urine pregnancy test at Day -1.
5. Female subjects who are postmenopausal or surgically sterile (having had a hysterectomy, bilateral oophorectomy, or tubal ligation). Determination of serum follicle-stimulating hormone (FSH) will be done with FSH levels > 35 mIU/mL being confirmative for menopause. For hysterectomy and tubal ligation, documented confirmation will be requested.
6. Non-vasectomized male subjects having a female partner of childbearing potential must agree to the use of an effective method of contraception until 90 days after the last administration of study drug.
7. Male subjects have to agree not to donate sperm until 90 days after the last administration of study drug.
8. Judged by the investigator to be in good health based upon the results of a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory findings.
9. Discontinuation of all medications (including over-the-counter and/or prescription medication, dietary supplements, neutraceuticals, vitamins and/or herbal supplements such as Ginkgo biloba or Saint John's wort), except occasional paracetamol use (maximum dose of 2 g/day and maximum of 10 g/2 weeks), at least 2 weeks prior to the first study drug administration. In addition, subjects must agree to the prohibitions and restrictions for this study.
10. Non-smokers, and not using any nicotine-containing products. A non-smoker is defined as an individual who has abstained from smoking for at least 1 year prior to ~~the~~ screening.
11. Negative urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone, and tricyclic antidepressants) at screening and Day -1.
12. Negative alcohol breath test at screening and Day-1.

Note: A retest can be done in case of an out of range clinical laboratory test value that will determine a subject's eligibility. This retest should preferably be done at an unscheduled visit. The result of the retest will be considered for subject eligibility. If the retest is outside normal reference ranges, the subject may be included only if the investigator judges the abnormalities to be not clinically significant.

Exclusion Criteria:

Subjects meeting any of the following criteria are excluded from participation in this study:

1. Known hypersensitivity to study drug ingredients or a significant allergic reaction to any drug as determined by the investigator, such as anaphylaxis requiring hospitalization.
2. Positive serology for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus (HCV) or any history of hepatitis from any cause with the exception of hepatitis A.
3. History of or a current immunosuppressive condition (e.g., human immunodeficiency virus [HIV] infection).
4. History of or evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) diagnosed by a positive QuantiFERON® TB-Gold In Tube test or a positive tuberculin skin test ("Mantoux") in case of a weak positive QuantiFERON® TB-Gold In Tube test.
5. Subjects with known clinically relevant immunological disorders.
6. History of severe allergic or anaphylactic reactions.
7. Symptoms of clinically significant illness in the 3 months before the initial study drug administration.
8. Presence or having sequelae of gastrointestinal, liver, kidney or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
9. History of malignancy within the past 5 years (except for basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
10. Clinically relevant abnormalities detected on ECG regarding either rhythm or conduction (e.g., QTcF > 450 ms [male subjects] or >470 [female subjects], or a known long QT syndrome). A first degree heart block or sinus arrhythmia will not be considered as a significant abnormality.
11. Clinically relevant abnormalities detected on vital signs
12. Significant blood loss (including blood donation [> 500 mL]), or had a transfusion of any blood product within 12 weeks prior to the initial study drug administration or plan one within 4 weeks after the end of the study.
13. Treatment with any drug known to have a well-defined potential for toxicity to a major organ in the last 3 months preceding the initial study drug administration.
14. The subject has a history of consuming more than 21 (14 for females) units of alcoholic beverages per week or has a history of alcoholism or drug/chemical/substance abuse within past 2 years prior to

screening (Note: one unit = 330 mL of beer, 110 mL of wine or 28 mL of spirits). Consumption of a large quantity of coffee, tea (> 6 cups per day) or equivalent.
15. Administration of an injectable drug within 30 days prior to the initial study drug administration.
16. Concurrent participation, or participation within 8 weeks prior to the initial study drug administration in a drug/device or biologic investigational research study, or participation within 15 weeks prior to initial study drug administration in an investigational research study with biologic response modifier administration.
17. Administration of a vaccine within 60 days prior to initial study drug administration.
18. Administration of any systemic immunosuppressant agent within 6 months prior to initial study drug administration.
19. Administration of any systemic steroid within 2 months prior to initial study drug administration;
20. Use of a prohibited therapy within 14 days prior to initial study drug administration.
21. Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof who is directly involved in the conduct of the study.
22. Any condition or circumstances that in the opinion of the investigator may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.
23. Pregnant or lactating women or women of childbearing potential.
24. Unsuitable vein for infusion and/or blood sampling.

Test Product, Dose, Mode of Administration:

- ARGX-113 is formulated as a sterile colorless, clear liquid for IV injection.
- The placebo will be provided as a sterile colorless, clear liquid for IV injection with the same formulation without the active ingredient ARGX-113.

ARGX-113/placebo will be administered according to the dosing schedules presented in the schematic overview of the study design.

Study/Treatment Duration:

Part 1 (SAD):

- The study consists of a screening phase (within up to 28 days before the first administration of study drug [ARGX-113 or placebo]), 1 confinement visit (Days -1 to 5), and 4 additional visits to the clinic. The total study length (per subject) will be up to 57 days; which includes the screening phase.

Part 2 (MAD):

- The study consists of a screening phase (within up to 28 days before the first administration of [ARGX-113 or placebo]), 1 confinement visit (Days -1 to 25), and up to 8 additional visits to the clinic. The total study length (per subject) will be up to 107 days; which includes the screening phase.

Criteria for Evaluation:

Safety

- Safety signals will be assessed to determine dose escalation. Blinded safety data review meetings (Safety Committee), consisting of (but not limited to) the sponsor's Medical Monitor and the Principal Investigator will be conducted after each cohort to confirm the decision to move forward with each dose escalation.
- If safety signals are detected, including observed toxicities and/or based on the available pharmacodynamic (PD) effect, the Safety Committee can advise that the dose in the following cohort can be repeated, replaced with an intermediate dose, or decreased (Part 1).
- The decision to repeat, decrease, increase, or select an intermediate dose will be made upon satisfactory review of blinded safety data (up to at least Day 5 for Part 1: SAD and up to at least 5 days post last dose for Part 2: MAD) in at least 5 subjects from the preceding dose level, as well as blinded PK and PD data obtained on an ongoing basis as available, by the Safety Committee.

Pharmacokinetic

Individual subject plasma ARGX-113 concentrations will be used to derive PK parameters using a non-compartmental method.

The following PK parameters will be estimated, where appropriate: C_{max}, t_{max}, C_{72h} (C_{168h}), AUC_{0-t}, AUC_{0-72h} (AUC_{0-168h}), AUC_{inf}, $t_{1/2,\lambda,z}$, CL, and V_z. Cumulative amount excreted (Ae) in urine for each collection interval and in total will be calculated in absolute and % of administered dose values. CL_R and CL_{CR} (to check urine collection compliance) will also be presented. In addition, after multiple dose administrations, R_{ac} will be calculated.

Other PK parameters may be calculated as appropriate.

Dose normalized parameters (C_{max}/dose, C_{72h}/dose, C_{168h}/dose, AUCs/dose, Ae%) will be assessed. Additional PK parameters may be calculated as appropriate.
Creatinine analysis will be performed in urine to check urine collection compliance. Creatinine clearance (CL_{CR}) will be calculated for each fraction.

Pharmacodynamics

Pharmacodynamic assessments will be conducted for the SAD and MAD studies to measure for the total immunoglobulin G (IgG) , IgG subtype (IgG 1, IgG 2, IgG 3, and IgG 4), IgA, IgD, IgE and IgM levels.
The PD effect will be measured by endogenous immunoglobulin concentration versus baseline change (in %). The following parameters will be calculated, where appropriate, from individual data of total IgG, IgG subtypes (1, 2, 3, and 4), IgA, IgD, IgE, IgM change from baseline: E_{max}, $t_{Emax,\ and}$ AUEC.
Unlike total IgG and IgG subtype levels, no changes in IgA, IgD, IgE, IgM levels are to be expected based on FcRn biology and pre-clinical data. As such, the abovementioned parameters will only be calculated for these types of immunoglobulins if a PD effect is observed.
The relationship between ARGX-113 concentration and total IgG or IgG subtypes 1, 2, 3, and 4, change from baseline values will be graphically presented. If appropriate, graphical relationship between main PK and PD parameters will also be assessed.
The PK/PD relationship will be assessed graphically.

Immunogenicity

Individual plasma titer of anti-drug antibodies (ADA) directed against ARGX-113 will be measured before first administration of ARGX-113 and at selected time points following first administration of ARGX-113 (SAD) and before every administration of ARGX-113 and at selected time points following last administration of ARGX-113 (MAD).

Statistical Methods:

Sample size

- As this is the first in human clinical study and no clinical data is available, no formal sample size calculations have been performed for both parts of the clinical study.
- The sample size has been selected for practical considerations and is based upon experience from similar past clinical study designs.
- The selected number of subjects is considered sufficient to achieve the clinical study objectives.

Pharmacokinetics

- In the SAD part, proportionality between the dose administered and the PK parameters will be assessed by means of a mixed-effects analysis of variance (ANOVA) model with cohort and dose (nested within cohort) as fixed effects, and subject (nested within cohort) as random effect in the model on the following ln-transformed ARGX-113 parameters: C_{max}/dose, C_{72h}/dose, $AUC_{0\text{-}72h}$/dose, AUC_{inf}/dose, total Ae %, CL_R and $t_{1/2,\lambda z}$ (if possible). In case of significant dose effect observed on these parameters, comparison between doses will be performed using Tukey's test. As t_{max} is a discrete variable dependent on selected blood sampling times, dose effect will be assessed using a non-parametric Kruskal-Wallis test and in case statistically significant, applying Wilcoxon's rank sum test with Moses' 90% confidence intervals for pairwise comparisons.
- In the MAD part, proportionality between the dose administered and the PK parameters will be assessed, when appropriate, by means of a mixed effects model on ln-transformed ARGX-113 (C_{max}/dose, C_{72h}/dose or C_{168h}/dose, AUC_{72h}/dose or AUC_{168h}/dose, and $t_{1/2,\lambda z}$,) with random subject effect and with day, dose and dose*day interaction as fixed effects. The dose effect on ln-transformed R_{ac} will be evaluated from a mixed effect analysis of variance with dose as fixed effect and subject as random effect. As t_{max} is a discrete variable dependent on selected blood sampling times, the dose effect will be assessed using a non-parametric Wilcoxon's rank sum test plus 90% CIs. The day effect will be tested using the non-parametric Wilcoxon's signed ranks test.

Pharmacodynamics

- In the SAD part, percent change at each postdose time point for IgG, AUECs and E_{max} will be compared between the treatment groups (placebo subjects pooled) using an ANOVA model with treatment as fixed effect. In case of a significant treatment effect, pairwise comparison between treatments will be performed using Tukey's test.
  As t_{Emax} is a discrete variable dependent on selected blood sampling times, comparison between treatment groups (placebo subjects pooled) will be assessed using a non-parametric Kruskal-Wallis test and in case statistically significant, applying Wilcoxon's rank sum test with Moses' 90% CIs for pairwise comparisons.

- In the MAD part, percent change at each postdose time point for IgG, AUECs and E_{max} will be compared, when appropriate, between the treatment groups (placebo subjects pooled), separately for each administration day, using an ANOVA model with treatment as fixed effect. In case of a significant treatment effect, pairwise comparison between treatments will be performed using Tukey's test.
  As t_{Emax} is a discrete variable dependent on selected blood sampling times, comparison between treatment groups (placebo subjects pooled) will be assessed using a non-parametric Kruskal-Wallis test, with pairwise comparisons using Wilcoxon's rank sum test plus 90% CIs (only in case the overall dose effect is statistically significant). The day effect will be tested using the non-parametric Wilcoxon's signed ranks test.

Safety

- The following safety parameters will be tabulated and analyzed descriptively: adverse events, clinical laboratory tests, ECGs, physical examinations, and vital signs.

TIME AND EVENTS SCHEDULE: PART 1

Time of Visit (days)	Screening[a]	Day -1	Day 1				Day 2	Day 3	Day 4	Day 5	Day 7	Day 15	Day 22	Day 29 / Follow-up Visit
			Hours relative to start of study drug infusion											
Time From Dose			0h[b]	2h[c]	4h	8h	24h	48h	72h	96h	144h	336h	504h	672h
Informed consent[d]	X													
In-/exclusion criteria	X	X												
Medical history/ concomitant diseases	X													
Demographic data	X													
Physical examination	X[e]	X[e]	X[g]				X			X				X
Vital signs[f]	X	X	X[g]	X	X	X	X		X	X	X	X	X	X
Single 12-lead ECG	X	X	X[g]	X	X	X	X		X	X	X	X	X	X
Clinical laboratory tests[h]	X		X[g]				X	X	X	X	X	X	X	X
Serum albumin determination			X[g]	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte typing: B, T_{subset} and NK cells	X		X[g]	X	X	X	X		X		X	X	X	X
Urinalysis	X		X[g]				X		X	X	X	X	X	X
Pharmacokinetics: Blood			X[g]	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics: Urine collection[i]		X	X ←						→ X					
Pharmacodynamics[j]			X[g]	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies (ADA)			X[g]							X	X	X	X	X
Urine drug screen and alcohol breath test[k]	X	X												
Pregnancy test[l]	X	X												X
Virology/Bacterial screen[m]	X													
Randomization			X[g]											
Administration of study drug[n]			X											
Confinement		Check-in ←								→ Check-out[o]				
Concomitant therapies[p]	X ←													→ X
Adverse events[p]	X ←													→ X

a. To take place between 1 and 28 days prior to administration of study drug.

b. 0h represents the start of infusion of study drug.

c. Assessments to take place immediately following end of study drug infusion.
d. No study-related assessment is to be carried out before signing of the informed consent form.
e. Includes weight, height and BMI at screening and weight only on Day-1.
f. Blood pressure and pulse rate (supine) and oral body temperature.
g. Assessments should be completed pre-dose.
h. Blood samples for safety assessments should be taken after an overnight fast (fasting for at least 10h) for unbiased glucose determination. Safety assessments to include Biochemistry, and Hematology.
i. Urine PK collections to be taken between first void (at which the subjects empty their urinary bladder) until 0 hours pre-dose and according to the following windows postdose: 0-4h, 4-8h, 8-12h, 12-24h, 24-48h, 48-72h.
j. Total IgG, IgG subtypes (IgG 1, IgG 2, IgG 3, and IgG 4), IgA, IgD, IgE and IgM.
k. Urine drug screen will test for: amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone, and tricyclic antidepressants.
l. For women, a serum pregnancy test at screening and urine pregnancy test at other visits will be performed.
m. Includes HbsAg and anti-HCV antibodies, HIV antibodies and TB serology.
n. Study drug will be administered as an IV infusion over 2h.
o. Subjects will be released from the unit once review (clinical laboratory test, albumin, physical examination, vital signs and ECG) has been completed of all Day 5 safety assessments.
p. Adverse events and intake of concomitant medication(s) will be monitored continuously from informed consent signature until the last study-related activity.

TIME AND EVENTS SCHEDULE: PART 2: 4-DAY DOSING INTERVAL (COHORT 7)

Time of Visit (days)	**Screening**[a]	**Day -1**	**Days 1, 5, 9, 13**[b]**, and 17**								**Day 21**	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 27**	**Day 30**	**Day 35**	**Day 42**	**Day 49 / FU Visit**	**Day 63 / FU Visit**[s,t]	**Day 77 / FU Visit**[s,t]
			Hours relative to start of study drug infusion								**Hours relative to start of study drug infusion**											
Time From Last Dose			**0h**[c]	**2h**[d]	**4h**	**8h**	**12h**	**24h**	**48h**	**72h**	**0h**	**24h**	**48h**	**72h**	**96h**	**144h**	**216h**	**336h**	**504h**	**672h**	**1008h**	**1344h**
Informed consent[e]	X																					
In-/exclusion criteria	X	X																				
Medical history/ concomitant diseases	X																					
Demographic data	X																					
Physical examination	X[f]	X[f]	X[h]								X[h]	X			X		X			X	X	X
Vital signs[g]	X	X	X[h]	X	X	X	X	X	X	X	X[h,i]	X	X	X	X	X		X	X	X[u]		X
Single 12-lead ECG	X	X	X[h]	X	X	X	X	X	X	X	X[h,i]	X	X	X	X	X		X	X	X[u]		X
Clinical laboratory tests[j]	X		X[h]					X		X	X[h]	X		X		X	X	X	X	X	X	X
Serum albumin determination			X[h]			X		X		X	X[h]	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte typing: B, T_{subset} and NK cells	X		X[h]					X			X[h]	X			X		X	X		X	X	X
Urinalysis	X		X[h]					X			X[h]	X		X		X	X	X	X	X	X	X
Pharmacokinetics: Blood			X[h]	X		X		X	X	X	X[h,i]	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics[k]			X[h]	X		X		X	X	X	X[h,i]	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies (ADA)			X[h]								X[h]			X		X		X	X	X		
Urine drug screen and alcohol breath test[l]	X	X																				
Pregnancy test[m]	X	X																		X[u]		X
Virology/Bacterial screen[n]	X																					
Randomization			X[o]																			
Administration of study drug[p]			X								X											

Confinement		Check-in ←													Check-out[q]						
Concomitant therapies[r]	X	←																→	X	X	X
Adverse events[r]	X	←																→	X	X	X

a. To take place between 1 and 28 days prior to administration of study drug.
b. The following assessments will not be completed on Day 13: serum albumin determination, lymphocyte typing, vital signs, and ECG.
c. 0h represents the start of infusion of study drug.
d. Assessments to take place immediately following study drug infusion.
e. No study-related assessment is to be carried out before signing of the informed consent form.
f. Includes weight, height and BMI at screening and weight only on Day -1.
g. Blood pressure and pulse rate (supine) and oral body temperature.
h. Assessments should be completed pre-dose on all study drug infusion days.
i. On Day 21, assessments should follow the same postdose collection schedule (at 2h, 4h, 8h, and 12h postdose where applicable) as for Days 1, 5, 9, 13 (where applicable), and 17.
j. Blood samples for safety assessments should be taken after an overnight fast (fasting for at least 10h) for unbiased glucose determination.
k. Total IgG, IgG subtypes (IgG 1, IgG 2, IgG 3, and IgG 4), IgA, IgD, IgE and IgM.
l. Urine drug screen will test for: amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone, and tricyclic antidepressants.
m. For women, a serum pregnancy test at screening and urine pregnancy test at other visits will be performed.
n. Includes HbsAg and anti-HCV antibodies, HIV antibodies and TB serology.
o. Randomization to be completed pre-dose on Day 1 only.
p. Study drug will be administered as an IV infusion over 2h every 4 days (96h) (i.e., on Days 1, 5, 9, 13, 17 and 21). The dosing interval for the Part 2 MAD Cohort 9 will be chosen following review of the blinded data from the Part 2 MAD Cohort 8 (see Section 3.4.2).
q. Subjects will be released from the unit once review (clinical laboratory tests, albumin, physical examination, vital signs and ECG) has been completed of all Day 25 safety assessments.
r. Adverse events and intake of concomitant medication(s) will be monitored continuously from informed consent signature until the last study-related activity.
s. These visits can be planned with a window of ± 2 days.
t. Not applicable for Cohort 9.
u. Only applicable for Cohort 9 and for subjects in Cohort 7 who do not consent to the additional visits added in this amendment.

TIME AND EVENTS SCHEDULE: PART 2: 7-DAY DOSING INTERVAL (COHORT 8, COHORT 9, AND COHORT 10)

Time of Visit (days)	Screening[a]	Day -1	Days 1, 8, and 15								Day 22	Day 23	Day 24	Day 25	Day 27	Day 28	Day 31	Day 36	Day 43	Day 50 / FU Visit	Day 64 / FU Visit[d,e]	Day 78 / FU Visit[d,e]
			Hours relative to start of study drug infusion								Hours relative to start of study drug infusion											
Time From Last Dose			0h[b]	2h[c]	4h	8h	12h	24h	72h	120h	0h	24h	48h	72h	120h	144h	216h	336h	504h	672h	1008h	1344h
Informed consent[f]	X																					
In-/exclusion criteria	X	X																				
Medical history/ concomitant diseases	X																					
Demographic data	X																					
Physical examination	X[g]	X[g]	X[i]								X[i]	X			X		X			X	X	X
Vital signs[h]	X	X	X[i]	X	X	X	X	X	X	X	X[i,j]	X	X	X	X	X		X	X	X[k]		X
Single 12-lead ECG	X	X	X[i]	X	X	X	X	X	X	X	X[i,j]	X	X	X	X	X		X	X	X[k]		X
Clinical laboratory tests[l]	X		X[i]					X	X	X	X[i]	X		X		X	X	X	X	X	X	X
Serum albumin determination			X[i]					X	X	X	X[i]	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte typing: B, T_{subset} and NK cells	X		X[i]					X		X	X[i]	X			X		X	X		X	X	X
Urinalysis	X		X[i]					X		X	X[i]	X		X		X	X	X	X	X	X	X
Pharmacokinetics: Blood			X[i]	X		X		X	X	X	X[i,j]	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics[m]			X[i]	X		X		X	X	X	X[i,j]	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies (ADA)			X[i]								X[i]			X		X		X	X	X		
Urine drug screen and alcohol breath test[n]	X	X																				
Pregnancy test[o]	X	X																		X[k]		X
Virology/Bacterial screen[p]	X																					
Randomization			X[q]																			
Administration of study drug[r]			X								X											

Confinement		Check -in ←												Check -out[s] →							
Concomitant therapies[t]	X	←																→	X	X	X
Adverse events[t]	X	←																→	X	X	X

a. To take place between 1 and 28 days prior to administration of study drug.
b. 0h represents the start of infusion of study drug.
c. Assessments to take place immediately following study drug infusion.
d. These visits can be planned with a window of ± 2 days
e. Not applicable for Cohort 9.
f. No study-related assessment is to be carried out before signing of the informed consent form.
g. Includes weight, height and BMI at screening and weight only on Day -1.
h. Blood pressure and pulse rate (supine) and oral body temperature.
i. Assessments should be completed pre-dose on all study drug infusion days.
j. On Day 22, assessments should follow the same postdose collection schedule (at 2h, 4h, 8h, and 12h postdose where applicable) as for Days 1, 8, and 15.
k. Only applicable for Cohort 9.
l. Blood samples for safety assessments should be taken after an overnight fast (fasting for at least 10h) for unbiased glucose determination.
m. Total IgG, IgG subtypes (IgG 1, IgG 2, IgG 3, and IgG 4), IgA, IgD, IgE and IgM.
n. Urine drug screen will test for: amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone, and tricyclic antidepressants.
o. For women, a serum pregnancy test at screening and urine pregnancy test at other visits will be performed.
p. Includes HbsAg and anti-HCV antibodies, HIV antibodies and TB serology.
q. Randomization to be completed pre-dose on Day 1 only.
r. Study drug will be administered as an IV infusion over 2h every 7 days (i.e., on Days 1, 8, 15, and 22). The dosing interval for the Part 2 MAD Cohort 9 will be chosen following review of the blinded data from the Part 2 MAD Cohort 8 (see Section 3.4.2).
s. Subjects will be released from the unit once review (clinical laboratory tests, albumin, physical examination, vital signs and ECG) has been completed of all Day 25 safety assessments.
t. Adverse events and intake of concomitant medication(s) will be monitored continuously from informed consent signature until the last study-related activity.