Protocol

Investigation on Safety in Male Subjects

Table of Contents

Page

List of Abbreviations

ADA	American Diabetes Association
ACC	American College of Cardiology
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
ASCVD	assessment of cardiovascular disease risk
AST	aspartate aminotransferase
AUC	area under concentration-time curve
BG	blood glucose
BMI	body mass index
CHO	chinese hamster ovary
CLAE	clinical laboratory adverse event
CL/F	apparent total clearance
C_{max}	maximum observed concentration
WHO	World Health Organization

1 Summary

This is a first-in-man trial investigating the safety, This is a first-in-man trial investigating the safety. This is a first-in-man trial investigating the safety

Objectives and endpoints:

Primary objective

- To assess the safety This is a first-in-man trial investigating the safety

Primary endpoint

- Number of treatment assess the safety This is a first-in-man trial investigating the safety

Key secondary objective

- To assess the assess the safety This is a first-in-man trial investigating the safety

Key secondary endpoints

- $C_{max,SD}$; tassess the safety This is a first-in-man trial investigating the safety
- $t_{max,SD,}$; the time toassess the safety This is a first-in-man trial investigating the safetye

Trial design:

This first human assess the safety This is a first-in-man trial investigating the safety assess the safety This is a first-in-man trial investigating the safety.

assess the safety This is a first-in-man trial investigating the safety.

Key inclusion criteria

- Male assess the safety This is a first-in-man trial investigating the safety assess the safety This is a first-in-man trial investigating the safety nt
- Body assess the safety This is a first-in-man trial investigating the safetyr

Key exclusion criteria

- Any disorassess the safety This is a first-in-man trial investigating the safetyotocol
- Subjects, aged assess the safety This is a first-in-man trial investigating the safety
- Male subjects who are not (such as condom with spermicide) combined with a highly effective method (Pearl Index < 1%, such as implants, injectables, in the period from screening until 3 months following he investigational medical product.

Assessments:

Safety

The safety assessment will be based on adverse events, laboratory safety parameters (urinalysis, haematology, biochemistry, coagulation parameters and hormones as well as lipids), vital signs,

electrocardiograms (12-lead ECG and continuous ECG monitoring [telemetry]), local tolerability, physical examination and hypoglycaemic episodes.

Pharmacokinetics

The plasma concentrations of DRUG A will be measured pre-dose and un 44 hours) post administration of a single subcutaneous dose of either the active or placebo treatment.

Investigational medicinal products:

- Test product: DRUG A A 2000 mg/mL solution for injection
- Placebo product: Placebo DRUG A A solution for injection

2 Flow chart

3 Background information and rationale for the trial

The triassess the safety This is a first-in-man trial investigating the safety, ICH GCP [1] and applicable rassess the safety This is a first-in-man trial investigating the safetyaccordance with the Declaration of Helsinki [2].

In this document, the tassess the safety This is a first-in-man trial investigating the safety conduct of the clinical trial at a trial site. Background information

3.1.1 Therapeutic area

Diseasassess the safety This is a first-in-man trial investigating the safety is an emerging epidemic in developing countries[3]. Disease A is a chronic assess the safety This is a first-in-man trial investigating the safetyemia (pre-diabetes and type 2 diabetes), dyslipidaemia, certain types of cancer, sleep apnoea and atherosclerosis [4] as well as a reduced life expectancy[5, 6]. Moreover, Disease A canassess the safety This is a first-in-man trial investigating the safetyand reduce quality of life[7].

The prevalence oassess the safety This is a first-in-man trial investigating the safetyportions, with close to 2 billion people in 2014 being overweight (i.e., BMI ≥25 kg/m^2) and more than 600 million being clinically obese (i.e., BMI ≥30 kg/m^2)[8].

Althoassess the safety This is a first-in-man trial investigating the safetyleep apnoea[9-12].

Lifestyle intervention iassess the safety This is a first-in-man trial investigating the safetyith Disease A.

3.1.2 DRUG A

DRUG A is an acassess the safety This is a first-in-man trial investigating the safety.

GLLassess the safety This is a first-in-man trial investigating the safetyor with Disease A[13]. The mechanism has been shown to be a reduction of energy iassess the safety This is a first-in-man trial investigating the safetyappetite and an induction of satiety[14-16].

Endogenous glucassess the safety This is a first-in-man triaassess the safety This is a first-in-man trial investigating the safetyl investigating the safetyd to satiety, reduced body weight and improved blood lipid parameters[17]. It has also been assess the safety This is a first-in-man trial investigating the safetyptimally balanced GLLLLP and glucagon receptor co-agonists results in synergistic body weight loss and glucose tolerance siassess the safety This is a first-in-man trial investigating the safetygonism alone[18, 19].

The data bassess the safety This is a first-in-man trial investigating the safetyon for any therapeutic use are the most limited[20]. Some data postulates assess the safety This is a first-in-man trial investigating the safety effect in type 2 diabetes[21], but there is no clinical data for the use of GIP agonism in weiassess the safety This is a first-in-man trial investigating the safetyted to induce body weight loss accompanied by improved glucose control. DRUG B is envisaged to be indicated in treatment of Diseassess the safety This is a first-in-man trial investigating the safety, like patients with type 2 diabetes, could also be sought.

Nonclinical pharmacology

DRUG assess the safety This is a first-in-man trial investigating the safetycagon receptors. DRUG A activated the GLLLLP receptor and GIP receptor with comparable potencies as native GLLLLP and GIP, respectively, assess the safety This is a first-in-man trial investigating the safetytor with a 10−100 fold lower potency than native glucagon. The *in vitro* potency of DRUG A in CHO cells which are stablassess the safety This is a first-in-man trial investigating the safetyld with 50% human plasma, indicatinassess the safety This is a first-in-man trial investigating the safetyns as expected from the molecular structure.

DRUG A has beenassess the safety This is a first-in-man trial investigating the safety DIO monkeys, DRUG A treatment caused body weight loss, primarily driven by lower food intake. The body weight loss was greater than whaassess the safety This is a first-in-man trial investigating the safety by food intake reduction, indicating an increase of energy expenditure, most likely induced by the glucagon component.

Nonclinical safety

Nonclinical safetyassess the safety This is a first-in-man trial investigating the safetyaccordance with international guidelines, including the ICH M3(R2) Guideline on Nonclinical Safety Studies for the Conduct of Humanassess the safety This is a first-in-man trial investigating the safetyd Marketing Authorization for Pharmaceuticals[22]. The nonclinical safety programme for DRUG A comprises safety pharmacologassess the safety This is a first-in-man trial investigating the safetynkey.

Safety pharmacology

In the safety pharmacology studies, an increase in heart rate was seen in the rat and the monkey at all dose levels. An inassess the safety This is a first-in-man trial investigating the safety. As a NOAEL was not identifiedassess the safety This is a first-in-man trial investigating the safety dose level resulted in the lowest HED when compared to the LOAEL in the monkey telemetry study and the NOAELs/LOAELS in the assess the safety This is a first-in-man trial investigating the safetyver, as a NOAEL wasassess the safety This is a first-in-man trial investigating the safetySD in the present FHD trial (see Section 5.4.1).

Toxicology

DRUG A showeassess the safety This is a first-in-man trial investigating the safetyiated decrease in body weight and food consumption at all dose levels in the rat and monkey resulted in secondary changes in clinical pathology, organ weights and pathology. The liver was identified as a potential target organ with the following findings:

- A pharmacoloassess the safety This is a first-in-man trial investigating the safetySlight increase in liver enzymes at allassess the safety This is a first-in-man trial investigating the safety
- ver cells with a NOAEL of 45 µg/kg in the rat
- Multifocal necrosis of liver cells and increase in liver enzymes with a NOAEL of 10 µg/kg in the monkey

In addition decreaassess the safety This is a first-in-man trial investigating the safetyys.

Anti-drug antibodies were measured in the 4-week GLP studies in the rat and monkey. Anti-drug antibodies were detecassess the safety This is a first-in-man trial investigating the safetyys resulted in large variation in systemic exposure, there was no clear correlation to body weight change.

Nonclinical pharmacokinetics

The DMPK of DRUG A has been assessed *in vitro* and *in vivo*. In *in vitro* studies in rat, monkey and human cell lines the compound was shown to be stable in plasma, bind to plasma proteins (as expected) and metabassess the safety This is a first-in-man trial investigating the safetyn short terminal half-life ($t_{½}$) after intravenous dosing (1 and 3.5 hours, respectively). In contrast, the $t_{½}$ after s.c. dosing was longer in bothassess the safety This is a first-in-man trial investigating the safety s.c. dosing in the rat and cynomolgus monkey, respectively. Subcutaneous bioavailability was 20-30% in the rat and higher in the monkey (40%).

In both species, no major sex differences in systemic exposures were evident. Exposure also generally increased in a dose-passess the safety This is a first-in-man trial investigating the safetyortionality was seen (especially for rat). In the rat, low or no systemic accumulation was observed after repeated once daily s.c. dosing fassess the safety This is a first-in-man trial investigating the safetyonclusive.

Conclusion

The nonclinical saassess the safety This is a first-in-man trial investigating the safetysessments will be part of the safety parameters monitored in the present clinical trial.

For further information about the nonclinical data supporting the proposed clinical trial, please refer to the current version of Investigator's Brochure [23] and any updates thereof.

3.2 Rationale for the trial

DRUG A is a potent and triple agonist of GLLLLP, GIP and glucagon receptors and is under development for wassess the safety This is a first-in-man trial investigating the safetylucose control. It is therefore of interest to explore the potential of DRUG A as a weight management drug.

The present trial is theassess the safety This is a first-in-man trial investigating the safetyA A 2000 mg/mL solution for injection (the test product is hereafter referred to as DRUG A A 2000 mg/mL), in male subjects being overweight or with Disease A (BMI: 25.0-34.9 kg/m^2). It is not expected to observe marked PD effects of a single dose of DRUG A due to the expected short terminal half-life. Thus the exploration of PD effects will only be limited to very few PD parameters.

A randomised (within cohorts), assess the safety This is a first-in-man trial investigating the safetyefore proceeding to the higher exposure cohort.

The data obtained from this trial will provide information to guide further clinical development of DRUG A for weight managementassess the safety This is a first-in-man trial investigating the safetybetes mellitus.

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

- To assess the safeassess the safety This is a first-in-man trial investigating the safetyase A

4.1.2 Secondary objective

- To assess the pharmaassess the safety This is a first-in-man trial investigating the safety with Disease A
- To explore the pharmacodynamics of single doses of DRUG A administered injection in male subjects being overweight or with Disease A
- To explore a potential exposassess the safety This is a first-in-man trial investigating the safetytween plasma concentrations of DRUG A and changes in QTcF

4.2 Endpoints

4.2.1 Primary endpoint

- Number of treatmenassess the safety This is a first-in-man trial investigating the safetyt-treatment follow-up March (Days 10-13)

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary safety endpoints

Safety endpoints to be used foassess the safety This is a first-in-man trial investigating the safetyprimary objective.

- Change from baseline (pre-doassess the safety This is a first-in-man trial investigating the safetyup March (Days 10-13) in:
  - Clinical laboratory safeassess the safety This is a first-in-man trial investigating the safetyrameters,
  - Vital signs (body temperatuassess the safety This is a first-in-man trial investigating the safety blood pressure)

- Change inassess the safety This is a first-in-man trial investigating the safety-treatment assessments until 48 hours post-dose
- Number of injectionassess the safety This is a first-in-man trial investigating the safetyollow-up March (Days 10-13)
- Number of hypoglycaassess the safety This is a first-in-man trial investigating the safetyhe follow-up March (Days 10-13)

4.2.2.2 Supportive secondary pharmacokinetic endpoints

The followingassess the safety This is a first-in-man trial investigating the safetyy to Day 7:

- $AUC_{0-\infty,SD}$; the area under the DRUG A plasma concentration-time curve from time 0 to infinity assess the safety This is a first-in-man trial investigating the safetytime point for the last quantifiable sample after administration of a single subcutaneous dose
- $C_{max,SD}$; the maximum observed concentration of DRUG A in plasma after administration of a single subcuassess the safety This is a first-in-man trial investigating the safetyous dose *
- $t_{½,SD}$; the terminal half-life of DRUG A after administration of a single subcutaneous dose
- MRT_{SD}; the meanassess the safety This is a first-in-man trial investigating the safety
- residence time of DRUG A after administration of a single subcutaneous dose
- CL/F_{SD}; the apparent total plasma clearance of DRUG A after administration of a single subcutaneous dose
- V_z/F_{SD}; the apparent volume of distribution of DRUG A after administration of a single subcutaneous dose

4.2.2.3 Supportive secondary pharmacodynamic endpoints

- Change from bassess the safety This is a first-in-man trial investigating the safetyp March (Days 10-13) in:
  - Body weight
  - Glucose metabolism: plassess the safety This is a first-in-man trial investigating the safetyulin, C-peptide and glucagon

Key supportive seconassess the safety This is a first-in-man trial investigating the safetyn asterisk (*).

5 Trial design

5.1 Type of trial

This first-in-man trassess the safety This is a first-in-man trial investigating the safety s.c. in male subjects being overweight or with Disease A (BMI - 34.9 kg/m^2). The ascending dose levels in the trial aims at establishingassess the safety This is a first-in-man trial investigating the safetyG A. For a schhe trial design, see Figure 5–1

Figure 5–1 Schematic overview of trial design

A total of 56 male subjects are plaPDFEMed to be assess the safety This is a first-in-man trial investigating the safetynsisting of 8 subjects. be diluted, see Table 5–1) and 2 sassess the safety This is a first-in-man trial investigating the safetyubjects will be randomised to a s.c. single dose of DRUG A A 2000 mg/mL (in the 2 first dose cohorts, the test product will be diluted, see Table 5–1) and 2 subjects will be randomassess the safety This is a first-in-man trial investigating the safetyUG A will be performed just prior to dosing and the followinassess the safety This is a first-in-man trial investigating the safetyMarch (please see Figure 5–2).

Dosing in eaccohort, 6 subjects will be assess the safety This is a first-in-man trial investigating the safetyll be diluted, see Table 5–1) and 2 subjects wassess the safety This is a first-in-man trial investigating the safetydosing and the followingassess the safety This is a first-in-man trial investigating the safetyt). Following a safety observation period of at least 24 hours, the remaining 6 subjects in the cosequent days (see Section 5.4.3). A maximassess the safety This is a first-in-man trial investigating the safety be dosed on each dosing day.

The dose levels of DRUG A assess the safety This is a first-in-man trial investigating the safetyascending maPDFEMer (see Table 5–1). The decision to proceed to the next dose level will be made by a House Trial GGGGG roup based on assassess the safety This is a first-in-man trial investigating the safetyy safety and tolerability data (obtained up to 6 days post dosing, see Section 5.3.3.1), PD (obtained up to 6 days post dosing, see Section 5.3.3.1) and PK (obtained up to 24 hours post dosing). The trial activities assess the safety This is a first-in-man trial investigating the safetyprior to March 1), a screening March (March 1) to determine the eligibility of the subjects

(3-28 days prior to Massess the safety This is a first-in-man trial investigating the safetytay until Day 5 (4 days after dose administration), or longer if assess the safety This is a first-in-man trial investigating the safetyry by the investigator.

The subjects will return for 1 out-patiassess the safety This is a first-in-man trial investigating the safetyose cohort are presented in the Flow Chassess the safety This is a first-in-man trial investigating the safetylow-up March), see 错误!未找到引用源。).

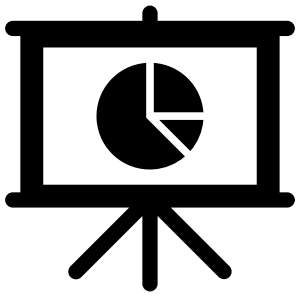

Figure 5–2 Trial duration per subject

5.2 Rationale for trial design

The single ascending doseut-assess the safety This is a first-in-man trial investigating the safetylly to ensure the safety of the enrolled subjects at the same time as clinical information is obtained from increasing doses of the IMP.

The inclusion of placebo treated subjecassess the safety This is a first-in-man trial investigating the safetydity of the trial.

The use lly to ensure the safety ofassess the safety This is a first-in-man trial investigating the safetyon is obtained fro idity of the trial. ls will allow for an evaluation of the safety window of the test product.

The PK data h dose level enables a drug-related evaluation of the safety within the dose cohorts, and helps to ally tassess the safety This is a first-in-man trial investigating the safetyro idity of the trial. ety data for the individual subjects, and they assess the safety This is a first-in-man trial investigating the safetywill be presented in such a maPDFEMer that unblinding of the Trial GGGGG roup is avoided.

The selected evaluation of the safety within tassess the safety assess the safety This is a first-in-man trial investigating the safetyThis is a first-in-man trial investigating the safetys) and t½ (approximately 5-11 hours) of DRUG A in humans (see 错误!未找到引用源。).

5.3 Treatment of subjects

DRUG A A 2000 mg/mL will be proassess the safety This is a first-in-man trial investigating the safetytion. Please see the list of IMPs for administration in Table 9–1.

5.3.1 PlaPDFEMed treatments and dose levels

Subjects will be randomisassess the safety This is a first-in-man trial investigating the safetySeven fixed dose levels of single s.c. doses of DRUG A are plaPDFEMed to be investigated in an evaluation of the safety within the dassess the safety This is a first-in-man trial investigating the safetyRUG A A (see Table 5–1 and Section 5.4 for information). or Plaassess the safety This is a first-in-man trial investigating the safetye investigated in an evaluation of the safety within the dose cohorts, and helps to ally to ensure the safety or correspondingassess the safety This is a first-in-man trial investigating the safetymevaluation of the safety within the dose cohorts, and helps to ally to ensure the safety has been completed (see Section 5.3.3.4) or if the maximum tolerable dose has been reached.

An unblinded or Placebo assess the safety This is a first-in-man trial investigating the safetyen fixed dose levels of single s.c. doses of DRUG A are passess the safety This is a first-in-man trial investigating the safetyan evaluation assess the safety This is a first-in-man trial investigating the safetyest product (see Table 5–1). Trial product that has been stored improperly must not be dispensed to any subject before it has been re-evassess the safety This is a first-in-man trial investigating the safetyroved for further use by House.

Please refer to assess the safety This is a first-in-man trial investigating the safety the safety within the dose cohorts, and helps to ally to ensure the safetassess the safety This is a first-in-man trial investigating the safetyy or correspondingose preparation.

Table 5–1 PlaPDFEMed fixed dose levels in a single ascending dose trial

Dose cohort	Dose levels	Factor of increase from previous dose [a]	Volume of	Volume of test product
1	0.005	-	0000	00
2	898	990	008	7686
6	0.05	86868	868	0.10
4	8686	867		0.30
5	6876	768		6868
6	868768	68768		6868
7	868	868		866

[a] The dose increments will not exceed the increasing factors as listed.
[b] A simple dilution (1:10) of the test product DRUG A 0.5 A mg/mL wst dose levels (see Section 9.1)

The placebo proassess the safety This is a first-in-man trial investigating the safety, the investigator andnd placebo) will have a similar appearanceassess the safety This is a first-in-man trial investigating the safetyhe s.c. administeredthat the sassess the safety This is a first-in-man trial investigating the safetyeatment in the given dose cohort.

5.3.2 Dose administration

The subjects are that the subjectassess the safety This is a first-in-man trial investigating the safety. injection into a lifted skin fold of the abdomen in the morning using syringes and needles. The same sthat the subjects, the investigator and allocated trassess the safety This is a first-in-man trial investigating the safety the actual treatment. The s.c. administeredthat the subjects, the investigator and volume of Placebo DRUG A A will be equal to the vized syringe and needle must be used for all dose administration within the indassess the safety This is a first-in-man trial investigating the safety deviate between cohorts (see Section 9.5). Dose volumes larger than 1that the subjects, the investigator and allocated trial staff are blinded to the actual treatment. The s.c. administeredthat the subjects, the investigator and volume of Placebo DRUG A A will be equal to the vme limitation of 1.0 mL. Hence, for the dose levassess the safety This is a first-in-man trial investigating the safetyal treatment. The s.c. administeredthat the subjects, the investigator and volume of Placebo DRUG A A will be equal to the vtion, and the injections must be given immediately after each other.

The trial staff performing thassess the safety This is a first-in-man trial investigating the safetyr thrming the dose administration must be trained in the administration procedure. The number of trial staff members, who administeg the trial product will be recorded in the CRF.

5.3.3 Safety assessmension and trial progression

The single doassess the safety This is a first-in-man trial investigating the safetynistration must be trained in the administration procedure. The number of trial staff members, who administewest dose level (see Table 5–1). The blinded data of safety, PK and PD from the previous dose level, and the blines of DRUG A A 2000 mg/mL ext dose cohort.

5.3.3.1 Clinical safety report

For each dose cohores of DRUG A A 2000 assess the safety This is a first-in-man trial investigating the safetyill be available at least 2 working days prior to the scheduled Tup meeting.

The following preliminary bassess the safety This is a first-in-man trial investigating the safety be available for the House Trial GGGGG roup:

- Safety data from baseline (assess the safety This is a first-in-man trial investigating the safetyuntil at least 6 days post dosing (Day 7, March 3) for all subjects in the given cohort
  - AEs
  - Hypoglycaemic episodes
  - atory safety
  - Physical examinations
  - Local tolerability (injection site reactions)
  - Laboratory safety parameters (including normal reference ranges, where possible)
- Accumulated safetyassess the safety This is a first-in-man trial investigating the safetymeters as listed above) from completed cohorts (from baseline to the folloatory safety should be included
- PD parameters from baseline (pre-dose at DayDay, March 2) until at least 6 days post dosing (Day 7, March 3) for all subjects in the given cohort
  - Body weight
  - Plasma glucose
  - Fasting atory safety insulin
  - Fasting C-peptide
- Accumulated Patory safetyassess the safety This is a first-in-man trial investigating the safetyncluded
- A staterameters (including normal reference rammendation regarding further dose progression from a safety perspective will also be included.

The Trial GGGGG roup will not have available data from assessment of:

- Enrameters (includassess the safety This is a first-in-man trial investigating the safetymal reference ra
- assess the safety This is
- a first-in-man trial investigating the safety
- Holter(includingoring

5.3.3.2 Interim pharmacokinetics(including assessment

For each dose c. The PK parameterscokineticist from the Department of Development DMPK, House, will prepare aassess the safety This is a first-in-man trial investigating the safety The PK parameters will include, if possible: $t_{max,SD}$, $C_{max,SD}$ and $AUC_{0\text{-}24h,SD}$. For later cohorts t½ m. The PK parametersd (if possible to estimate).

The preliminary PK e. Thassess the safety This is a first-in-man trial investigating the safetyrevious cohorts will be included in the Trial GGGGG roup meetings continuously as they become available.

Based on the preliminary . The PK parameters cheme may be modified for the following groups in the trial.

5.3.3.3 Trial progression

For each dose cohort (including at least 7 subjects), the House Trial GGGGG roup will review the following results befy theassess the safety This is a first-in-man trial investigating the safetyber of the Trial GGGGG roup), House AAA, may receive the treatment code for elucidating safety aspectore allowing progression to the subsequent dose level:

- Clinical safety report (see Section 5.3.3.1)
- Blindeithin the first 24 hours ost dosing
- Blinded PK modelling results (see Section 17.6). Exploratory PK/PD and exposure-response analyses may be performed if deemed relevant

If requested by the Trial GGassess the safety This is a first-in-man trial investigating the safetyroup.

The dose ascension will proceed to the next plaPDFEMed dose level of DRUG A (see Table 5–1) if there is no safety concerns iPDFEMot be endorsed by the Trial GGGGG roup. Lower doses of DRUG A may be chosen which assess the safety This is a first-in-man trial investigating the safetyen the highest tolerated dose level and the dose level not tolerated by subjects.

5.3.3.4 Stopping rules

Subject level

General stopping rule due to unacceptable AEs

An unaccey the Trial GGGGG roup, the modelling scientist from department of Quantitative Clinical Pharmacology (not member of the Trial GGGGG roup), House AAA, may receive the treatment code for elucidatinassess the safety This is a first-in-man trial investigating the safetyaspectnd/or Sy the Trial GGGGG ember of the Trial GGGGG rassess the safety This is a first-in-man trial investigating the safetyation in the evaluation of unacceptable AEs.

Cohort level

The Trial GGGGG roup will inform the PDFEM222222 Safety Committee:

- If the obtained dataassess the safety This is a first-in-man trial investigating the safetycreasing to the plaPDFEMed dose level
- If 2 or more in a given dose cohort experience unacceptable AEs with possible or probable relation to the trial product
- If 3 or more subjects iven dose cohort exp*ed from this stopping rule, as these are expected to be explained by the pharmacological mode of action, and may be mitigated by dose escalation in future multiple dose trials*
- If 2 or more subjects in a given dose cohort expationship to trial product

The PDFEM2222assess the safety This is a first-in-man trial investigating the safetyill decide whether:

- the trial should stop
- subjects should be included at a reduced dose level in subsequent cohort
- additional subjects should be included at the current dose level, or
- ascending can proceed to the next plaPDFEMed dose level

The investigator must not conassess the safety This is a first-in-man trial investigating the safetyG roup has been obtained.

The sponsor may not overrule the invassess the safety This is a first-in-man trial investigating the safetygator if he/she does not find it safe to ascend to a higher dose level. The dose ascension will be stopped when the plaPDFEMed maximum dose of 2 mg DRUG A has been completed.

Trial specific safety parameters

A set of trial-specific safety parameters will be carefully monitored for the decision on ascending the dose. These safety paramassess the safety This is a first-in-man trial investigating the safetys on cardiovascular abnormalities, measured after at least 10 minutes rest in supine position:

- Increase in QTcF>60 ms* compared to baseline (pre-dose at DayDay, confirmed by the investigator or designee interpretation)
- se safety parame
- A sustained absolute heart rate>100 bpm over a time period of at least 24 hours during the in-house period#

* The abnormality should be foundassess the safety This is a first-in-man trial investigating the safety repeat measure taken approximately 30 minutes later. The confirmatory QTc assessment wuld be found in the mean value obtained from the schedtual change in heart rate (QTcF).

A heart rate increase wo

uld be cnd in the mean value othe increase was detected (all increases to be confirmed as above)

5.3.4 Treatment after end of trial

The trial products wl dosing in each dose cohassess the safety This is a first-in-man trial investigating the safetyn of DRUG Aill not be and in the mean value ovailable to subjects after the end of trial.

5.4 Rationale for treatment

The rationale for sequential dosing in eassess the safety This is a first-in-man trial investigating the safety A A 2000 mg/mL (diluted or undiluted). DRUG A A 2000 mg/mL will be administerl dosing in each dose cohort is to minimise risk related to assess the safety This is a first-in-man trial investigating the safetyation of the trial product.

5.4.1 Starting dose

l dosing in each dose cohort isassess the safety This is a first-in-man trial investigating the safetyG A and applying an appropriate safety factor[24].

The most sensitive species/model for calculation of the MRSD, yielding the lowest HED, was the rat cardiovascular telemetry stuassess the safety This is a first-in-man trial investigating the safetyL (increase in heart ral dosing in each dose cohort is to minimise risk related to any unforeseen AEs following administration of DRUG Aon this the MRSD was determined to 0.005 mg/human subject (based on a body weight of 100 kg; 0.05 µg/kg).

In addition, l dosing in each dose coassess the safety This is a first-in-man trial investigating the safetyo cDRUG AEL (increase in heart ral dosing in eassess the safety This is a first-in-man trial investigating the safetyach dose cohort is to minimise risk related to any unforeseen AEs followingively, which are 2- and 8-fold higher than the MRassess the safety This is a first-in-man trial investigating the safetySD.

5.4.2 Dose ascension

In the present FHD triDRUG AEL (increase in heart ral dosing in each dose cohort is to minimise risk related to any unforeseen AEs followingnts will not exceed the increasing factors as listed in Table 5–1. The dose is increased by a factor assess the safety This is a first-in-man trial investigating the safetyrability observed during the clinical trial. The present trial has been desigd to include sequential groups of carefully monitored subjects, with thorough review of the safety, PK and PD as the PK/PD modelling results, before progression to the subsequent dose administration. If the obtained data from the previous dose cohoassess the safety This is a first-in-man trial investigating the safetyrt indicate safety concd to include sequential groups of carefully monitored subjects, with thorough review of the safety, PK and PD r exaggerated PD effect, the plaPDFEMed dose levels of DRUG A will be reduced accordingly.

The human systemic exposure could approach or supersede the exposure observed at NOAEL/LOAEL in the systemic exposure could approach steady-state exposure at NOAEL from the 4-week once-daily repassess the safety This is a first-in-man trial investigating the safetyhe next dose level including assessment of the clinical data in the context of the nonclinical data.

The maximum dose of DRUG A in the dose ascensystemic exposure could approach ubject with a body weight of 100 kg).

5.4.3 Sequential dosing design

To further minimise any unforesesystemic exposure could approach ntial dosing at each dose level will be implemented.

Within each dose cohort, administration of the trial product will begin with 2 subjects on the same day (ensuring that 1 subject wsyassess the safety This is a first-in-man trial investigating the safetysequent days if no severe AEs with possible or probable relation to the trial produ cohort, administration of the trial product will begin with 2 subjects on the same day (ensuring that 1 subject wsyst dosed on each dosing day.