1. Title page

A Phase I, Randomised, Open Label, Single Center, Single Oral Dose, Three Treatment, Three Period, Three Sequence, Change-over Bioequivalence Study of Paracetamol Orodispersible Tablet 500 mg (Haleon) to assess Bioequivalence with Alvedon 500 mg Film-Coated Tablet (Haleon, Sweden) and Panadol 500 mg Film-Coated Tablet (Haleon, Australia) in Healthy Adult Subjects Under Fasting Conditions

Working title: Paracetamol bioequivalence trial with oral single dose administration

Version: **Final revised** Date 2024-05-07

Trial No.: **SocraTec R&D study No.: 1449pa23ct**
Sponsor study No.: 300141

EuCT No. **2024-514198-23-00**

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Clinical trial protocol - clinical trial phase: I

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2. Synopsis and flow chart

2.1 Synopsis

Study phase	I	
Study No.	SocraTec R&D GmbH:	1449pa23ct
	Haleon CH SARL (Switzerland):	300141
EuCT No.	2024-514198-23-00	
Indication studied	Bioequivalence, therapeutical indication not studied	
Test product, dosage, and route of administration	Test:	CCI ODT (Haleon CH SARL), containing 500 mg paracetamol CCI)-; oral administration
Reference products, dosage, and route of administration	Reference 1:	Alvedon Film-Coated Tablet (Haleon Sweden) containing 500 mg paracetamol (CCI); oral administration
	Reference 2	Panadol Film-Coated Tablet (Haleon Australia) containing 500 mg paracetamol (CCI); oral administration
Treatments	A	oral single dose fasted administration of 1 orodispersible tablet of Test
	B	oral single dose fasted administration of 1 film-coated tablet of Reference 1
	C	oral single dose fasted administration of 1 film-coated tablet of Reference 2
Duration of treatment	Three (3) treatment periods with oral single dose administration each separated by a washout period of at least 72 hours, but not more than 7 days, i.e., 3 to 7 days Total duration of active treatment will be 3 non-consecutive days	
Study objectives	Primary objective: • Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus Haleon´s paracetamol 500 mg film-coated tablets marketed in Sweden under the name of Alvedon tablets (Reference 1) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations and/or • Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus the marketed Haleon´s paracetamol 500 mg film-coated tablets marketed in Australia under the name of Panadol tablets (Reference 2) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations. Secondary objective: • Assess the pharmacokinetic profile of paracetamol after fasted single dose administration of Test, Reference 1 and Reference 2. • Descriptive characterisation of safety and tolerability of Test and Reference products considering adverse events observed during the trial.	
Study design	Single center, open-label, randomised (order of treatments), balanced, 3-period, 3 -sequence, single dose, change-over trial with oral administration under fasting conditions separated by a washout period of at least 72 hours	
Subject population	Fifty-four (54) randomised healthy subjects of both sexes fulfilling the following inclusion criteria: 1. written informed consent, after having been informed about benefits and potential risks of the clinical trial, as well as details of the insurance taken out to cover the subjects participating in the clinical trial 2. sex: male/female 3. age: 18 to 55 years (including) 4. body-mass index (BMI): ≥18.5 kg/m² and ≤ 30.0 kg/m² 5. body weight ≥50.0 kg for males and ≥45.0 kg for females 6. good state of health	

Synopsis, continued

Subject population, continued	7. willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures 8. female subject of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 7 days after the last dose of assigned treatment 9. non-smoker or ex-smoker for at least 3 months (including non-nicotine vapers nicotine chewing gum or pouches or nicotine replacement therapy)
Total dose per subject	3 x 500 mg paracetamol resulting in 1.5 g paracetamol in total
No. of study centers	1
Total number of subjects, statistical rationale provided	54 subjects are intended to be randomised for statistical rationale see chapter 15.4
Analytical methodology	Paracetamol in plasma samples will be analysed by use of a validated LC-MS/MS; intended LLOQ for paracetamol is CCI ng/mL
Baseline characteristics	• demographic (age, sex) and anthropometric data (body weight, height, BMI) • medical history (including prior and concomitant medication) and any pre-planned surgical treatments or procedures • physical examination (incl. 12-lead-ECG, vital signs (BP, PR, body temperature)) • clinical laboratory investigation: blood analysis including haematology, haemostatic system, clinical chemistry, hormones, serology, urinalysis • test of alcohol, cotinine and drug abuse • lifestyle habits (caffeine, alcohol and nicotine consumption) • general well-being • check of applicable restrictions • female status (check of childbearing potential and pregnancy test in all female subjects with childbearing potential) • check of inclusion and exclusion criteria
Safety measures	• AEs will be collected from informed consent signature till the end of follow up period. • pregnancy test
Safety parameters	• vital signs (BP, PR, body temperature)
Pharmacokinetic variables	• Primary variables: C_{max}, AUC0-t_{last}, t_{max} • Secondary variables: $AUC_{0\text{-}inf}$, $AUC_{expol\%}$, L_z, $t_{1/2}$
Plan for data analysis	<u>Plasma concentrations</u> will be listed individually per analyte, period and scheduled time in the analytical report; Individual concentrations and their descriptive evaluation (number of subjects (N), arithmetic means, SD, geometric means, geometric CV, medians, minimum and maximum) will be listed per analyte, treatment and scheduled time in the integrated clinical study report. Mean concentrations will be listed in tabular form including descriptive statistics (at least N, (if applicable N_{obs}, N_{miss}), arithmetic mean, SD, minimum, median, maximum) based on scheduled times for the PKAS. Individual, overlays of individual and mean concentration vs. time curves will be provided, both linearly and log-linearly considering treatment and analyte, as appropriate. Individual concentration vs. time profiles will be based on real sampling times, mean curves will be based on scheduled times. <u>Pharmacokinetic parameters</u> will be derived by means of non-compartmental analysis and will be listed and evaluated descriptively (number of subjects (N), arithmetic mean, SD, CV%, geometric mean, geometric CV, median, minimum and maximum, Q1 and Q3) separately per treatment.

Synopsis, continued

Plan for data analysis, continued	Statistical analysis Analysis of Variance (ANOVA, parametric analysis) will be performed and used as basis for the calculation of point estimates and 90 % confidence intervals for the comparison of Test vs. Reference 1 and Test vs. Reference 2 considering $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$, and C_{max}-values based on PKAS. A Wilcoxon Signed Rank test will be used to analyze t_{max} nonparametrically. Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on PKAS. $AUC_{0\text{-tlast}}$, C_{max} and t_{max} will be considered as primary decision criteria for bioequivalence assessment. Bioequivalence between a new CCI ODT 500 mg (Test) and the marketed Panadol/Alvedon 500 mg film-coated tablet (Reference, pairwise comparison) in fasted state will be declared: • If the 90% confidence intervals (CIs) for the ratio (%) of the geometric means of the primary PK parameters, $AUC_{0\text{-tlast}}$ and C_{max} of the paracetamol profiles are completely within the 80.00% to 125.00% range. • If there is no statistically significant difference between the 2 treatments in terms of t_{max}. In this study, two different reference products will be compared separately with the test product. Hence, two separate comparisons will be run, and no multiplicity adjustment will be performed. Demographic data, data from screening and end of study examination will be listed and evaluated descriptively (number of subjects (N), arithmetic mean, SD, median, minimum, maximum). Pre-Treatment Adverse Events will be listed and evaluated descriptively with regard to action taken, frequency, seriousness, and intensity. Adverse Events will be listed and evaluated descriptively with regard to action taken, frequency, seriousness, intensity, relationship to the IMP, and outcome, as well as period and treatment.
Plan for data analysis, cont.	Safety parameters Blood pressure, pulse rate, body temperature, rate, and clinical laboratory parameter will be listed and evaluated descriptively (N, arithmetic mean, SD median, minimum, maximum).
Planned start of clinical trial	September 2024

2.2 Flow chart by procedures

Procedure	screening examination	schedule for period I, II and III [A]			end of study examination
Study day	-28 to -2	-1	1	2[B]	2 [D]
Hours p.a.		-12	0	24	
Written informed consent - enrolment	•				
Demographic and anthropometric data	•				
Lifestyle habits	•				
Medical history	•				
Physical examination [C]	•	•			•
BP and PR [E]	•		•		•
Body temperature [E]	•	•	•	(•)	•
Haematology	•				•
Clinical chemistry	•				•
Haemostatic system	•				•
Hormones [F]	•				
Urinalysis	•				•
Serology [G]	•				
ECG and HR [H]	•				
Urine drug screen [I]	•	•			
Alcohol breath test [I]	•	•			
Cotinine test [I]	•	•			
Urine pregnancy test [J]	•				•
Serum pregnancy test [J]		•			
Inclusion/Exclusion criteria	•	•	•		
Inclusion		•			
In-house period [K]		-12 to +24 h p.a. •			
Randomisation [L]		•			
Fasting [M]		•	•		
Standardised meals and beverages [M]		•	•		
Administration of IMPs [N]			•		
PK blood sampling [O]			•	•	
General well-being (AE collection) [P]	•	•	•	(•)	•
Checks for medication [Q]	•	•	•	(•)	•
Check of restrictions [R]	•	•			•
Discharge from clinical trial [S]					•

A Identical procedures to be followed for all periods, washout phase of at least 72 hours i.e. 3 treatment free days, but not more than 7 days, i.e., 3 to 7days

B In study day 2 of period 3, the measurements of body temperature, general wellbeing and checks for medication, will be taken as the measurements for end of study examination.

C A full physical examination will be performed at screening and a brief physical examination will be performed on Day -1 in each treatment period and at End of Study. These assessments are also to be conducted for subjects who discontinue study drug.

D End of study examination will be performed before discharge, on study Day 2 of Period 3. These assessments are also to be conducted for subjects who discontinue study drug.

E BP will be measured at screening examination and at end-of-study examination in supine position after the subjects have been resting for 15 min.

During the study periods BP and PR measurements will be recorded in a sitting/supine position after the subjects have been resting for 5 minutes.

Blood pressure (BP), pulse rate (PR), body temperature (ear): pre-treatment on Day 1 (within 1 hour before drug administration) of each treatment period. Body temperature (ear) on Day -1, Day 1 and Day 2 of each treatment period (Note: the body temperature (ear) obtained on Day 2 of Period 3 can be used as the oral body temperature required at End of Study).

F Determination of Follicle-stimulating Hormone (FSH) will only be done in female subjects who have been amenorrhoeic for at least 12 months.

G HBs-AG, anti HCV-AB, anti-HBc IgM and anti-HIV-AB 1+2

H During screening examination, the ECG will be recorded by means of a 12-lead ECG system over 10 sec while the subjects will rest in supine position after 15 minutes resting.

I Test for alcohol, cotinine and drug abuse will be performed at screening examination and on study day -1 of each period. However, tests for alcohol, cotinine, drug abuse and COVID-19 (i.e., SARS-CoV-2 rapid antigen test) can always be performed in case of suspicion during the clinical trial.

J Serum pregnancy tests for all female subjects with childbearing potential will be performed on study day -1. Additionally, pregnancy tests in urine will be performed during screening examination and at the end of study examination.

K In-house period starts in the evening of each study day -1 and ends at the earliest 24 h p.a. on study day 2.

L Randomisation will take place in the evening of the first in-house period (study day -1) in period I immediately after checks (for general well-being, of restrictions and concomitant medication) have been evaluated. Assignment to a randomisation number will be in the order of subject's arrival time at the CPU at study day -1 of period I. For more details see section 11.2.

M Following an overnight fast of at least 10 hours, subjects will receive the investigational medicinal product in the fasted state. In the evening of pre-profiling day (i.e. study day -1) of each period subjects may receive a standardised dinner, which has to be finished at least 10 h prior to the intended time of administration. The subjects will fast for at least 10 h overnight (no food, no beverages, water is allowed until 1 hour prior to administration of the IMPs). In case the subject has already eaten or is not hungry and the dinner will not be performed on the CPU, this will not be considered as a deviation, provided that the fasting period of at least 10 h overnight has been observed.

On the day of administration of the IMP. subjects will receive standardised meals 4 h, 8 h and 12 h p.a. Drinking water will not be allowed from 1 h pre and until 1 h p.a. From 1 h until 10 h p.a. 150 ml of non-carbonated water (room temperature) will be given every hour. Only permitted liquids are non-carbonated water for 24 hours after dosing.

The first meal after administration of the IMP at the Study Day 1 has to be ingested completely and start time should not be earlier than 4 h p.a. For deviation with regard to an early ingestion or incomplete meal intake comment/reason will be given. For subsequent meal intake, a deviation from the scheduled time and the ingested amount is without relevance and will not be considered as protocol deviation.

N The IMPs will be administered at the trial site under the supervision of the study team. Administration will be performed in the morning approximately between 7:00 and 9:00 am with appropriate intervals between subjects, to allow sample collection and any additional clinical observations and measurements necessary.

For Reference products: 1 film-coated tablet will be taken orally together with 200 ml tap water (room temperature) in an upright position followed by an inspection of the oral cavity and empty hands.

For Test product: Before administering 1 ODT, the mouth will be wet with 20 mL of water. The water will be swallowed by the subject. When the mouth is empty and immediately after of the "wetting process" the ODT will be placed on the upper surface of tongue of the subject, with a dry finger by the study personnel, allowed to dissolve and subsequently be swallowed. The subject will be in a standing, upright position.

To standardize gastric emptying, subjects will remain in sitting position for 30 minutes after dosing. Thereafter, they will be asked to remain in an upright position until 4 hours after administration of study medication, after which no restrictions concerning posture or movement are applied. However, subjects are allowed to walk to the bathroom as necessary (after one hour post administration).

O An indwelling cannula will be inserted in the morning of study day 1 prior to administration of the IMPs. Based on case-by-case decision samples can be withdrawn by direct venipuncture.

PK blood samples (4.9 ml each) will be collected

- within one hour prior to dosing
- 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 75, 90, 120, 150, 180 minutes, and
- at 4, 5, 6, 8, 10, 12, 14, 16 and 24 hours following dosing in each treatment period.

P Checks for general well-being will be performed in a non-leading manner

In addition to the checks for general well-being at the screening examination and at the time of in-house period, checks for general well-being will also be performed at the end of study examination.

Furthermore, the subjects will be asked to report any PTAE/AE spontaneously, whether or not they occur during confinement. PTAE/AEs and therefore also all serious adverse events (SAEs) will be collected immediately after a subject provides consent to participate in the study by the completion of the informed consent form.

Q Checks for medication will be performed at the following time points: at screening examination, at each study day and at the end of study examination.

R Check of restrictions will be performed at screening examination (so far as applicable) as well as upon each in-house period (evening of day -1), and at the end of study examination.

S As soon as all results of the end of study examination are available, have been evaluated by the investigator and PTAE/AEs-follow up is performed the subject can be discharged from the trial. In order to perform the follow-up the staff of the clinical facility has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.

3. Table of contents

Appendix to the protocol

SocraTec R&D

4. List of abbreviations and definition of terms

4.1 List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz, German Medicinal Products Act
ANOVA	Analysis of Variance
ANVISA	Agência Nacional de Vigilância Sanitária
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the Curve
BE	Bioequivalence
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte, German health authority
BMI	Body-Mass Index
BP	Blood Pressure
BLOQ	Below Limit of Quantitation
BUN	Blood urea nitrogen
C	Concentration
CH	Switzerland
CI	Confidence Interval
CDQA	Clinical Development Quality Assurance
CHMP	Committee for Medical Products for Human Use
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019 caused by SARS-CoV-2
CPMP	Committee for Proprietary Medicinal Products
CPU	Clinical Pharmacology Unit
CTFG	Clinical Trial Facilitation Group
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
csv	Comma separated value
CV	Coefficient of Variation
CYP	Cytochrome P
DCF	Data Clarification Form
DE	Germany
DMP	Data Management Plan
DRM	Data Review Meeting
DVP	Data Validation Plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
CCI	CCI
EMA	European Medicines Agency
ETL	Error Tolerance Limit
EU	European Union
EWP	Efficacy Working Party (of the EMEA)
EXCEL/xls	Commercial Database System
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastro intestinal
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC-MS	High Pressure Liquid Chromatography with Mass Spectrometry

HR	Heart Rate
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IP	Investigational product
IRB	Institutional Review Board
ISCV	Intra-subject coefficient of variation
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
l/L	Litre
LC-MS/MS	Liquid Chromatography Hyphenated with Tandem Mass Spectrometry
LDH	Lactate dehydrogenase
LLOQ	Lower Limit of Quantitation
ln	Natural logarithm
log	Logarithmic
MDD	Maximal day dose
MDMA	Methylenedioxymethamphetamine (ecstasy)
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
min	Minutes
Min	Minimum
MS	Microsoft
MSE	Mean Square Error
N	Number of subjects
n.a.	Not applicable
n.d.	Not determined
N_{miss}	Number of missing values
No.	Number
N_{obs}	Number of planned observations
ODT	Orodispersable Tablet
OTC	Over the counter
p.a.	Post administration
PCP	Phencyclidine
PDF	Portable Document Format
PG	Prostaglandin
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PKP	Pharmacokinetic Population
PQ	Interval from P-wave to Q-peak in electrocardiogram
PR	Pulse Rate
PT	Prothrombin time
PTAE	Pre-Treatment Adverse Event
QA(U)	Quality Assurance (Unit)
QC	Quality Control
QP	Qualified Person
QRS	QRS complex is the combination of three of the graphical deflections seen on a typical electrocardiogram
QTL	Quality Tolerance Limit
QWP	Quality Working Party (of the EMEA)
RAF	Risk Assessment Form
RDC	Resolução de Diretoria Colegiada
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System (statistical software developed by SAS institute)
SD	Standard Deviation
SDS	Source Data Sheet
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety Population
SR	Subject Record
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TOST	Two One-Sided t-tests Procedure
TT	Text Table
TMF	Trial Master File
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantitation
WHO	World Health Organisation

For abbreviations of clinical laboratory parameters see Appendix III (TT 3). Abbreviations of pharmacokinetic parameters are given in chapter 13.3.9.

4.2 Definition of terms

The terms clinical trial, clinical study, trial and study as well as investigational product (IP) and investigational medicinal product (IMP) are synonymous.

4.2.1 Start, initiation, completion, temporary halt and end of the clinical trial

Start of the clinical trial (= trial initiation date) is defined as the day of the signature of the Informed Consent Form (ICF) of the first subject.

The date of the first act of recruitment of a potential subject is the date on which the first act of the recruitment strategy described in the protocol was performed, e. g. the date of a contact with a potential subject or the date of the publication of an advertisement for a particular clinical trial. For full recruitment strategy details, see chapter 12.

Date of individual discharge of a subject is defined as the date, when all results of the study examinations are available, have been evaluated by the investigator and AE-follow up is performed.

End of a clinical trial is defined as the day of discharge of the last subject from the clinical trial.

Following definition in the Regulation (EU) No 536/2014, end of trial has been defined as last subject, last visit. Formal discharge of a subject from the trial after review of all data available including laboratory data from the last visit normally occurs after the last visit. Furthermore, for follow-up of AEs unresolved at the date of last visit see chapter 13.3.6.2.1.

The planned total duration by subject of the clinical trial is approximately 3 to 7 weeks including the screening examination and the end of study examination.

Temporary halt of a clinical trial means an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it.

4.2.2 Termination of the project

The termination of the project is defined as time point of archiving the clinical trial's Trial Master File (TMF).

4.2.3 Recruiting, screening, enrolment, inclusion, and randomisation

All measures to find the appropriate subjects according to the inclusion/exclusion criteria before screening are understood as recruitment.

A subject is defined as screened (entered in pre-trial screening and documented on the screening log) when a signed and dated ICF is available (screened = subject enrolled).

A subject is defined as included when judged eligible for trial participation by the investigator.

Randomisation is defined as allocating a randomisation number (= subject number) to an included subject.

4.2.4 Definition of study periods for PTAE and assignment

Period pre lasts from enrolment to the first administration of the IMP of period I, comprises the assessments during screening examination, inclusive randomisation, and ends just prior to the first administration of the IMP.

Period I starts with the first administration of the IMP and ends just before the second administration of the IMP.

Period II starts with the second administration of the IMP and ends just before the third administration of the IMP.

Period III: starts with the third administration of the IMP, includes the end of study examination and lasts until the discharge of the subject from the clinical trial.

4.2.5 Screening failures

Screening failures are subjects who are enrolled but not randomised.

4.2.6 Dropouts

A dropout is a subject, who prematurely discontinues participation after being randomised.

All relevant data with regard to safety will be reported including drug concentrations until removal of the subject.

Subjects, who will be excluded from the randomised population (see chapter 15.2) after having completed the clinical trial, will not be considered as dropouts, but as excluded subjects.

4.2.7 Medical history and underlying disease

Medical history comprises all diseases, historical findings or surgeries in the past of a subject resolved at the time of screening examination.

Underlying diseases comprise all current acute and current chronic diseases starting prior to and being still ongoing at the time of screening examination.

Physical examination is the process when the body of a subject is investigated for signs of disease or abnormalities.

4.2.8 Prior and concomitant therapy

Prior and concomitant therapy comprises all medications (drugs) and therapeutic procedures before and during the clinical trial, planned and not planned, permitted (including rescue medication) and not permitted.

Prior medication comprises all medication prior to IMP treatment administered within the observation phase and finished until the first dose of the IMP treatment.

Concomitant medication comprises all medication except IMP between time of first dose of the IMP treatment until discharge of the subject from the clinical trial.

For observation phase of prior and concomitant medication intake see chapter 13.2.3.

4.2.9 Women of childbearing potential and postmenopausal state

Women are considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4.2.10 Analysis sets

For definitions of analysis sets see chapter 15.2.

4.2.11 Definition of PTAE and AEs

A **Pre-Treatment Adverse Event (PTAE)** is defined as any acute existing disease or symptom, which occurs after screening examination (i.e. after signing the informed consent form) until first administration of the IMP.

If after administration of the IMP a deterioration of the intensity of the existing PTAE is observed, this sign or symptom will be documented as an Adverse Event.

An **Adverse Event (AE)** is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.

  Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

A **Serious Pre-treatment Adverse Event (Serious PTAE)** is defined as any untoward medical occurrence after signature of the informed consent but before first administration of the IMP meeting the definitions given for Serious Adverse Events (SAE) / Serious Adverse Drug Reaction (Serious ADR) below.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (Serious ADR)** is defined as any untoward medical occurrence that at any dose and after signature of the informed consent

- results in death, or
- is life-threatening, or
- requires inpatient hospitalisation or prolongation of existing hospitalisation, or
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect or miscarriage.

The term „life-threatening“ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Important medical reactions that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Examples of such events are intensive treatment in an emergency unit or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

A hospitalisation does not automatically result in classification as Serious Adverse Event if it is due to,

- an elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under the clinical trial and has not worsened since the start of IMP;
- a treatment on an emergency outpatient basis or ambulatory care for an event not fulfilling any of the definitions of a SAE given above;
- a social reason or respite care in the absence of any deterioration in the subject's general condition.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Adverse Drug Reaction (ADR): In the pre-approval phase clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered Adverse Drug Reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an Adverse Event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product (see paragraph 5 of the EU Directive 2010/84/EU of December 2010).

Unexpected Adverse Drug Reaction: An ADR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an unapproved product or package insert/summary of product characteristics for an approved product) (see the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Suspected Unexpected Serious Adverse Reaction (SUSAR): A serious and unexpected adverse reaction presumably related to the clinical trial drug or to the respective comparison drug. Any untoward and unintended response to a non-IMP serious and unexpected which does not result from a possible interaction with an IMP is, by definition, not a SUSAR. For more information about the reporting of SUSARs see chapter 13.3.6.3.

4.2.12 Pharmacokinetic parameters

For definitions of pharmacokinetic parameters see chapter 13.3.9.

5. Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The documents required by the Clinical Trials Regulation (Regulation (EU) No 536/2014) of 16 April 2014 including clinical trial protocol, subject information including the ICF, as well as any subsequent amendments will be submitted to the relevant Independent Ethics Committee (IEC) for favourable opinion.

5.2 Ethical conduct of the clinical trial

The clinical trial will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, ICH-GCP guidelines (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practice), the Clinical Trials Regulation (Regulation (EU) No 536/2014) of 16 April 2014 and the requirements of the German Medicinal Products Act (Arzneimittelgesetz, AMG) including the GCP regulation.

The clinical trial will only be initiated when written and dated positive vote by the IEC and approval by the national health authority (BfArM) is received for the documents required by the Clinical Trials Regulation (Regulation (EU) No 536/2014) of 16 April 2014 including clinical trial protocol, subject information including the ICF as well as any subsequent amendments.

Any substantial change in the clinical trial protocol and/or subject information including the ICF and/or IB updates related to safety will be presented to the named IEC and any substantial change in the clinical trial protocol to the BfArM. Substantial amendments have to be approved by them before implementation (except to eliminate immediate hazards).

5.3 Subject information and consent

The subject will receive a subject information document together with an ICF. The subject information document contains all relevant information about the clinical trial in accordance with the GCP requirements.

Every subject has to be informed verbally and also in writing by receiving the subject information document. The written subject information document must be evaluated and approved by the Ethics Committee. The subjects will receive the subject information document prior to their agreement to participate. The consent form must be signed and dated by the subject prior to the first measures/activities. The ICF must be signed and dated by the physician (investigator) who conducted the informed consent discussion. A copy of the signed and dated consent form must be given to the subject.

Every subject has the right to withdraw consent any time without any resulting detriment and without having to provide any justification, i.e., without incurring any disadvantages.

According to the stipulations of the EU-GDPR (General Data Protection Regulation) 2016/679, confidentiality and pseudonymity of the subjects are assured.

5.4 Data Protection

Each subject will be assigned to a unique identifier after obtaining her/his informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.

The participants will be informed, that the sponsor will use their personal study-related data in accordance to the local data protection and privacy laws. The level of disclosure will also be

explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.

The participant will be informed that his/her medical records may be examined by monitors, auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons have to strictly maintain participants' confidentiality.

Further details are given in the data protection agreement created between sponsor and SocraTec R&D. For details with regard to record keeping, see chapter 18.

In the event of a data breach, the company management (same working day) and the data protection officer (next working day at the latest) have to be informed immediately and a distinct error assessment including root cause analysis has to be performed and documented.

In the event of a risk for the rights and freedoms of the data subject, the supervisory authority (data protection commissioner of the respective federal state) must be notified immediately, if possible, within 72 h after the data breach became known (including description of the event, category of data, number of persons and data sets affected, contact details of the data protection officer, description of the possible consequences and the measures taken).

In the event of a high risk for the personal rights and freedoms of the data subject and no effective technical and organisational or other measures could be taken to mitigate this risk, the data subject has to be notified without undue delay.

5.5 Insurance

Every subject is insured in accordance with the German Medicinal Products Act § 40 (3) against damage to health which might occur during the conduct of the clinical trial and the material damages which might occur in connection thereto.

The subject insurance as well as the home-to-clinic insurance is taken out by Haleon CH SARL. A copy of the insurance certificate will be available at the trial site.

6. Investigators and study administrative structure

Sponsor	
Sponsor	Haleon CH SARL Route de l'Etraz, 2, Case postale 1279 CH- 1260 Nyon 1, Switzerland Tel.: +41 22 567 20 00
Clinical Study Manager	PPD Haleon, St George's Avenue, Weybridge, KT13 0DE United Kingdom Tel.: PPD e-mail: PPD
Sponsor's representative in the EU	Haleon Germany GmbH Barthstraße 4; 80339 München, Germany Tel.: PPD
Drug Safety	CCI
Clinical Development Quality Assurance (CDQA) Director	PPD Haleon CH SARL Route de l'Etraz 2, Case Postale 1279 CH-1260 Nyon 1, Switzerland e-mail: PPD
Contract Research Organisation	
Contract Research Organisation	SocraTec R&D GmbH Im Setzling 35, 61440 Oberursel, Germany Tel.: +49-6171-58571-0 Fax: +49-6171-5857-25
Scientific Director of the Clinical Trial	Dr. PPD SocraTec R&D GmbH Im Setzling 35, 61440 Oberursel, Germany Tel.: PPD Fax: +49-6171-5857-25 e-mail: PPD
Author of the Protocol / Project Manager	PPD SocraTec R&D GmbH Im Setzling 35, 61440 Oberursel, Germany Tel.: PPD Fax: +49-6171-5857-25 e-mail: PPD

Investigators and study administrative structure, continued

Monitoring	SocraTec R&D GmbH Im Setzling 35, 61440 Oberursel, Germany Tel.: +49-6171-58571-0 Fax: +49-6171-5857-25
Clinical Trial Site	
Clinical Trial Site	SocraTec R&D GmbH, Clinical Pharmacology Unit Mainzerhofplatz 14, 99084 Erfurt, Germany Tel.: +49-361-60205-0 Fax: +49-361-60205-25
Principal Investigator	Ulrike Burkhardt SocraTec R&D GmbH, Clinical Pharmacology Unit Mainzerhofplatz 14, 99084 Erfurt, Germany Tel.: PPD Fax: +49-361-60205-25 e-mail: PPD
Pharmacokinetic Evaluation and Clinical Biometrics	
Clinical Data Management	SocraMetrics GmbH Mainzerhofplatz 14, 99084 Erfurt, Germany Tel.: +49-361-60205-37 Fax: +49-361-60205-25 e-mail:PPD
Drug Safety	
Drug Safety	Dr. PPD SocraMetrics GmbH Leipziger Platz 15, 10117 Berlin, Germany Tel.: PPD Fax: +49-361-74734003 e-mail: PPD
Clinical Laboratory Tests	
Clinical Laboratory Tests	MVZ Labor Limbach Erfurt GmbH Nordhäuser Str. 74 D-99089 Erfurt Tel.: +49-361-781-2701 Fax: +49-361-781-2702
Investigational products	
Packaging, Labelling and Qualified Person Release	CCI CCI United Kingdom
Release for Clinical Trial (Sponsor release acc. to Annex 13)	Haleon, 1211 Sherwood Avenue, Richmond, VA 23220, USA
Bioanalytics	
Bioanalytics	Anapharm Bioanalytics Encuny 22, 2nd floor 08038 Barcelona, Spain Phone: +34 93 223 8636 info@anapharmbioanalytics.com

7. Introduction

The anilide paracetamol (acetaminophen), one of the most widely used analgesics, is a well-known and widely used drug belonging to the group of anilides, with analgesic and antipyretic activity, but with minimal anti-inflammatory effects. It is used in infants, children and adults, including the elderly, for treatment of mild-to-moderate pain and treatment of fever [13].

While the mechanism of action continues to evolve, inhibition of prostaglandin (PG) synthesis by paracetamol appears to underlie both the analgesic and antipyretic activity. Its analgesic action may also involve the serotonergic system [14], [15], [17] and its antipyretic action may involve cannabinoid receptor activation in the brain [16].

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. Food intake delays paracetamol absorption [7]. After single oral dose administration of 500 mg paracetamol in fasted state mean maximum concentrations were reported to be around 8 to 10 µg/ml and mean $AUC_{0\text{-tlast}}$ values were 23 to 28 µg*h/ml [4].

Paracetamol is distributed into most body tissues. Binding to plasma proteins is minimal at therapeutic concentrations but increases with increasing doses [7]. At therapeutic doses in adults, paracetamol is mainly metabolized to pharmacologically inactive paracetamol glucuronide (50 to 60% urinary metabolites), and paracetamol sulfate (25 to 30% urinary metabolites) [13]. Less than 5 % of the drug is excreted unchanged [6]. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione. However, it can accumulate following paracetamol overdosage (more than 150 mg/kg or 10 g total paracetamol ingested) and, if left untreated, can cause irreversible liver damage [2], [3].

Paracetamol oral doses are usually selected based on body weight, with 10 – 15 mg/kg being a typical oral single dose in adults as well as in infants and children up to a maximum of 60mg/kg body weight as a total daily dose. However, daily doses should not exceed 4,000 mg paracetamol [2], [3], [5].and should be separated in 4 single doses in an interval of 4 h to 6 h between each dose up to MDD of 4g/day in order to avoid hepatotoxicity [2], [3].

The elimination half-life of paracetamol varies from about 1 to 3 hours and it is excreted in the urine, mainly as the inactive glucuronide and sulphate conjugates. Approximately 85% of a dose of paracetamol is excreted as free and conjugated paracetamol within 24 hours after ingestion [5], [2], [7].

8. Study objectives

The primary aims of this clinical trial are:

- Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus Haleon´s paracetamol 500 mg film-coated tablets marketed in Sweden under the name of Alvedon tablets (Reference 1) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations.

and/or

- Demonstrate the bioequivalence (BE) of a new paracetamol 500 mg ODT versus the marketed Haleon´s paracetamol 500 mg film-coated tablets marketed in Australia under the name of Panadol tablets (Reference 2) under fasted conditions by means of $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained from paracetamol plasma concentrations.

The secondary aims of this clinical trial are:

- Assess the pharmacokinetic profile of paracetamol after fasted single dose administration of Test, Reference 1 and Reference 2.
- Descriptive characterisation of safety and tolerability of Test and Reference products considering adverse events observed during the trial.

9. Study design

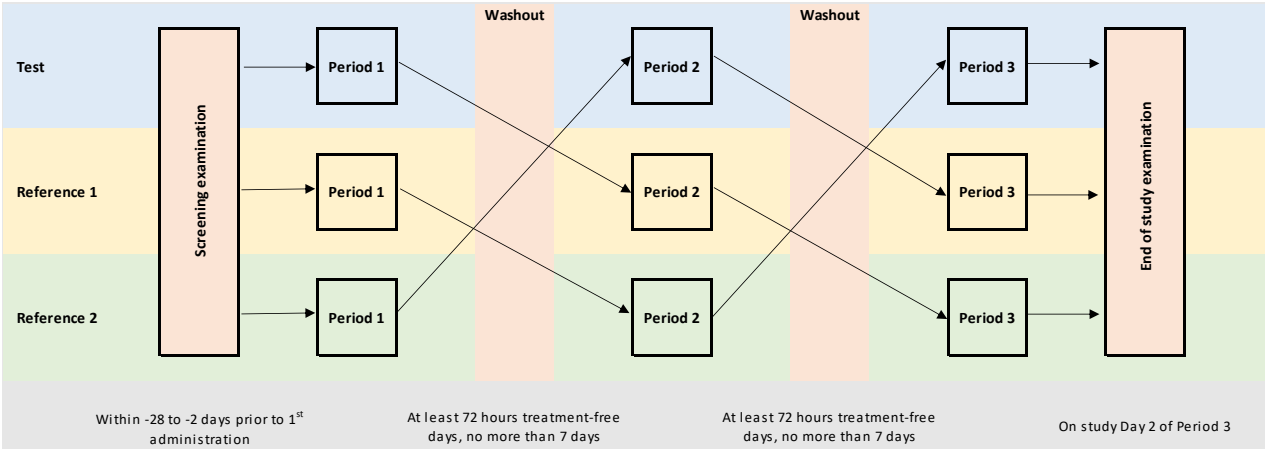
This single center, open-label, randomised (order of treatments), balanced, single dose trial will be performed in a 3-period, 3-sequence-change-over design. Fifty-four (54) healthy subjects of both sexes (27 male, 27 female) are intended to be randomised in order to obtain 42 evaluable subjects.

The IMPs will be administered in fasted state as single oral doses of 500 mg paracetamol. 1 tablet of Test and 1 film-coated tablet of Reference 1 and 1 film-coated tablet of Reference 2 will be administered. Blood sampling will be performed over 24 h post dose in order to characterise pharmacokinetic parameters.

The clinical trial will be performed as a change-over investigation with intra-individual comparison, thus reducing variability of the pharmacokinetic parameters, which is expected to be higher between subjects than within an individual subject.

The washout between administrations will be at least 72 hours, in order to ensure that the entire active ingredient from the preceding treatment period will be cleared from the body before administration of the subsequent treatment.

Figure 1: IMP administration scheme



9.1 Treatments

Within this clinical trial, there will be 3 different treatments. The treatments are defined as follows:

A: oral single dose administration of 1 orodispersible tablet of Test under fasting conditions

B: oral single dose administration of 1 film-coated tablet of Reference 1 under fasting conditions

C: oral single dose administration of 1 film-coated tablet of Reference 2 under fasting conditions

The subjects will be randomly assigned to one of the 3 possible treatment sequences with a balanced distribution of sequences according to Latin square. For further details on randomisation see chapters 4.2.3 and 11.2.

10. Rationale and discussion of study design, including the choice of control groups

A new paracetamol-containing, orodispersible tablet (ODT) dosage form has been developed by Haleon CCI

CCI

This clinical trial aims to evaluate the bioequivalence of new formulated ODT containing 500 mg paracetamol in comparison to the European marketed Alvedon (paracetamol) 500 mg film-coated tablets and the Australian marketed Panadol (paracetamol) 500 mg film-coated tablets as Reference products.

Furthermore, safety and tolerability of the IMPs considering adverse events observed in the trial will be assessed.

Bioequivalence will be evaluated for the active ingredient paracetamol based on its plasma concentrations. Testing for bioequivalence will be performed considering $AUC_{0\text{-tlast}}$, C_{max} and t_{max} obtained after oral single fasted dose of 500 mg paracetamol in fasting conditions.

Sample collection will be performed over 24 h after administration. This time is considered adequate to characterise plasma concentration vs. time profiles long enough for reliable estimation of the extent of absorption, i.e., the AUC derived from measurements is expected to cover at least 80 % of the AUC extrapolated to infinity. Since elimination half-life of paracetamol is about 2 h after single oral doses of paracetamol [8], a washout period of at least 72 hours

between treatment periods is considered adequate to ensure that drug concentrations are below the lower limit of bioanalytical quantification prior to subsequent application. CCI

CCI

For bioavailability and bioequivalence trials, the change-over design is recommended by the Committee for medicinal products for human use (CHMP) [1]. It offers the advantages that

- each subject serves as his own control. Thus, this design allows a within subject comparison.
- removing the intersubject variability from the comparison, e.g. of treatments.

With a proper randomisation of subjects to the sequence of formulation administration, it provides the best unbiased estimates for the differences or ratios between treatments.

In a change-over design, the direct drug effect may be confounded with other effects and such effects that can be reasonably assumed to have an effect on the response should be taken into account. Thus, a statistical model with the effects of sequence, subject within sequence, period, and treatment (or formulation) is generally used.

For the determination of concentration profiles over time, the open-label design is adequate. Blinding is not necessary as neither the subject nor the investigator can influence primary target parameters. The responsible staff of the bioanalytical department will be blinded for the treatments.

According to the recommendations of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) healthy subjects of both sexes aged from 18 to 55 years old and of weight within the normal range according to accepted normal values for the BMI (i.e. $\geq$ 18.5 kg/m² and $\leq$ 30.0 kg/m²) will be selected for inclusion in this clinical trial.

Study design was chosen in accordance to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) for immediate release products including orodispersible tablets.

No information is given in the SmPC that either paracetamol has a relevant influence on the pharmacokinetics of oral contraceptives or oral contraceptives have a relevant influence on the pharmacokinetic of paracetamol or any gender specific safety issues might arise for female subjects. Thus, both sexes will be enrolled in the clinical trial and hormonal contraception will be acceptable for female subjects participating in this clinical trial.

Reference is made to the following guidelines:

- Declaration of Helsinki, current version
- ICH Guideline for good clinical practice (EMA/CHMP/ICH/135/1995), December 2016
- German Medicinal Products Act (AMG), current version
- Clinical Trials Regulation (Regulation (EU) No 536/2014) of 16 April 2014
- Federal Directives applicable to the Medical Corps (Berufsordnung der Landesärztekammer Thüringen), current version
- GMP Regulation, Annex 13, July 2010
- Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95), June 1995
- Detailed Guidance on the Collection, Verification and Presentation of Adverse Events / Reaction Reports arising from Clinical Trials on Medicinal Products for Human Use ('CT-3') (2011/C 172/01) June 2011

- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), January 2010
- ANVISA Resolution – RDC N° 41 of April 28, 2000
- ANVISA Resolution – RE No 1170 of April 19, 2006
- ANVISA Resolution – RDC No 742 of August 10, 2022
- Recommendations related to contraception and pregnancy testing in clinical trials, HMA Working groups, CTFG/2014/09
- Guideline on bioanalytical method validation, July 2011 (EMEA/CHMP/EWP/192217/2009, Committee for Medicinal Products for Human Use (CHMP))
- ICH guideline M10 on bioanalytical method validation and study sample analysis, (EMA/CHMP/ICH/172948/2019, 25 July 2022 / US FDA Guidance for Industry, November 2022)
- Commission Directive 2005/28/EC, 8 April 2005
- Note for Guidance on structure and content of clinical study reports (CPMP/ICH/137/95), December 1995
- Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples, EMA/INS/GCP/532137/2010, adopted Feb 2012
- Paracetamol oral use immediate release formulations product-specific bioequivalence guidance (EMA/CHMP/356877/2017 Rev.1), 26 April 2023

11. Investigational products

11.1 Selection of doses in the clinical trial

In this single-dose clinical trial, 500 mg of paracetamol (1 orodispersible tablet of Test or 1 film-coated tablet of Reference 1 or 1 film-coated tablet of Reference 2) has been chosen as an individual dose. According to data obtained earlier, mean maximum plasma concentrations of approximately 8 – 10 µg/ml for paracetamol are expected after a dose of 500 mg [4]. CCI [redacted] The analytical method planned for this clinical trial is intended to allow a LLOQ CCI ng/ml for paracetamol. Under these conditions, plasma concentration vs. time profiles are expected to be quantified appropriately after doses of 500 mg.

The maximum allowed exposure of paracetamol 4 g dose is considered well tolerated and safe in healthy human. Therefore, no additional safety margins were deemed necessary.

11.2 Method of assigning subjects to treatment groups

The clinical part of the clinical trial will be open and randomised with no blinding procedure.

During screening the subjects will be identified by a four-digit number (SocraTec R&D Screening number). Assignment to a randomisation number (001 – 054) will be in the order of subjects' arrival time at the CPU.

The treatment sequences for each subject will be determined by a randomisation list prepared by SocraMetrics with the help of SAS software program.

The appropriate number of the randomisation schedule and associated treatment will be allocated for each subject whose entry in the randomised part of the clinical trial is confirmed. The randomisation list will be part of the TMF.

11.3 Investigational medicinal products (IMP)

11.3.1 Identity of the IMPs

Test product has been produced for the clinical trial by Haleon. Prior to start of the clinical trial the Test product will be checked by Haleon with respect to the relevant parameters of pharmaceutical quality, especially *in-vitro* dissolution and content. Batches selected for the clinical trial have to be of appropriate quality and have to be manufactured according to GMP standards. Batches will be selected by Haleon in line with the requirements for bioequivalence trials.

The Reference product 1, Alvedon 500 mg film-coated tablets has a Swedish marketing authorization. Samples originate from normal production batches.

The Reference product 2, Panadol 500 mg film-coated tablets has an Australian marketing authorisation. Samples originate from normal production batches,

Prior to start of the clinical trial each Reference product will be checked by Haleon with respect to the relevant parameters of pharmaceutical quality, especially *in-vitro* dissolution and content. Batches selected for the clinical trial have to be of appropriate quality and have to be manufactured according to GMP standards. Batches will be selected by Haleon in line with the requirements for bioequivalence trials.

The following samples of the investigational medicinal products are chosen for the clinical trial:

TT 1: Pharmaceutical information on Test and Reference product

Pharmaceutical information	Test product	Reference product 1	Reference product 2
Product name	CCI Orodispersible Tablet *	Alvedon film-coated Tablet	Panadol film-coated Tablet
Manufacturer / MA Holder	Haleon CH	Haleon Denmark Aps	Haleon Australia Pty. Ltd Trading Limited
Member state where the reference product is purchased from	N/A	Ireland	Australia
Dosage form	Orodispersible Tablet (ODT)	Film-coated tablet	Film-coated tablet
Active ingredient	paracetamol	paracetamol	paracetamol
Strength	500 mg	500 mg	500 mg
Batch No.	Will be given in the clinical study report and TMF	Will be given in the clinical study report and TMF	Will be given in the clinical study report and TMF
Expiry date/use-by date	Will be given in the clinical study report and TMF	Will be given in the clinical study report and TMF	Will be given in the clinical study report and TMF
Excipients	CCI	Cornstarch, Pregelatinized Starch (Corn), Povidone, Potassium Sorbate, Talc, Stearic Acid, Hypromellose, Triacetin	Starch – pregelatinised maize, Starch – maize, Talc – purified, Stearic acid, Hypromellose, Povidone, Glycerol triacetate, Potassium sorbate, Carnauba wax
Storage conditions	Store tightly sealed between 15°C to 25°C	No special storage instructions	Store below 30°C
Licence No.	NA	5734	AUST R 13591
MFC	CCI	CCI	CCI

*Depending on the approved name of the paracetamol range originator for this new registration

11.3.2 Packaging and labelling of IMPs

The IMPs will be provided, packed and labelled by Haleon.

The Reference products will be provided in a labelled commercial carton containing 10 labelled blisters of 10 tablets each, in total 100 tablets.

The Test product will be provided in a labelled bottle with 60 tablets.

The IMPs will be labelled in accordance with the GMP Annex 13 and with the Clinical Trials Regulation (Regulation (EU) No 536/2014, 16 April 2014).

The label of the IMPs, Test product (primary packages), and Reference product (secondary packages) should include in German language:

a. a clinical trial reference code allowing identification of the trial, site, investigator and sponsor (e.g. sponsors study code, EuCT number), if not given elsewhere
b. treatment number: A, B or C
c. Test or Reference in accordance to the random list
d. name, address and telephone number of the main contact for information on the product, clinical trial (e.g. sponsor, CRO or investigator);
e. name and strength or potency of the active ingredient
f. pharmaceutical formulation
g. route of administration
h. quantity or number of pieces
i. batch number starting with Ch.-B
j. expiry date/re-test date
k. declaration of the intended purpose: “For clinical trial use only”
l. storage conditions
m. directions for use

The information EuCT No., dosage schedule as well as name, address and telephone number of the sponsor, will not be provided on the label of the IMPs but will be given in the subject information.

All clinical trial supplies are to be stored in a locked area in accordance with the storage conditions. An adequate number of retention samples for each product will be stored at the sponsor’s site.

11.3.3 Accountability of IMPs

The use and fate of IMPs must be documented. After completion of the clinical trial, the containers including any remaining IMPs as well as empty containers will be forwarded to the responsible department of the sponsor for orderly disposal, destroyed at site or sent to designated vendor for destruction. A written explanation regarding the disposition of missing products or their containers is required.

11.3.4 Administration of investigational medicinal products

The IMPs will be administered at the trial site under the supervision of the study team. Administration will be performed in the morning approximately between 7:00 and 9:00 am with appropriate intervals between subjects, to allow for sample collection and any additional clinical observations and measurements necessary. The subjects will be in a standing, upright position during the administration of the products.

For Test product: Before administering 1 ODT, the mouth will be wet with 20 mL of water. The water will be swallowed by the subject. When the mouth is empty and immediately after wetting process the ODT will be placed on the upper surface of tongue of the subject with a dry finger by the study personnel.

The ODT will not be chewed or swallowed whole. Subjects will be instructed to let the ODT dissolve in their mouth. Once the tablet is dissolved the subjects will swallow the saliva. This will be followed by an inspection of the oral cavity and of the hands. Dosing time will be set to the time the tablet is placed in the mouth.

For Reference products: 1 film-coated tablet will be taken orally together with 200 ml tap water (room temperature) in an upright position followed by an inspection of the oral cavity and of the hands.

To standardize gastric emptying, subjects will remain in sitting position for 30 minutes after dosing. Thereafter, they will be asked to lie on their right sides for the remainder of the first hour after administration. Subjects should remain recumbent until 4 hours after administration of study medication, after which no restrictions concerning posture or movement are applied. However, subjects are allowed to walk to the bathroom as necessary (after one hour post administration).

12. Selection of clinical trial population

Non-institutionalised healthy male or female subjects will be enrolled in the clinical trial. Subjects will be selected from the subject database at the trial site and by advertisements in accordance with the inclusion and exclusion criteria (see chapter 12.1 and 12.2), then contacted verbally, by telephone or in writing.

12.1 Inclusion criteria

Subjects of both sexes, who will be included, must fulfil all the following criteria (for definition of inclusion see chapter 4.2.3):

1. written informed consent, after having been informed about benefits and potential risks of the clinical trial, as well as details of the insurance taken out to cover the subjects participating in the clinical trial
2. sex: male/female
3. age: 18 to 55 years (including)
4. body-mass index[1] (BMI): ≥18.5 kg/m² and ≤ 30.0 kg/m²
5. Body weight: ≥50.0 kg for males and ≥45.0 kg for females.
6. good state of health
7. willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
8. female subject of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 7 days after the last dose of assigned treatment
9. non-smoker or ex-smoker for at least 3 months (including non-nicotine vapers, nicotine chewing gum or pouches or nicotine replacement therapy)

[1] Calculated from body weight and height according to the formula: weight (kg)/height^2 (m^2)

12.2 Exclusion criteria

Subjects must not be randomized in the study if any of the following criteria are fulfilled:

Safety concerns

1. Existing cardiac and/or haematological diseases or pathological findings, which might interfere with the safety or tolerability of the active ingredient
2. Existing renal diseases or pathological findings, which might interfere with the safety or tolerability, and/or pharmacokinetics of the active ingredient
3. Current evidence of ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if more than one of the following lab value deviations are found: 1) AST (≥ 1.2 ULN), ALT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) total bilirubin (> 2.00 mg/dL, except in case of existing Morbus Gilbert-Meulengracht deduced from anamnesis/medical history) or creatine kinase (≥ 3 ULN), and creatinine > 0.1 mg/dL ULN (limit of > 0.1 mg/dL correspondents to of > 9 µmol/l ULN). A single deviation from the above values is acceptable and will not exclude the candidate, unless specifically advised by the investigator
4. Existing gastrointestinal diseases or pathological findings, which might interfere with the safety, tolerability, absorption and/or pharmacokinetics of the active ingredient
5. History of relevant CNS and/or psychiatric disorders and/or currently treated CNS and/or psychiatric disorders
6. History or clinical evidence at screening of pancreatic injury or pancreatitis
7. History of inflammatory bowel disease or gastrointestinal bleeding including peptic ulcers
8. Diagnosis of systemic lupus erythematosus, thyroid diseases, secondary Raynaud's syndrome; known hyperkalemia
9. Evidence of urinary obstruction (e.g. due to benign prostate hyperplasia) or difficulty in voiding at screening
10. Status of glutathione depletion (eating disorder, cystic fibrosis, HIV infection, starvation, cachexia) due to metabolic deficiencies
11. Oral surgery within 4 weeks of dosing, dental work or extractions within 2 weeks of dosing, or presence of any clinically significant (as determined by the principal investigator or designee) oral pathology including lesions, sores or inflammation
12. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling or gastric banding (note: this is not applicable for minor abdominal surgery without significant tissue resection, e.g., appendectomy and herniorrhaphy)
13. Subjects, who report a frequent occurrence of migraine attacks
14. Acute or chronic diseases which may interfere with the pharmacokinetics of the IMP
15. Clinically relevant chronic or acute infectious illnesses or febrile infections within two weeks prior to start of the study.
16. History or current evidence of renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine (> 1.43 mg/dL) or BUN (≥ 35 mg/dL) or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria
17. Systolic blood pressure < 90 or > 139 mmHg
18. Diastolic blood pressure < 50 or > 89 mmHg
19. Heart rate < 50 bpm or > 90 bpm
20. QTc interval > 450 ms for men and > 470 ms for women
21. Hemoglobin value < 12.0 g/dL for males and < 11.5 g/dL for females

22. Evidence or history of medication overuse headache, or allergic disease to medication within the last 5 years that may increase the risk associated with study participation
23. Laboratory values out of normal range unless the deviation from normal is judged as not relevant for the clinical trial by the investigator
24. Positive anti-HIV-test (if positive to be verified by western blot), HBs-AG-test and anti-HBc IgM or anti-HCV-test
25. Known allergic reactions to the active ingredients used or to constituents of the pharmaceutical preparations
26. Any history of asthma, urticaria, or other significant allergic diathesis or allergic reaction to any other pain reliever/fever reducer. Subject with uncomplicated seasonal allergic rhinitis can be accepted if expected allergy season is clearly outside enrollment/treatment period
27. History of severe allergies or multiple drug allergies unless it is judged as not relevant for the clinical trial by the investigator

Lack of suitability for the clinical trial

28. History of illegal or legal drug abuse within 1 year prior to screening or recreational use of soft drugs (such as marijuana, codeine) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, any opioid derivatives such as heroin or fentanyl, and amphetamine derivatives) within 3 months prior to screening
29. Positive alcohol, cotinine or drug test at screening examination
30. History of alcohol abuse in the last 5 years or regular intake of alcoholic food or beverages of ≥ 24 g pure ethanol for men or ≥ 12 g pure ethanol for women per day
31. Subjects who are on a diet which could affect the pharmacokinetics of the active ingredient
32. Regular intake of beverages or food containing xanthine derivatives or xanthine-related compounds (e.g., coffee, tea, caffeine-containing sodas and chocolate), equivalent to ≥ 500 mg xanthine per day
33. Performance of strenuous physical exercise (body building, high performance sports) from 2 weeks prior to admission and throughout the entire study.
34. Subject reports consumption of any drug metabolizing enzyme (e.g. CYP3A4 or other cytochrome P450 enzymes) inducing or inhibiting aliments, beverages or food supplements (e.g. broccoli, Brussels sprouts, grapefruit, grapefruit juice, star fruit, St. John's Wort etc.) within 2 weeks prior to admission to the unit
35. Use of any systemic or topical medication (including OTC medications, herbal remedies, cannabidiol cosmetics and any anticholinergic medicines or other medicines that may cause dry mouth) within 2 weeks or within less than 10 times the elimination half-life of the respective drug (whichever is longer) before first scheduled study drug administration, or is anticipated to require any concomitant medication during that period or at any time throughout the study. For details on allowed medication see chapter 13.2.3
36. Any history of long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes
37. Any vaccination, including COVID-19 vaccine, within 14 days prior to the first dose
38. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to dosing
39. Participation in a clinical trial in which they have tried an IMP, a medical device or a marketed medicinal product during the last 6 months prior to individual enrolment of the subject
40. Simultaneous participation in another clinical trial with active ingredients, medical devices or marketed medicinal products

For female subjects with childbearing potential only:

41. Positive pregnancy test at screening examination
42. Pregnant or lactating women
43. Female subjects who do not agree to apply highly effective contraceptive methods (highly effective contraceptive methods are defined in chapter 13.2.1)

Administrative reasons

44. Close affiliation with the sponsor or the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee of or student at the investigational site), employee of the sponsor or affiliates
45. Subjects who are unable to understand the written and verbal instructions, in particular regarding the risks and inconveniences they will be exposed to during their participation in the clinical trial

The exclusion criteria are chosen to assure that subjects with specific risks for administration of the IMPs and subjects with conditions, which may have an impact on pharmacokinetic parameters, cannot be included.

12.3 Removal of subjects from treatment or assessment

Only data of subjects who are part of at least one of the analysis sets will be presented in the integrated clinical study report. For definitions of analysis sets see chapter 15.2.

Screening failures including reason will be listed in the screening list. In case that an eCRF is available it will be archived, but data will not become part of the database and will consequently not be presented in the integrated clinical study report.

All eCRFs generated within the clinical trial have to be kept in the documentation of the clinical trial.

Reasons for withdrawal of randomised subjects will be presented in the integrated clinical study report.

12.3.1 Withdrawal criteria for included subjects

Safety related withdrawal criteria

- SAEs at the Principal Investigator's discretion, only if they are classified as not related
- serious ADR (i.e. a related SAE, however, all SAEs will be handled as if they are IMP-related as long as other causes are not clearly established)
- diseases, PTAE, or AEs that occur after inclusion, which do not constitute SAEs but which, in the opinion of the Principal Investigator, would probably prevent achievement of the clinical trial objectives or which unacceptably endangered the safety of the subject
- withdrawal of consent
- positive alcohol, drug, cotinine, or pregnancy test after inclusion

Safety and study aim related withdrawal criteria

- non-adherence to the trial conditions, violation of any restriction (see chapter 13.2.1) or relevant deviations from procedures as established in the clinical trial protocol with regard to medical aspects at the Principal Investigator's discretion and with regard to pharmacokinetic aspects (e.g., if $AUC_{0\text{-tlast}}$ and/or C_{max} cannot be determined adequately) at the Principal Investigator's discretion in agreement with the Scientific Directors and with the sponsor (Haleon).
- due to vomiting: Subjects vomiting within 24 h **prior to IMP** intake should be carefully studied for upcoming illness/diseases. Withdrawal pre dosing is at the Principal Investigator's discretion. Due to t_{max} being achieved within 10 to 60 minutes after oral administration of

paracetamol, subjects vomiting **after administration** until up to 2 h p.a. are to be excluded. In case that later vomiting occurs withdrawal will be at the Principal Investigator's discretion.

- due to diarrhoea: subjects with liquid stool for more than three times on day of administration
- due to migraine attacks: acute migraine attacks on the PK profiling day depending on whether the investigator assesses them as potentially interacting with the GI-transit

12.3.2 Replacements

Dropouts will not be replaced.

12.3.3 Removal of subjects from assessment

In general, removal of a subject from the assessment in the Safety Population is not applicable (see chapter 15.2).

Major protocol deviations considered a reason for exclusion from the PKAS are:

- Primary study aim cannot be assessed.
  - Absence of a valid set of data that would allow treatment comparisons.
  - No primary variable available.
- Violation of any inclusion criterion, that prevents collection or use of data valid for assessment of primary study aim.
- Deviation from the regulations of the clinical trial protocol, that prevent unbiased assessment of the treatment effect:
  - Intake of concomitant medication with a (potential) impact on the primary outcome parameter
  - Any other deviation that resulted or should have resulted in withdrawal from the clinical trial as it is expected to interfere with the primary outcome parameter in accordance with chapter 12.3.1.

12.3.4 Premature termination of the clinical trial

Premature termination of a clinical trial may occur upon decision of the sponsor, upon decision of the Principal Investigator, by request of an authority or because of withdrawal of positive vote by the responsible IEC. Furthermore, the Principal Investigator / sponsor have the right to close the center, at any time, although this can occur only after consultation between involved parties.

The IEC/IRB, the competent authority (BfArM), and the local authority have to be informed within 15 days. The investigator is obliged to inform the local authority whereas information of the IEC/IRB and competent authority (BfArM) is to be performed by the CRO on behalf of the sponsor.

If the trial/center has to be closed prematurely, SocraTec R&D GmbH will provide all essential documents necessary for the sponsor's TMF as defined in the Guideline for good clinical practice (EMA/CHMP/ICH/135/1995).

The clinical trial will be terminated prematurely in the following cases:

- if AEs occur for which frequency of intensity differs from the data reported in the IB and as a consequence the benefit-risk ratio is not reasonable anymore
- if a serious ADR (i.e. a SAE considered at least possibly related to the IMP administration) occurs in 1 subject
- if severe non-serious ADRs (i.e. severe non-serious AEs considered at least possibly related to the IMP administration) occur in 2 subjects, independent of within or not within the same system organ class

- if the pattern of AEs observed in the clinical trial interferes significantly with the Benefit-Risk evaluation of the Principal Investigator provided prior to the start of the clinical trial
- if the number of dropouts is so high that proper completion of the clinical trial will not realistically be expected
- if the results of parallel clinical trials show evidence for unacceptable risks
- if the clinical trial will not reveal new knowledge and consequently is ethically not justifiable anymore
- if severe violations of GCP, the trial protocol and misconduct occur which unacceptably affect the safety or rights of the subjects or render questionable the validity of the trial results

13. Performance of the clinical trial

13.1 Study assessment and procedures

13.1.1 Screening examination

Screening examination for confirmation of eligibility will be performed prior to inclusion to ensure that subjects are clinically healthy.

The following assessments will be performed within 28 to 6 days (for female subjects with childbearing potential) and within 28 to 2 days (for all other subjects) before the first intended administration of the IMP:

- demographic (age, sex) and anthropometric data (body weight, height, BMI)
- medical history (including prior and concomitant medication) and any pre-planned surgical treatments or procedures
- physical examination
- ECG (12-leads) with HR,
- BP, body temperature,
- clinical laboratory investigation: blood analysis including haematology, haemostatic system, clinical chemistry, hormones, serology, urinalysis, (for parameters see TT 3 in Appendix III)
- test of alcohol, cotinine and drug abuse
- lifestyle habits (caffeine, alcohol and nicotine consumption or smoke-free products consumptions)
- general well-being
- check of applicable restrictions
- female status (check of childbearing potential and urine pregnancy test in all female subjects with childbearing potential)
- check of inclusion and exclusion criteria

For blood volume withdrawn during screening examination see chapter 13.5.1.

Commercially available tests, which will be used in the clinical trial, are specified in chapter 13.4.1.

Additionally, within 24 hours (study day -1) before IMP administration the state of health will be confirmed by performing the following assessment:

- medical history (including prior and concomitant medication)
- physical examination
- vital signs (body temperature)

- test of alcohol, cotinine and drug abuse
- general well-being
- female status (check of childbearing potential and serum pregnancy test in all female subjects with childbearing potential)
- PTAE
- Inclusion/exclusion assessment

Based on these data the subject's inclusion into the trial will be performed.

13.1.1.1 Re-Screening

Re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is not allowed – with the following exceptions:

- The subject had so far successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).
- The subject has not fulfilled inclusion/exclusion criteria at first screening but is expected to pass the screening procedures successfully at a later time point because of plausibly anticipated changes in medical conditions, i.e. expected convalescence from acute disease.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject has to resign the informed consent form, even if it was not changed after the subject's previous screening.

Re-screening under the mentioned circumstances will be permitted only once per subject.

If a re-screened subject is a screening failure for the second time, no further rescreening will be allowed.

Re-measurements, e.g. single laboratory parameters or vital signs, due to implausible values or in case of safety follow-up are not understood as re-screening.

13.1.2 In-house procedure

Following procedures will be repeated for period I to period III.

Study day -1 (day of hospitalization)

On study day -1 the subjects report to the site. The following measures will be performed:

- report at the Clinical Pharmacology Unit,
- check of identity and of luggage for forbidden items,
- put an irremovable identification sign around the wrist, which will be worn throughout the in-house period,
- physical examination
- vital sign: body temperature (ear)
- tests for alcohol, cotinine, and drug abuse. Commercially available tests will be used, see in chapter 13.4.1. However, tests for alcohol, cotinine, drug abuse and COVID-19 (i.e., SARS-CoV-2 rapid antigen test) can always be performed in case of suspicion during the clinical trial

- serum pregnancy test for all female subjects with childbearing potential,
- checks for general well-being (see chapter 13.3.6.1),
- checks of restrictions (see chapter 13.2.1) and medication (see chapter 13.2.3),
- prior to randomisation recheck of the inclusion and exclusion criteria,
- check for medication

Afterwards and only in period I randomisation will take place subsequently (see chapter 4.2.3).

Furthermore

- hand-out of a clinical trial identification card together with the information to keep this clinical trial identification card until discharge from the clinical trial (only in period I),
- intake of standardised food and beverages (see chapter 13.2.2), will take place.

Study day 1 (profiling day)

The following measures will be performed:

- an indwelling cannula will be inserted in the morning prior to administration of the IMPs and the first blood sample will be collected. Based on case-by-case decision samples can be withdrawn by direct venipuncture,
- measurements of blood pressure (BP), pulse rate (PR), body temperature (ear), within 1 hour before drug administration,
- recheck of the inclusion and exclusion criteria,
- check for general well-being,
- administration of the IMPs (see chapter 11.3.4),
- checks for restrictions (see chapter 13.2.1),
- PK blood sampling (see Appendix II, chapter 1),
- intake of food and beverages (see chapter 13.2.2),
- check for medication.

In case that several measurements (e.g. vital signs, food and beverage intake, general well-being) are planned for the same time point, blood sampling has to be performed in the exact time schedule whereas further measurements have to be adapted in an appropriate time range.

Morning of study day 2

The following measures will be performed:

- PK blood sampling (see Appendix II, chapter 1),
- measurements of body temperature (ear),
- checks for general well-being,
- check for medication.

The measurement of body temperature, checks for general wellbeing and check for medication in SD 2 of period 3, will just be recorded as end of study evaluation.

Subjects will remain confined to the Clinical Pharmacology Unit until 24 h p.a., the morning of study day 2. At the discretion of the Principal Investigator the in-house confinement, if necessary, may be prolonged.

After the last measure has been performed on study day 2 and the end of study examination has been performed the subjects will leave the CPU.

13.1.3 End of study examination

The end of study examination is performed in order to verify that the subject bears no sign of illness or health damage. An end of study examination should generally be performed in case that a subject has been exposed to any IMP.

The end of study examination will be performed on day 2 of Period 3, except for dropped-out subjects, in which case the end of study examination will be scheduled individually at a separated visit.

The following examinations will be performed within the end of study examinations:

- re-assessment of physical examination,
- BP, pulse rate (PR), body temperature (ear),
- clinical laboratory investigation: blood analysis (including haematology, haemostatic system, clinical chemistry) and urine analysis, for parameters see TT 3 in Appendix III (except serology),
- general well-being and use of concomitant medication,
- check of restrictions,
- pregnancy test in all female subjects with childbearing potential.

As soon as all results of the end of study examination are available, have been evaluated by the investigator and AE-follow up is performed the subject can be discharged from the trial.

For blood volume withdrawn during end of study examination see chapter 13.5.1.

For follow-up of any AE, which remains unresolved at the time point of subject's end of study examination see chapter 13.3.6.2.1.

If the subject refuses to follow the instructions of the investigator and an end of study examination cannot be performed, the latter is released from responsibility to perform an end of study examination.

13.2 Restrictions during the study and concomitant treatment(s)

13.2.1 Restrictions

Checks for restrictions will be performed at the following time points: at screening examination (so far as applicable) as well as upon each in-house period (evening of day -1) and at the end of study examination.

Medication	Use of any systemically available medication, which is known to induce or irreversibly inhibit transporters and/or enzymes, is not permitted within 2 weeks prior to the first intended administration of the IMP until the last PK blood sample has been withdrawn. Use of medication with short-acting effect on absorption (e.g. laxatives, metoclopramide, loperamide, antacids) is not permitted within 2 days prior to each intended start of the IMP administration or during in-house confinement. Use of medication with pharmacologically persisting effect on absorption (e.g. H_2-receptor antagonists, proton pump inhibitor, etc.) is

	not permitted within 7 days prior to each intended start of IMP administration or during in-house confinement. All active ingredients, which might interfere with CYP 3A4/CYP 2E1 must be eliminated completely from the body prior to each intended administration. In case of oral administration of such an active ingredient, the time span between last administration of the CYP 3A4 / CYP 2E1 interfering active ingredients and the investigational product must exceed 2 weeks. Use of any medications containing the active ingredient of the Test or reference product administered in the trial is not permitted within 7 days prior to first intended start of IMP administration until the last PK sample has been withdrawn.
Vaccination	Vaccinations are not permitted within 14 days prior to 1st intended IMP administration until the last PK blood sample has been withdrawn.
Physical activities	Usual physical activities are permitted. No strenuous physical activities are allowed from 2 weeks prior to admission and throughout the entire clinical trial
Alcohol consumption	Consumption of alcohol containing food or beverages is not permitted from 36 h prior to each intended administration of the IMP until the last PK blood sample has been withdrawn in each period. Consumption of alcohol-containing food and beverages is not permitted for 24 h prior to the end of study examination. Furthermore, subjects will be asked not to consume alcohol containing food or beverages within 24 h prior to the screening examination.
Consumption of poppy seeds	Subjects will be asked not to ingest poppy seeds containing food or beverages (poppy seed rolls, cake, yoghurt etc.) within 4 days prior to the screening examination until after the last PK blood sample of the last period has been withdrawn as far as the information can be given to the individual subjects prior to the screening examination.
Xanthine consumption	Intake of xanthine containing products (coffee, black and green tea, cola, cocoa, chocolate, and other xanthine containing confectioneries like chewing gum or candies, energy drinks, etc.) is not permitted from 36 h prior to each intended administration of the IMP until the last PK blood sample has been withdrawn in the last period.
CYP450	Intake of grapefruit/pomelo containing food or beverages, star fruit containing food or beverages, St. John's wort and consumption of Brussels sprouts or broccoli (known CYP450 inhibitors and inducers) is not allowed from 2 weeks prior to the first intended administration of the IMP until after the last PK blood sample of the last period has been withdrawn.
Effective contraceptive methods (female)	Female subjects are to be informed that they have to apply highly effective contraceptive methods. Highly effective contraceptive methods include (following the CTFG recommendations[2]): • combined (estrogen and progestogen containing) hormonal contraception e.g. oral, intravaginal, transdermal

[2] Vasectomized partner of a female subject will not assess as highly effective method

	• and progestogen-only hormonal contraception e.g. oral, injectable, implantable as well as • intrauterine device (IUD) and • intrauterine hormone-releasing system (IUS) each in combination with male condom to increase safety effect • bilateral tubal occlusion • heterosexual abstinence during the clinical trial. Furthermore, female subjects are to be informed that it can never completely be ruled out that the IMP may cause foetal harm when administered in pregnant women.
Blood donation/Trial participation	Simultaneous participation in another clinical trial is not permitted during participation in this clinical trial. Participation in a clinical trial with administration of any investigational medicinal product, medical devices or any marketed medicinal products during the last 6 months prior to individual enrolment of the subject. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to dosing is not permitted. At the end of study examination each clinical trial subject participating in this clinical trial will be advised not to donate blood for at least 2 months, or participate in any clinical trials with active ingredients for a minimum period of six months following this clinical trial.

13.2.2 Food and beverages

Food intake

Intake of food and beverages will be standardised over the entire course of in-house confinement. Food (including candy and chewing gum) and beverages not supplied by SocraTec R&D will be forbidden during in-house period

In the evening of pre-profiling day (i.e. study day -1) of each period subjects may receive a standardised dinner, which has to be finished at least 10 h prior to the intended time of administration. The subjects will fast for at least 10 h overnight (no food, no beverages, water is allowed until 1 hour prior to administration of IMPs). In case the subject has already eaten or is not hungry and the dinner will not be performed on the CPU, this will not be considered as a deviation, provided that the fasting period of at least 10 h overnight has been observed.

On the day of administration of the IMP (i.e. study day 1) subjects will receive standardised meals 4, 8 and 12 h p.a.

The first meal after administration of the IMP at the PK day has to be ingested completely and start time should not be earlier than 4 h p.a. For deviation with regard to an early ingestion or incomplete meal intake comment/reason will be given. For subsequent meal intake, a deviation from the scheduled time and the ingested amount is without relevance and will not be considered as protocol deviation.

Fluid intake

Fluid intake will be standardised over 10 h p.a. in the following way: From 0 h until 1 h p.a. no fluid intake, from 1 h until 10 h p.a. 150 ml of non-carbonated water (room temperature) will be

given every hour, i.e., 150 ml will be given nine times. After this time interval fluid intake of non-carbonated water is *ad libitum*.

13.2.3 Prior and concomitant therapy

Prior and concomitant medication will be documented for treatment of PTAE/AE in the eCRF. In case of therapeutic procedures other than medication the non-specific term “other” will be used.

Intake of medication prior to the first intended administration of the investigational products, which is listed in the exclusion criteria (see chapter 12.2) and in the restrictions (see chapter 13.2.1) including COVID-19 vaccination will prevent randomisation or will lead to withdrawal from the clinical trial.

The observation phase for intake of medication will start 2 weeks prior to intended start of the treatment and will end with the discharge of the subject from the clinical trial.

Permitted medication

Use of medication is not planned except

- systemic contraceptives and hormone replacement therapy, as long as female subject is on stable treatment for at least 3 months before first scheduled study drug administration and continues treatment throughout the study, as well as
- exceptional use of ibuprofen 200 mg (up to 1200 mg daily). In the 4 hours prior and 4 hours after IMP administration, the use of ibuprofen will be completely restricted.

However, medication to overrule an AE/PTAE will always be permitted and has to be documented in the eCRF.

If a subject needs additional medication during the clinical trial, the responsible investigator should be asked, who will contact the Principal Investigator before any treatment will occur to ensure that only medically necessary treatment is to be given.

The Principal Investigator will then decide together with the Scientific Director of SocraTec R&D whether the subject has to be excluded due to any medically necessary treatment.

13.2.4 Treatment compliance

During and after administration of the particular IMPs as well as during the withdrawal of blood samples the subjects will behave themselves according to the instruction of the investigator or study team.

Each IMP will be administered under supervision of study team. The study personnel will check the oral cavity and empty hands of each subject after administration.

Retrospectively, treatment compliance can be retraced via drug dispensing log and plasma concentration vs. time profiles.

13.3 Trial parameters

Specific safety parameters are described in the appropriate chapters (4.2.11 and 13.3.6).

13.3.1 Demographic and anthropometric data

As demographic parameters age, sex, and as anthropometric data body weight, height, BMI will be captured. Body weight and height will be measured with commercial instruments.

Results of medical history (including prior and concomitant medication), underlying disease, surgeries and physical examination will also be considered as demographic data and will be

assessed as related to the definitions in chapter 4.2.7 and 4.2.8, as well as the inclusion/exclusion criteria listed in chapter 12.

Furthermore, lifestyle habits (caffeine, alcohol and nicotine consumption) and female status (check of childbearing potential and pregnancy test in all female subjects with childbearing potential) will be documented.

13.3.2 Physical Examinations

The full physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the study site covering at least the organs of the cardiovascular, respiratory, and abdominal system. Orientating tests of neurological function will be included.

Brief physical examination will cover organs of cardiovascular and respiratory system, any additional organ that the investigator considers clinically relevant, and a basic neurological examination.

Abnormal physical examination findings are recorded either as medical history or as adverse events.

13.3.3 Vital signs measurements

Systolic and diastolic arterial blood pressure will be measured by oscillometry using an automatic non-invasive device.

During screening and end of study examination measurements of pulse rate, systolic and diastolic blood pressure will be recorded in supine position after the subjects have been resting for 15 min. During the periods, measurements of systolic and diastolic blood pressure including pulse rate will be recorded in sitting/supine position after the subjects have been resting for 5 min.

During the trial, Blood pressure (BP), pulse rate (PR), and body temperature (ear) will be measured as follows: at screening, pre-treatment on Day 1 (within 1 hour before drug administration) of each treatment period and at the end of study examination. Ear body temperature on Day -1, Day 1 and Day 2 of each treatment period and at screening and end of study examination.

Body temperature (ear) will be measured with commercial instruments.

Body temperature (ear) will be measured on Day -1, Day 1 and Day 2 of each treatment period.

Clinically relevant abnormal findings during these safety measurements will be reported as adverse events and will be followed up and/or treated as medically appropriate.

13.3.4 Clinical laboratory investigations

For clinical laboratory parameters determined, see Appendix III.

13.3.5 Electrocardiogram

During screening heart rate will be measured via ECG. In case of safety measurement during the periods and at end of study examination, pulse rate will be measured by oscillometry using an automatic non-invasive device.

The ECG will be recorded by means of a 12-lead ECG system over 10 sec while the subjects will rest in supine position. The chart speed will be set at 50 mm per sec. The ECG patterns will be analysed qualitatively with particular emphasis on changes in the T-wave morphology. Heart rate and time intervals of the ECG such as PQ, QRS and QT interval will be computed automatically by the ECG system, whilst the heart rate corrected QT_c interval will be calculated by the system according to Bazett & Fridericia formula.

All ECGs recorded during the trial will be evaluated by the investigator, who will document the overall assessment of the findings and their clinical relevance.

ECG printouts will be signed by the nurse after being recorded and will be signed and dated by the investigator after being assessed.

During screening, measurements of ECG and heart rate will be recorded in supine position after the subjects have been resting for 15 min. Same machine will be used for all ECG for a specific subject. Meals will be consumed after ECGs to avoid the influence of food intake on heart rate, T-Wave morphology, and QT assessment.

Any QT prolongation above 30 ms or other ECG abnormalities such as Torsade Pointe, ventricular tachycardia, ventricular fibrillation, flutter or any other new cardiac abnormality at the ECG or during physical examination considered clinically significant will be reported as AE and followed up/treated according to the institutional standard practice.

13.3.6 Pre-Treatment Adverse Events and Adverse Events

13.3.6.1 Checks for general well-being

The observation phase for PTAE will start with screening examination (i.e. after signing the informed consent form) and will end with the discharge of the subject from the clinical trial.

The observation phase for AEs will begin with start of the treatment (for definition of treatment see chapter 9.1) and will end with the discharge of the subject from the clinical trial.

The observation phase for SAE will start with screening examination (i.e. after signing the informed consent form) and will end with the discharge of the subject from the clinical trial.

Checks for general well-being will be performed in a non-leading manner. In addition to the checks for general well-being at the screening examination and at the time of in-house period, checks for general well-being will also be performed at the end of study examination. Deviation from time scheduled for check for general well-being will not be considered as protocol deviation. Furthermore, the subjects will be asked to report any PTAE/AEs spontaneously, whether or not they occur during confinement.

A registered physician (investigator) will be available throughout the entire clinical trial at least by phone and all subjects will be observed for signs of clinical toxicity during the entire clinical trial.

13.3.6.2 Documentation of AEs and PTAE

Reporting of any PTAE or AE (including clinically relevant laboratory values) will be done individually for each clinical trial subject. Any PTAE or AE, reported by a subject or observed by the study personnel will be documented in a source data sheet (SDS) at first by the study personnel using the German language. All relevant information will be later transferred to the eCRF and assessed by the investigator using the English language. For each PTAE or AE, start and end date, start and end time, type, any action taken (e.g. medical action taken to overrule the PTAE or AE) seriousness, and intensity will be recorded. Evaluation of outcome, and the relationship with the IMPs (causality) will be classified only for AEs.

Each PTAE of subjects being part of the analysis sets defined in chapter 15.2 and each AE that occurred for these subjects will be listed and described in the report. The relationship of each AE will be assessed. Investigators will be responsible for any ratings of PTAE and AEs including causality (for all AEs).

Classification of PTAE or AEs with regard to maximum intensity

In the course of the clinical trial, the investigator will determine whether any PTAE or AE has occurred and will grade their intensity as follows:

Mild	The PTAE/AE impairs the normal functional level of the subject only slightly, if at all.
Moderate	The PTAE/AE impairs the normal functional level of the subject to a certain extent.
Severe	The PTAE/AE represents a clear-cut, marked impairment of the subject's normal functional level.

The maximum intensity of a PTAE/AE is to be considered for classification.

Classification of causality of AEs to the IMP

Every AE experienced during the clinical trial must be evaluated for its relationship to the IMP administered. The causal relationship of an AE with the IMP(s) will be classified as follows:

The causal relationship between the AE and the IMP will be assessed as having a reasonable possibility of causal relationship (“related”) or not having a reasonable possibility of causal relationship (“not related”). AEs with unassessable relationship will be classified as “related”.

According to the ICH E2A definition of Adverse Drug Reactions (“Note for Guidance on clinical safety data management: definitions and standards for expedited reporting”), causal relationship between a medicinal product and an adverse event is judged as related if there is at least a reasonable possibility of causal relationship, i.e., the relationship cannot be ruled out.

Specification of the outcome of AEs

The outcome of an AE is to be classified as follows:

resolved
resolved with sequelae
not yet resolved
death
unknown

13.3.6.2.1 Follow-up of subjects after Treatment Emergent Adverse Events

The staff of the clinical facility has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.

Any AE which remains unresolved at the time point of subject’s last visit requires detailed evaluation and follow-up until the AE has been resolved or in case of non-IMP related AEs a reasonable explanation for its persistence is found.

In case of AEs related to the IMPs every effort has to be made to follow-up clinical trial subjects in order to determine the final outcome. If follow-up cannot be completed until release of eCRF by the investigator the individual eCRF will be released and transferred to the Clinical Data Management. In this case, follow-up information will be documented separately in the subjects’ record and outcome including a short description on follow-up procedures performed must be sent to the sponsor.

It is the investigator’s responsibility to assure that subjects experiencing adverse reactions will receive appropriate treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e. if treatment or hospitalisation is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests yielding clinically abnormal results at the end of study evaluation.

Any serious adverse event or death should be immediately reported, regardless of the circumstances or the suspicion of a causal relationship with the drug, in the event it occurs or is known by the investigator at any time during the study up to the last follow-up visit required by the protocol or up to 30 days after the last administration of the study drug, whichever occurs last.

If a subject refuses to follow the instructions of the investigator for follow-up, the latter is released from responsibility to perform follow-up.

13.3.6.3 Action taken in case of Serious Adverse Events

SAEs are to be documented in detail on the SAE Report form of Haleon in addition to the regular AE documentation on the eCRF from the time of signature of the ICF of the first subject until the discharge of the last subject from the clinical trial. The Principal Investigator must report SAEs immediately, and without any undue delay, under no circumstances later than 24 h after becoming aware of obtained knowledge, and send the SAE Report form via email to the Drug Safety Department of the sponsor, Haleon:

CCI [redacted]

The PI will also send the SAE report to Haleon study manager and to SocraTec project manager. SAEs, which, according to present knowledge, might be caused by the IMP require immediate, thorough medical assessment by the Principal Investigator. The decision regarding termination of the entire clinical trial will be taken on the basis of this assessment and in accordance with the AMG and the legal requirements of other involved countries.

The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), the Ethics Committee and to the regulatory authority(ies) of all ADRs that are both serious and unexpected.

The sponsor shall notify ANVISA, through a specific electronic form, of unexpected serious adverse events occurring in the country, in which causality is possible, probable or defined for the product under investigation.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject, the investigator shall report the serious adverse event to the drug safety department of Haleon. Such cases will require expedited reporting if meeting the criteria of a serious and unexpected ADR (SUSAR).

Expedited reporting is also required for other safety issues where they might alter the benefit-risk assessment for the Test product, required changes in the Test product administration or affect the conduct of the clinical trial. Such expedited reports should comply with the applicable regulatory requirement(s) and with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95).

SocraTec R&D will supply Haleon, the Ethics Committee and regulatory authorities with any additional requested information, notably for reported deaths of a subject. Haleon will supply the Ethics Committee and regulatory authorities with any additional requested information, notably for reported deaths of a subject.

Haleon will write the case narrative based on the SAE report received from the investigator. Haleon will notify the competent authority(ies) and the Ethics Committee in writing of any SUSARs without undue delay and no later than within 7 days (life-threating and / or fatal cases) or without undue delay and no later than 15 days (all other cases), respectively.

13.3.6.4 Procedures in case of pregnancy

Since there are only limited information on the direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development of paracetamol, women participating in the clinical trial must be either post-menopausal, permanently surgically sterilized or, if of childbearing potential and sexually active, using a reliable form of contraception prior to and during the clinical trial (see also chapter 13.2.1).

A subject who during the clinical trial (after randomisation) intends to or actually becomes pregnant should contact the investigator. The investigator must immediately withdraw the subject from the clinical trial and notify the sponsor.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under clinical trial may have interfered with the effectiveness of a contraceptive method. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) in subjects who received the IMP at least once must be followed up and documented even if the subject was discontinued from the clinical trial. The principal investigator and the sponsor must follow up the mother and the child during the pregnancy and until labour.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the relevant region-specific Haleon Single Case Processing mailbox CCI , with copy to the appropriate Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the relevant Haleon region specific Single Case Processing mailbox CCI , with copy to the appropriate Study Manager. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

13.3.7 Primary efficacy variables

Not applicable.

13.3.8 Secondary efficacy variables

Not applicable.

13.3.9 Pharmacokinetic parameters

13.3.9.1 Pharmacokinetic parameter

Considering plasma concentration and the appendant scheduled and real sampling times the following pharmacokinetic parameters will be determined by means of non-compartmental analysis for

- paracetamol.

Determination will be repeated considering scheduled times for information, descriptive statistics and treatment comparisons will be provided; however, the primary analysis will be based on actual times allowing for more appropriate calculation.

$AUC_{0\text{-}tlast}$	area under the concentration vs. time curve from dosing time to the last measurement time point with a concentration value above the lower limit of quantitation, *calculated by means of the linear up/log down method (linear trapezoidal rule for increases in concentration/logarithmic trapezoidal rule for decreases in concentrations*
$AUC_{0\text{-}inf}$	$AUC_{0\text{-}tlast} + AUC_{expol}$
$AUC_{expol\%}$	$AUC_{expol} \times 100 / AUC_{0\text{-}inf}$, where $AUC_{expol} = C_{last}/Lz$
C_{max}	maximum observed concentration, directly taken from measured concentration values

C_{last}	observed concentration at the last time point with a concentration value above the lower limit of quantitation, directly taken from measured concentration values
t_{max}	time to reach maximum concentration, obtained directly from measured values
t_{last}	last time point with a concentration value above the lower limit of quantitation, directly taken from measured concentration values
$t_{1/2}$	apparent terminal elimination half-life, $t_{1/2}$ = ln(2) / Lz
L_z	apparent terminal elimination rate constant determined by log-linear regression; the regression should generally involve at least 3 consecutive measurable concentrations that decrease over time
t_{lag}	time from IMP administration to last sampling time point before first concentration value above the lower limit of quantitation, directly taken from measured concentration values

Due to technical requirements of the Phoenix software program considered for the pharmacokinetic and statistic evaluations, the following symbols may be used during the evaluation synonymously: ∞ = inf, λ = L_z, τ = T/Tau, $t_{1/2}$ = HL_Lambda_z, "," = "_".

Parameters will also be calculated for subjects excluded from the valid analysis set and be reported separately, as far as feasible.

13.4 Appropriateness of measurements

All methods used for safety assessments are standard methods for which reliability, accuracy and relevance have been documented (e.g. BP, body temperature, urine dip stick, alcohol breath test).

13.4.1 Clinical laboratory parameters

Standard methods for determination of clinical laboratory parameters (blood and urine) will be used. Documentation of the methods employed and reference ranges for all laboratory tests conducted will be part of the clinical file and the study report. Furthermore, the quality certificates being valid during the time of the clinical trial will be files centrally. Location of the laboratory as well as accreditation certificate will be available in the study documentation.

Laboratory printouts will be signed and dated by the investigators after being assessed. The investigator will assess all laboratory values out of reference ranges if they are clinically relevant in correlation to the aim of the clinical trial and the trial performance.

The following commercially available test(s) will be used at the Clinical Pharmacology Unit:

Alcohol breath test	CCI [redacted] Germany
Cotinine test	CCI [redacted] Cologne (urine dip stick)
Pregnancy test	CCI [redacted] Switzerland (urine dip stick)
Test for drug abuse	CCI [redacted] CCI [redacted] Germany (urine dip stick): amphetamines, cocaine, marijuana, morphine, ecstasy (MDMA)
SARS-CoV-2 rapid antigen test	SARS-CoV-2 Rapid Antigen Test, CCI [redacted] CCI [redacted] Germany

13.5 Risks related to the participation in the clinical trial

13.5.1 Procedure related risks

	number and volume of samples	Total volume
Screening examination	-	16 ml
PK samples	75 x 4.9 ml	367.5 ml
End of study examination	-	13 ml
		396.5 ml

Blood withdrawal might be painful or the subjects might temporarily become dizzy. Subjects may also experience intermittent complaints like re-bleeding or puncture site bruises, blood clot (thrombus) in the punctured vessel (rarely), puncture site infections (rarely) or mechanical nerve damage (very rarely). After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to vein puncturing for further blood sampling.

The total volume of blood withdrawn during the entire clinical trial will be approximately 400 ml within approximately 3 - 7 weeks and is lower than the volume of a normal blood donation. However, in single cases it might be necessary to repeat single blood withdrawals, e.g. an additional sample has to be taken due to re-measurements of clinical laboratory samples, starting PK-blood withdrawal has to be stopped due to bad vein conditions and a new sample must be taken from another vein, etc. Thus, the total blood volume may deviate in single cases by a small amount. No safety related risk is expected from this blood withdrawal.

13.5.2 Risks related to the investigational medicinal products

The investigational product contains paracetamol as the active ingredient.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). IB updates or any new information of the investigational drug will be communicated to the investigators, ethics committee and competent authority (see chapter 5.2). Any new information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

According to the SmPCs of the Reference products Alvedon and Panadol, side effects caused by paracetamol are generally rare. The most common side effects are skin reactions and elevated liver transaminase. Liver damage when using paracetamol has occurred in connection with alcohol abuse. Very rare cases of serious skin reactions have been reported. The concomitant use with other products containing paracetamol may lead to an overdose. Administration of N-acetylcysteine or methionine may be required. For more information refer to IB.

13.5.3 Precautionary measures

Study specific safety measurements are planned and described in the chapters 13.3.3, 13.3.4 and 13.3.5.

In case of emergency, standard emergency procedures will be employed. The Principal Investigator is to be consulted and informed immediately.

The Principal Investigator will provide all the necessary emergency equipment and specially trained staff to handle emergency events during this clinical trial.

Contact to an intensive care unit located in easy access area from the hospitalization location is granted during the trial.

All cases of emergency have to be immediately reported as required by SocraTec R&D-SOPs comprising legal stipulations.

13.5.4 Risk/benefit evaluation

As given in chapter 7 Paracetamol is a well-established analgesic and antipyretic product firstly introduced on the international market in the USA in the 1950´s and by Haleon in Spain in 1955 [9]. Its effects and side effects are comprehensively characterised.

In the current clinical trial, a new paracetamol-containing, orodispersible tablet (ODT) dosage form has been developed CCI
CCI

Inclusion and exclusion criteria have been carefully selected considering the risks and precautions known for the IMPs and summarised in the IB / SmPC, in order to minimize the risks for the participating subjects.

During in-house confinement, the subjects will be monitored for any deterioration in general well-being and they will be asked to report any PTAE/AEs spontaneously, whether or not they occur during confinement.

As sufficient information about the IMPs is already available, no special safety investigations will be carried out during the clinical trial. Vital signs will be measured during the trial in study day 1 of each period in order to guarantee a good state of health of the subjects.

In summary, the following measures will be taken to mitigate potential risks and to ensure adequate safety of the subjects participating in this clinical trial:

- Study specific inclusion and exclusion criteria as well as further safety criteria for withdrawal of included subjects
- Checks for general well-being at several time point during in-house confinement

After consideration of the benefits and risks, the performance of the clinical trial is considered ethically justifiable, as the expected future therapeutic benefits of the IMP appear to be greater than the risks to the subjects.

13.6 Handling and documentation of clinical data

The Principal Investigator has to ensure that all data required according to this protocol will be entered in source data sheets promptly. Source data as well as reported data should be attributable, legible, contemporaneous, original, accurate, and complete.

In general, all subject-related clinical parameters to be collected during the clinical trial are identified in the “list of clinical parameters” (see Appendix I). In this list it is also indicated which data are to be entered in the eCRF (as data or just as assessment of inclusion/exclusion criteria) and which not. Those not documented in the eCRF will be documented in the source documents only. Furthermore, the source document and the location of primary documentation (subject record (SR), separate source data sheet (SDS) or eCRF) for each parameter will be specified.

During the clinical trial each data transfer will be checked by an independent person of the study team. Fields for which no data are available (missing or unknown) will be crossed out. For the purpose of quality control, a member of the study team will check data in the eCRFs for formal correctness and completeness.

Entries in source documents must be made with a ball-point pen and must be legible. Pencils and correction fluids are not to be used.

If corrections are necessary (source data), they will be entered by a member of the study team in the following manner: the wrong entry will be crossed out; however, it must remain legible, and the correct entry will be placed in the correction field (if applicable) or next to the wrong entry. Changes and corrections will be initialled and dated. For changes and corrections of source data a reason must be provided, except in case of self-explanatory correction.

As eCRF will be used in this clinical trial, all data required according to the protocol will be recorded in source documents at first and then entered in the eCRF by authorized personnel.

14. Clinical data management

All data management procedures and evaluation of clinical data will be carried out by SocraMetrics GmbH. Methods will be described in the affiliated Data Management Plan (DMP), Data Validation Plan (DVP), and Statistical Analysis Plan (SAP).

Data from the eCRF will be exported as .csv file from the eCRF and imported into the trial database.

Adequate quality control methods will be applied as specified in the internal SOPs and in the study specific DMP. Edit checks on completeness, correctness, plausibility (such as cross checks) will be performed as defined in the study specific DVP.

The data manager will query identified discrepancies, which do not allow application of self-evident-correction procedures, by using (auto-)queries and forward them to the investigator. The completed (auto-)queries will become part of the patient eCRF pdf and, therefore, the original (auto-)queries will be filed with the original eCRF.

The data manager and the monitor will clarify identified discrepancies within the eCRF system which do not allow application of self-evident-correction procedures, by using Queries.

Data of clinical laboratory will be implemented in the database by electronic data capture by import from plain text charts with comma separated values (.csv file format).

Furthermore, listedness of AEs classified by the pharmacovigilance department of Haleon will be entered into the database.

Any observed protocol deviation will be reviewed and during Data Review Meeting decisions will be made whether deviations are classified as “minor” or “major”, i.e. leading to exclusion from analysis set. Furthermore, assignment of subjects to the analysis set will be performed.

Database will be hard locked after for each eCRF the source data verification was performed, the last query/DCF was resolved, Data Review Meeting took place and the overall approval by investigator/sponsor took place.

In case that the database has to be re-opened, this will be done only after agreement with the sponsor. All changes after database hard lock will be tracked.

All clinical data included in the database will be listed.

Access to the final trial datasets is only given by SocraMetrics GmbH.

14.1.1 Data coding

For data coding (e.g. PTAE, AEs, medical / surgical history, medication) internationally recognised and accepted dictionaries will be used (Medical Dictionary for Regulatory Activities (MedDRA) for PTAE, AEs, medical / surgical history. Medication will be coded according to ATC classification system and WHO Drug dictionary). Coding will be performed according to the SOPs of SocraMetrics. In general, the latest version of medical dictionaries valid at the beginning of the coding will be used for coding throughout the clinical trial.

15. Statistical evaluation

Evaluation will be carried out by SocraMetrics GmbH after database lock and will be described in a Statistical Analysis Plan (SAP).

Additional details of the proposed statistical analysis will be documented in the aforementioned SAP, which will be written following finalization of the protocol and prior to study analysis and finalized/ratified prior to database lock.

15.1 Interim analysis

No interim analysis is planned.

15.2 Analysis sets

Screened Population: The Screened Population is defined as all subjects who were screened. Listings which include screen failure subjects or eligible subjects who were not randomised will be used for the Screened Population.

Randomised Population: The Randomised Population is defined as eligible subjects who are randomised to participate in the study.

Safety population (SP): The Safety Population is defined as all randomised subjects who receive at least one dose of study medication.

PK Population (PKP): The PK Population is defined as all randomised subjects who have at least one measurable PK parameter. This population will be used for PK listings.

PK Analysis Set (PKAS): The PKAS is defined as all subjects in the PK population who complete at least two periods with one test formulation and who have no major protocol deviations concerning pharmacokinetics. This analysis set will be used in PK summaries and the primary and secondary analysis.

A subject may remain in a specific analysis set but may be excluded from a specific evaluation/treatment comparison.

Furthermore, prior to bioanalysis subjects may be excluded from statistical analysis based on criteria as defined in chapter 12.3.3 in the trial protocol.

Comprehensive justification for the classification of a protocol deviation as “major” will be given in the integrated clinical study report.

15.3 Evaluation of trial parameter

15.3.1 Evaluation of demographic and anthropometric data

For definition of parameters please refer to chapters 13.3.1.

Statistical evaluation will be performed for the SP and PKP (for definition see chapter 15.2), with exception of childbearing potential, for which statistical evaluation will be performed only for the randomised population.

Continuous data will be evaluated descriptively (number of subjects (N), arithmetic mean, SD, median, minimum, maximum) and will be provided overall and by sequence.

A frequency analysis will be conducted for sex and childbearing potential, as well as for the results of prior and concomitant medication.

15.3.2 Evaluation of vital signs

For definition of parameters please refer to chapters 13.3.3.

Statistical evaluation will be performed for the randomised population (for definition see chapter 15.2).

Evaluation will be conducted for vital signs and body temperature.

Descriptive statistics (number of subjects (N), arithmetic mean, SD, minimum, median, maximum) will be created.

Vital signs and body temperature will be analysed with regard to time point of assessment and treatment.

15.3.3 Evaluation of clinical laboratory parameters

Statistical evaluation will be performed for the randomised population (for definition see chapter 15.2).

Descriptive statistics (number of subjects (N), arithmetic mean, SD, minimum, median, maximum) will be calculated for clinical laboratory parameters determined, where possible.

Frequencies of values inside and out of normal range (with further classification of above or below normal range) will be provided, where possible.

15.3.4 Evaluation of PTAEs and AEs

For definition of parameters see chapter 13.3.6.

Statistical evaluation will be performed for the randomised population (for definition see chapter 15.2).

The data management will perform assignment of AEs to period and treatment.

PTAE and AEs will be evaluated considering action taken, frequency, seriousness, and intensity. Furthermore, AEs will be evaluated considering relationship to the IMP, outcome as well as treatment and period. Both will be described by absolute and relative frequency.

15.3.5 Evaluation of primary efficacy data

Not applicable.

15.3.6 Evaluation of secondary efficacy data

Not applicable.

15.3.7 Evaluation of pharmacokinetic data (plasma)

For definition of parameters please refer to chapter 13.3.9.

All kinetic parameters will be determined model-independently for each treatment using Phoenix WinNonlin, software program. Pharmacokinetic characteristics will be determined directly from the measured concentrations.

15.3.7.1 Pharmacokinetic data handling and documentation

Data entry will be performed by import of analytical data and relative real blood sampling time points from Excel charts (.xls file format) and. Quality-controlled real blood sampling times documented in the eCRFs will be used for evaluation. Therefore, pharmacokinetic parameters will be calculated using real sampling times. Import of data from Excel-file will be checked with regard to the data given in a then requested signed PDF-file provided by the analytical laboratory.

15.3.7.1.1 Handling of bioanalytical data for pharmacokinetic evaluation

Prior to the non-compartmental evaluation of bioanalytical data, given data sets will be checked for remarks of the bioanalytical laboratory (e.g. n.d., BLOQ) by the responsible pharmacokineticist.

Missing data, pre-dose concentrations and any other relevant deviations regarding pharmacokinetic evaluations will be discussed in the DRM.

Missing data will generally not be transformed and remain untouched. Calculations and statistics will be given including the underlying number of individual values (N), i.e. missing values will not be included.

During evaluation of plasma concentration data, the software will automatically interpolate between the concentration value before, and the value after a "missing" value, if possible. Missing data will not be considered for calculation of mean concentrations. In case of missing time data, the observation time point will not be considered in all evaluations that would require the time data.

In cases of missing value for a pharmacokinetic metric, this value will be reported as missing. For pairwise comparisons also the value being compared to will be considered missing, i.e., it will be excluded from the comparison.

Values below the limit of quantitation (e.g. labelled as “BLOQ”, “<LLOQ”; hereinafter referred to as BLOQ value) will be handled as follows:

- For evaluation and general graphical presentation of analytical data:
  - BLOQ marks will be transformed to “zero”.

Values below the LLOQ are to be omitted from the calculation of K_{el} and $t_{½}$.

15.3.7.2 Statistical evaluation of pharmacokinetic data

The statistical analysis will be performed as a valid case analysis including all subjects of the PKAS (or PKP for listings) (for definitions of study populations see chapter 15.2). No subgroup analysis is planned.

Determination will be repeated considering scheduled times for information. Descriptive statistics and treatment comparisons will be provided; however, the primary analysis will be based on actual times allowing for more appropriate calculation.

Data from subjects could be excluded from statistical analysis based on clinical reasons according to chapter 12.3.1. Moreover, analytical reasons (relevant analytical failure) may be considered for exclusion from statistical analysis.

If no or only very low concentrations are observed after administration of one of the Reference products or after the administration of Test, the following procedure is used: if the $AUC_{0\text{-}tlast}$ is less than 5% of the geometric mean of all other values observed for Reference or Test product, the affected period should be excluded from all BE assessments. Thus, the subject would be excluded from BE assessment in an affected Test vs. Reference comparison.

If verified pre-dose concentrations occur, the following procedure is used: If the pre-dose concentration is less than or equal to 5 % of the C_{max} value in that subject, the subject’s data without any adjustments can be included in all pharmacokinetic measurements and calculations. If the pre-dose value is greater than 5% of $C_{max,}$ the affected period should be excluded from all BE assessments. Thus, the subject would be excluded from BE assessment in an affected Test vs. Reference comparison.

Concentration data and pharmacokinetic parameters from dropped out or excluded subjects will be presented in the individual listings, if available, but will not be included in the summary statistics. Bioequivalence assessment will be based on the results calculated without the data of the excluded subjects, i.e., the PKAS.

15.3.7.2.1 Presentations and descriptive statistics

Individual plasma concentrations will be listed per analyte, period, and per scheduled time in the analytical report; individual concentrations and their descriptive evaluation (number of subjects (N), arithmetic means, SD, geometric means, geometric CV, medians, minimum, and maximum) will be listed per analyte, treatment and per scheduled time in the integrated clinical study report. Individual blood sampling times (relative to time of administration of IMP) will be listed by period.

Individual, overlays of individual and mean concentration vs. time curves will be provided, both linearly and log-linearly considering treatment and analyte as appropriate.

Individual concentration vs. time profiles will be based on real sampling times; mean curves will be based on scheduled times.

Mean concentrations will be listed in tabular form including descriptive statistics (at least N, (if applicable N_{obs}, N_{miss}), arithmetic mean, SD, minimum, median, maximum) based on scheduled times for the PKAS.

Individual values of PK parameters will be tabulated for the PKP and PKAS. For the PKAS, descriptive statistics (number of subjects (N), arithmetic means, SD, CV%, geometric means, geometric CV, medians, minimum, maximum, Q1, and Q3) will be presented for all pharmacokinetic parameters, separately for each treatment.

15.3.7.2.2 Confirmatory statistics and additional evaluations

Treatment comparisons will be performed as a valid case analysis including all subjects of the PKAS in the pairwise comparisons as appropriate (for definitions of study populations see chapter 15.2).

In this study, two different reference products will be compared with the test product. Hence, two separate comparisons will be run, and no multiplicity adjustment will be performed.

The statistical analysis will be carried out on the basis of a multiplicative model for values of $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$ and C_{max}-values.

An Analysis of Variance (ANOVA) model will be fitted to the ln-transformed PK variables (AUC and C_{max}), as the dependent variable, and treatment, period, sequence and subject nested within sequence as fixed effects in order to provide the parametric analysis in accordance with current guideline [1].

For each pairwise comparison, only the data from the 2 corresponding treatments will be included in the model.

Least-squares estimate of treatment effects will be calculated and a 90% CI for the treatment difference will be computed. The treatment difference and its CI will be exponentiated to obtain the ratio of the geometric least square means between the test and reference and its CI.

Analyses of variances will be performed as pairwise comparison of $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max}-values after ln-transformation for:

- Test vs. Reference 1
- Test vs. Reference 2

Intra-subject variability will be estimated, and period, subject and sequence effects will be determined.

Affiliated statistical analyses will be performed with an error probability of 0.05 (type-I error probability).

A Wilcoxon Signed Rank test will be used to analyze $t_{max.}$ nonparametrically. Median of differences between treatments will be presented with 90% CI for the median difference based on a method by Hodges and Lehman based on PKAS for:

- Test vs. Reference 1
- Test vs. Reference 2

A possible deviation from normal Gaussian distribution of investigated parameters is addressed considered by performing logarithmic transformation prior to entering analyses, i.e. transformation to the natural logarithm (ln) is performed for approximation. Concentration dependent pharmacokinetic parameters (e.g. $AUC_{0\text{-tlast}}$, C_{max}) will be ln-transformed while purely time dependent parameters (e.g. t_{max}) will remain untouched and, insofar as they are evaluated, enter analyses without transformation. Obtained results, e.g. point estimates and 90 % confidence intervals for the difference of ln-transformed values, will then be retransformed into the linear scale.

CV_{ANOVA} (%) will be calculated for every parameter evaluated from the residual variance indicated in the corresponding ANOVA output. In general, CV_{ANOVA} (%) is derived as $CV_{ANOVA}=100\bullet(e^{MSE}-1)^{0.5}$, where MSE is the (residual) mean square error from ANOVA.

15.3.7.2.2.1 Test for equivalence

$AUC_{0\text{-tlast}}$, C_{max} and t_{max} -values are chosen as primary target variables.

The BE between a new CCI 500 mg ODT (Test) and the marketed Panadol/Alvedon 500 mg film-coated Tablet (Reference) in fasted state will be declared:

- If the 90% confidence intervals (CIs) for the ratio (%) of the geometric means of the primary PK parameters, $AUC_{0\text{-t}}$ and C_{max} of the paracetamol profiles are completely within the 80.00% to 125.00% range.
- If there is no statistically significant difference between the 2 treatments in terms of t_{max}.

For AUC and C_{max} the assessment of equivalence will, thus, be based upon a two-sided 90 % confidence interval for the ratio of the (adjusted) geometric means for the primary endpoints using a pre-set acceptance range. This method is equivalent to the two one-sided t-tests procedure (TOST), each at the 5 % significance level. That is, if the classical (100-2•α) % confidence interval for difference or ratio is within the equivalence limits (including), then both the H_0 given below for the 2 tests are also rejected at the α level by the two one-sided t-tests procedure.

In general, the following hypotheses are covered for ln-transformed data:

H_0: (T - R) ≤ -δ or (T - R) ≥ δ versus

H_1: - δ < (T - R) < δ (acceptance of bioequivalence),

where T and R are the means of logarithmically (natural) transformed PK parameter for the test and reference, respectively and δ is the PK equivalence limit that defines the acceptance range on the logarithmic scale.

Bioequivalence assessment should be based on the results calculated without the data of the excluded subjects (see chapter 15.3.7.2).

15.4 Determination of sample size

It is the intention of this clinical trial to separately demonstrate bioequivalence of Test in comparison to Reference 1 and to demonstrate bioequivalence of Test in comparison to Reference 2. $AUC_{0\text{-tlast}}$, C_{max} and t_{max} will be considered as primary decision criteria for

bioequivalence assessment. For parametric 90 % confidence intervals, acceptance limits of 80.00 % - 125.00 % for $AUC_{0\text{-tlast}}$ and C_{max} will be applied (see also chapter 10).

The highest intra-subject CV% (ISCV) was selected for the calculation of the sample size from the published literature as follows:

- The PK profile of 500 mg Paracetamol Smelt orodispersible tablets from the public assessment report of the Medicines Evaluation Board in the Netherlands under fasting conditions (20.54% for $C_{max,}$ 6.16% for $AUC_{0\text{-t,}}$ and 7.16% for $AUC_{0\text{-inf}}$) [10];
- The PK profile of Paracetamol Nordic 500 mg granules from the public assessment report of the Medicines Evaluation Board in the Netherlands under fasting conditions (21.7% for C_{max} and 9% for $AUC_{0\text{-t,}}$) [11];
- The PK profile of Panadol S 500 mg film-coated tablets from the public assessment report of the Medicines Evaluation Board in the Netherlands under fasting conditions (35.09% for C_{max} , 9.17% for $AUC_{0\text{-t,}}$ and 9.17% for $AUC_{0\text{-inf}}$) [12].

Based on the available literature data and considering relevant orodispersible tablets/granules dosage forms (without water administration), the paracetamol 500 mg immediate release dosage forms are low to moderate variable products and average bioequivalence approach was used to calculate sample size by Power TOST (Version 1.5.3 built 2021-01-18 with R 4.0.3).

The sample size of 42 subjects will provide at least 80% power at 5% significant level to establish bioequivalence of the test and the reference products. The true ratio that was used in the sample size calculation was 1.11 and the % ISCV was 21.7%.

To ensure that at least 42 evaluable subjects complete the study, considering a drop out or unevaluable rate of 20%, approximately 54 randomised subjects will be needed. Therefore, the study will enrol and randomize approximately 54 healthy male and female adult subjects.

For regularities concerning replacement see chapter 12.3.2.

16. Quality assurance

The quality management approach implemented in the trial embraces the following measures:

Quality assurance includes all activities undertaken during and after a clinical trial to verify and control quality. It embraces internal quality control by the staff itself and by independent second persons and external controls and reviews as well as monitoring and separate auditing activities and regulatory inspections. All activities will be performed according to written procedures of the sponsor and/or the CRO and the facilities involved.

At SocraTec R&D GmbH all processes of planning, performance and evaluation are embedded in a comprehensive quality assurance system to manage the quality of the clinical trial and to provide assurance that the data and results reported are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected. It consists of

- structural QA measures: provision of resources, organisational structures, qualification of personnel and premises and equipment of formal controlled procedural documents, such as general standard operating procedures (SOPs) and templates, defining the procedures and the generation of study-specific documents in the context of the planning, preparation, performance and documentation and reporting of the clinical trial, ensuring efficient clinical trial protocols and tools and procedures for data collection and processing; and
- analytical QA measures: quality control, monitoring, auditing.

Applied risk management embraces

- risk assessment and risk-based quality control of processes, described in SOPs,

- risk-based error management to identify, analyse, assess, correct/prevent/improve, document and communicate non-compliance/deviations, including standardised error management as well as for possible data security breaches
- study-specific risk assessment via Risk Assessment Form (RAF) with risk identification, assessment and control (including definition of quality tolerance limits, if any), as well as risk communication and risk review
- risk-based planning of clinical staff and
- risk-based monitoring (see 16.6).

In the QMS Error-Tolerance-Limits (ETLs) for acceptable deviations for data/measurements from the specified target are established and described systematically in the SOPs and in the present clinical trial protocol. Any deviations from established ETLs will be discussed during the data review meeting, assessed with regard to minor or major deviations and will be presented in final report.

Quality Tolerance Limits (QTLs) are those acceptable deviations for data/measurements from the specified targets, which will be established and described in the RAF additionally to the ETLs, if any.

In the clinical study report important deviations from the predefined quality tolerance limits and remedial actions taken, if any, will be summarised.

Quality assurance of specific parts of the clinical trial, especially when carried out by subcontracted organisations, is described in the corresponding chapters of this clinical trial protocol and in the SOPs of the subcontracted organisation.

In the case of monitor visits or study audits initiated by the sponsor or by regulatory authorities, the Principal Investigator and SocraTec R&D GmbH grant the monitor/auditor access to all documents and source data related to the trial. The monitor/auditor is obliged to also observe adequate confidentiality so that the pseudonymity of the participating subjects will not be impaired.

16.1 Reporting of serious breaches

The Investigator is asked to inform the sponsor about all suspected serious breaches occurred throughout the whole study period up to study closure as soon as the Investigator becomes aware of them.

Any suspected serious breach will be notified by the Investigator (or delegates) to the sponsor by means of e-mail in Portable Document Format (pdf) using the “Suspected serious breach notification” form (Haleon form) provided by the Sponsor.

The form should be addressed to the following email addresses:

PPD

Haleon personnel should confirm the receipt of the notification to the Investigator by email. If no acknowledgement of receipt is received at site within the day after sending (only business days), the Investigator will be instructed to verify the notification receipt by means of a phone call to the Study Manager (details of the contacts are reported in chapter 6).

The information to be provided is:

- Date of (suspected) serious breach
- Brief description of the (suspected) serious breach
- Reason for (suspected) serious breach occurrence

- Other relevant details / information (i.e. immediate actions performed)

Follow up reports of the suspected serious breach should be sent to the Sponsor when additional information is available, using the “Suspected serious breach notification” form, by means of e-mail in pdf format. The form should be addressed as detailed above.

16.2 Reporting of any product compliant

In case quality defects related to the investigational medicinal product are detected at the site, the Principal Investigator or delegate shall promptly send a written communication to the sponsor contact person or to the monitor/CRA who will immediately notify the sponsor.

16.3 Quality control of clinical data

All processes as well as quality control steps will be performed according to the SOPs of SocraMetrics GmbH. Quality control measures include checks of data, checks of calculations as well as formal checks of tables, listings and figures. Steps of quality control will be documented.

16.4 Quality control of statistical procedures

All processes as well as quality control will be performed according to the SOPs of SocraMetrics GmbH. Quality control measures include checks of data, checks of calculations as well as formal checks of tables, listings and figures. All steps of quality control will be documented by signature of the reviewer and date of review. Within the review of the results general applicability of the planned statistical procedure on the trial data set will be checked. If findings of the review suggest changes to the procedures given by the clinical trial protocol, those changes will be appropriately addressed.

16.5 Audits

Auditing will be performed by the independent QAU of SocraTec R&D GmbH in accordance with the requirements of the Guideline for good clinical practice (EMA/CHMP/ICH/135/1995) in a systematic manner comprising overall as well as study specific audit activities in order to check the quality assurance systems with the goal of quality improvement by investigation of error causes and systematic error correction. Auditing by the independent QAU of SocraTec R&D GmbH covers in general all trial-related activities at SocraTec R&D GmbH and SocraMetrics GmbH. Trial activities to be audited will be selected according to the general company audit plan of SocraTec R&D GmbH and SocraMetrics GmbH.

The following audit activities in this specific clinical trial has been pre-planned to be audited:

Audit activities will be documented by the QAU and archived. If processes or documentation for this specific clinical trial will be audited, audit certificates, listing all study specific audit activities will be part of the study report.

16.6 Monitoring

Monitoring of the clinical trial will be performed by the monitoring unit of SocraTec R&D GmbH in accordance with the requirements of the Guideline for good clinical practice (EMA/CHMP/ICH/135/1995) and on the basis of the monitoring plan.

16.7 Regulatory inspections

Review of IEC/IRB or regulatory inspections (with direct access to source data) are permissible.

17. Reporting

An integrated clinical study report according to ICH standard and SocraTec R&D GmbH SOP will be presented to the sponsor.

18. Record keeping

All documents derived from the clinical trial are to be filed in the ISF except subject's records, which will be filed separately in the Clinical Pharmacology Unit. After completion of the clinical trial, the ISF is to be forwarded to the SocraTec R&D archive. The sponsor of the trial will continuously receive all essential documents of the trial for maintaining his TMF.

Any documents related to the clinical trial (except subject's records) must be retained for at least 25 years after finalisation of the integrated clinical study report or at least 2 years after the last approval in an ICH region or at least 2 years after the formal discontinuation of the clinical development, whichever is longer. Subject's records must be retained in accordance with national law. The sponsor will inform the investigator about developments, which affect the storage period.

18.1 Statement of confidentialities and subject's privacy

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Subject's privacy will be ensured by using subject identification code numbers. Data protection and data security measures are implemented for the collection, storage and processing of subject's data in accordance with the EU-GDPR (General Data Protection Regulation) 2016/679 and German Drug Law.

Treatment data may be given to the subject`s personal physician or to other appropriate medical personnel responsible for the subject`s welfare. Data generated as a result of the trial need to be available for inspection on request by the sponsor`s representatives, by the IRB/IEC and the regulatory authorities.

19. Publication policy

Results of the trial will be made publicly available in the extent of regulatory and ethical requirements, including the pertinent European clinical trial database and other relevant clinical registries. Further publication of the results is generally favoured irrespective of the outcome and require explicit agreement of the sponsor, the Principal Investigator and SocraTec R&D GmbH. Sources of funding, institutional affiliations, and any possible conflict of interests shall be declared.

20. Signature page

20.1 Signature page CRO

PPD

Date, Signature

Ulrike Burkhardt
Principal Investigator
SocraTec R&D GmbH

PPD

Date, Signature

PPD
CRO's project manager, author of the protocol
SocraTec R&D GmbH

PPD

Dr. PPD
PPD
SocraTec R&D GmbH

20.2 Signature page Sponsor

PPD

Date, Signature

PPD

Haleon

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Appendix I: List of clinical parameters

TT 2: List of clinical parameters

Parameter	Source document	Data entered in
site number	eCRF	yes
screening number	SDS	yes
Screening examination		
Study dates		
date of signed Informed Consent (= date of enrolment)	ICF	yes
time point of signature	ICF	no
visit performed (yes/no)	eCRF	n.a.
start date of screening examination	SR	yes
Demographic and anthropometric data		
age	SR	yes
sex	SR	yes
height	SR	yes
weight	SR	yes
BMI	SR	yes
Female status		
female status: childbearing potential (yes/no, for women only)	SR	yes
female status: reason for non-childbearing potential (for women without childbearing potential only)	SR	no
female status: information about effective contraceptive method	SR	no
result of pregnancy test	SR	yes, via assessment of inclusion/exclusion criterion
Medical history, underlying diseases and physical examination	SR	
Medical history number	SDS	yes
findings from medical history (finding, date of onset/end with month/year)	SR	no
findings from medical history being of relevance in the context of the clinical trial according to the assessment of the investigator (but do not necessarily lead to exclusion of the subject), date of onset/end with month/year	SR	yes
findings from underlying diseases (finding, date of onset/end with month/year or ongoing)	SR	no
findings from underlying diseases being of relevance in the context of the clinical trial according to the assessment of the investigator (but do not necessarily lead to exclusion of the subject), date of onset/end with month/year or ongoing	SR	yes
findings from surgery (finding, date with month/year)	SR	no

eCRF – Case Report Form SR – Subject Record SDS – Source Data Sheet

Parameter	Source document	Data entered in
findings from surgery being of relevance in the context of the clinical trial according to the assessment of the investigator (but do not necessarily lead to exclusion of the subject), with month/year	SR	yes
findings from physical examination, except scars	SR	yes
results of vital signs measurement: systolic/diastolic blood pressure, pulse rate incl. re-measurements	SR	no
results of vital signs measurement (valid cases): systolic/diastolic blood pressure, pulse rate	SR	yes
result and time points of body temperature (ear) measurement incl. re-measurements	SR	no
results and time points of re-measurements: body temperature (oral)	SR	no
ECG printout (with date and time of measurement) and heart rate	SR	no
ECG: heart rate	SR	yes
ECG: all findings	SR	no
ECG: check with regard to study relevant findings in the ECG, which lead to non-inclusion into the clinical trial and specification of the findings	SR	yes, via assessment of inclusion/exclusion criterion
Clinical laboratory (blood and urine)	SR	
labcode No.	SR	yes
date and time of sampling (also in case of re-measurement)	SR	yes
date of shipment of blood samples	SDS	no
check for re-measurement, re-measured laboratory parameter, new labcode No.	SR	yes
results of clinical laboratory (with date and time of result) including assessment of clinical relevance in case of outside normal range and reason for re-measurement (due to follow-up or because of implausible initial result, due to missing initial result)	print-out lab assessment	no
reason for re-measurement (due to follow-up or because of implausible initial result)	SR	yes
Clinical laboratory tests	SR	
result of alcohol breath test	SR	yes, via assessment of inclusion/exclusion criterion
result of urine drug screen	SR	yes, via assessment of inclusion/exclusion criterion
result of cotinine test	SR	yes, via assessment of inclusion/exclusion criterion
Other information		

eCRF – Case Report Form SR – Subject Record SDS – Source Data Sheet

Parameter	Source document	Data entered in
female status: subject will be informed about adequate contraception methods and will agree to apply one of the methods during the clinical trial	SR	yes, via assessment of inclusion/exclusion criterion
alcohol consumption	SR	yes, via assessment of inclusion/exclusion criterion
caffeine consumption	SR	yes, via assessment of inclusion/exclusion criterion
special diet	SR	yes, via assessment of inclusion/exclusion criterion
information on blood donation/blood loss	SR	yes, via assessment of inclusion/exclusion criterion
information on participation on a clinical trial	SR	yes, via assessment of inclusion/exclusion criterion
findings from physical examination (except scars)	SR	yes, via assessment of inclusion/exclusion criterion
drug and alcohol dependency	SR	yes, via assessment of inclusion/exclusion criterion
pregnant and/or lactating women	SR	yes, via assessment of inclusion/exclusion criterion
ability to judge and to agree	SR	yes, via assessment of inclusion/exclusion criterion
assessment that subject has understand written and verbal instruction and will follow these during the clinical trial	SR	yes, via assessment of inclusion/exclusion criterion
Checks to be performed during screening examination		
check of restrictions, medication/therapy and of AEs/PTAE	SDS	no
check for urine drug screen, alcohol test, cotinine test and nicotine test	SR	no
Termination of screening examination		
statement of objections against subject's participation	SR	yes
Inclusion		
assessment of eligibility by check of inclusion and exclusion criteria	SR	yes
date of inclusion	SR	yes
reason for non-inclusion	SR	no
Within-study		
in-house period: date and time	SDS	no
visit performed (yes/no) eCRF n.a. eCRF n.a.	eCRF	n.a.
date of visit (-1, 1, 2)	SDS	yes
check of identity	SDS	no

eCRF – Case Report Form SR – Subject Record SDS – Source Data Sheet

SocraTec R&D

Parameter	Source document	Data entered in
check of luggage	SDS	no
handover of clinical trial identification card and explanation	SDS	no
Tests		
result of alcohol breath test	SDS	yes
performance of alcohol test in case of suspicion with date and result	SDS	yes
result of urine drug screen	SDS	yes
performance of urine drug screen in case of suspicion with date and result	SDS	yes
result of cotinine test	SDS	yes
performance of cotinine test in case of suspicion with date and result	SDS	yes
Clinical laboratory Test		
result of serum pregnancy test	SDS	yes
Checks to be performed		
brief physical examination	SDS	yes
vital signs	SDS	yes
Safety measurements due to COVID-19		
SARS-CoV-2 rapid antigen test in case of suspicion with date of sampling and result	SDS	no
Randomisation		
recheck of the inclusion and exclusion criteria (on study day -1 and study day 1 only)	SR	yes
date of randomisation (on period I, study day -1 only)	SR	yes
randomisation number (subject number)	SR	yes
decision upon non-randomisation/exclusion	SR	yes
Food and beverages		
date and end time of dinner intake (study day -1)	SDS	no
date and start time food intake 4 h, 8 h, 12 h p.a.	SDS	no
handing over of standardised food	SDS	no
standardised fluid intake: time and amount	SDS	no
deviation regarding meal fluid intake (yes/no)	SR	yes
specification of time point, date and kind of deviation: • fasting period of at least 10h not observed • start time of 1st meal is < 4h (specification of real start time, comment, reason) and it has to be ingested completely • deviation amount of water for more than 50 ml fluid-difference in the restricted time span (comment/reason)	SDS	yes
Administration of IMPs (on study day 1 of each period)		
date and time of each administration	SR	yes
specification of IMP and amount	SR	yes
intake with 200 ml water (for reference 1 and reference 2)	SR	yes

SocraTec R&D

Parameter	Source document	Data entered in
wetting of mouth with 20 ml of water (for test only)	SR	yes
empty oral cavity and hands	SR	yes
upright position during administration	SR	yes
PK sampling		
approximate volume of blood samples	SR	yes
tubes for sample collection	SR	yes
sampling time points (date and time)	SR	yes
reason for deviation > 5 min (except samples before administration)	SR	yes
deviations with regard to immediately sample work-up (no mixing after withdrawal, no placing into ice-water bath, no sufficient ice-water-bath) or information about no deviations	SR	yes
sample work-up	SDS	no
start of centrifugation: date and time	SDS (via EDC)	no
placement from ice-water-bath into centrifuge and check for ice-water-bath, date and time	SDS (via EDC)	no
freezing on ice: date and time	SDS (via EDC)	no
storage in the freezer: date and time	SDS	no
relevant deviation from sample work-up (specification of period, sample No., kind of deviation)	SDS (via print out from EDC)	yes
check for observations regarding haemolysed or lipaemic samples with sample no. and time point	SDS	no
observations regarding haemolysed or lipaemic samples with sample no., time point and kind (haemolysed or lipaemic)	SDS	no
Safety measurements		
vital signs measurements: systolic/diastolic blood pressure, pulse rate (results and time) (all cases)	SDS	no
vital signs measurements: systolic/diastolic blood pressure, pulse rate (results) (all valid cases)	SDS	yes
comment/reason for more than 30 min deviation in schedule time for vital signs with specification of time point and period	SDS	yes
body temperature (oral), measurement incl. re-measurements (results and time)	SDS	no
result of body temperature (oral) measurement (valid cases)	SR	yes
comment/reason for more than 30 min deviation in schedule time for body temperature with specification of time point and period	SDS	yes
ECG printout (with date and time of measurement) and heart rate	SDS	no
ECG: all findings	SDS	no
clinical laboratory (blood/urine): labcode No.	SR	no
date of shipment of blood samples	SDS	no
check for re-measurement, re-measured laboratory parameter, new labcode No.	SR	no

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SocraTec R&D

Parameter	Source document	Data entered in
results of clinical laboratory (with date and time of result) including assessment of clinical relevance in case of outside normal range and reason for re-measurement (due to follow-up or because of implausible initial result, due to missing initial result)	print-out lab assessment	no
reason for re-measurement (due to follow-up or because of implausible initial result)	SDS	no
Checks to be performed during the clinical trial including periods I, II and III		
check of restrictions, medication / therapy and of PTAE/AEs (if applicable)	SDS	no
any protocol deviation (including violation of restrictions), not documented anywhere in the eCRF	SR	yes
time point, date and kind of deviation • intake of forbidden medication • strenuous physical activity • end of study examination performed too early/late • no blood obtained (specification) • other (specification)	SDS	yes
test of alcohol, cotinine, drugs and SARS-CoV-2 in case of suspicion	SDS	no
End of study examination		
start date of end of study examination	SDS	yes
physical examination (changes to screening examination)	SDS	yes
result of physical examination (check of good state of health or specification of relevant findings)	SDS	no
result of urine pregnancy test	SDS	yes
time points for determination of vital signs (incl. re-measurements)	SDS	no
result of vital signs measurement (valid cases): systolic/diastolic blood pressure, pulse rate	SDS	yes
results of vital signs measurement: systolic/diastolic blood pressure, pulse rate incl. re-measurements	SDS	no
result and time points of body temperature (oral) measurement (valid cases) incl. re-measurements	SR	no
Clinical laboratory (blood and urine)		
labcode No.	SDS	yes
date and time of sampling (also in case of re-measurement)	SDS	no
date and time of shipment of blood samples	SDS	no
check for re-measurement, re-measured laboratory parameter, new labcode No.	SR	yes
results of clinical laboratory (with date and time of result) including assessment of clinical relevance in case of outside normal range and reason for re-measurement (due to follow-up or because of implausible initial result, due to missing initial result)	print-out lab assessment	yes (copy)
reason for re-measurement (due to follow-up or because of implausible initial result)	SR	yes

eCRF – Case Report Form SR – Subject Record SDS – Source Data Sheet

Parameter	Source document	Data entered in
Checks to be performed at end of study examination		
check of restrictions, medication/therapy and of AEs/PTAE	SDS	no
Trial completion for randomised subjects		
check of regular completion (yes/no)	SR	yes
in case of withdrawal: date and person responsible for withdrawal (subject/investigator)	SR	yes
reason for withdrawal (SAEs at the Principal Investigator's discretion; serious ADR; diseases, PTAE, or AEs that occur after inclusion, which do not constitute SAEs but which, in the opinion of the Principal Investigator, would probably prevent achievement of the clinical trial objectives or which unacceptably endangered the safety of the subject; withdrawal of consent; positive alcohol, drug, cotinine, or pregnancy test after inclusion; non-adherence to the trial conditions, violation of any restriction or relevant deviations from procedures as established in the clinical trial protocol with regard to medical aspects at the Principal Investigator's discretion and with regard to pharmacokinetic aspects at the Principal Investigator's discretion in agreement with the Scientific Directors; due to vomiting; due to diarrhoea; due to migraine attacks)	SR	yes
last performed visit	SR	yes
date of discharge from clinical trial	SR	yes
statement completeness and correctness eCRF	SR	yes
Prior / Concomitant therapy		
medication starting 2 weeks prior to intended first administration	SDS	yes
kind of medication (prior or concomitant)	SDS	yes
trade name/generic name	SDS (PTAE/AEs)	yes
route of administration	SDS (PTAE/AEs)	yes
dosage form and administered dosage (per administration)	SDS (PTAE/AEs)	yes
start date, ongoing, end date (if applicable)	SDS (PTAE/AEs)	yes
start time and end time (if applicable) in case of concomitant medication	SDS (PTAE/AEs)	yes
indication (e.g. medical history finding, PTAE, AE incl. number)	SDS (PTAE/AEs)	yes
dosage scheme (e.g. QD, BID, TID)	SDS (PTAE/AEs)	yes
use of allowed and already documented concomitant medication only in the morning at each profiling day: trade name, date and time; check by clinical staff	SDS	no
PTAE observed, mentioned upon general questioning or spontaneously reported		

eCRF – Case Report Form SR – Subject Record SDS – Source Data Sheet

Parameter	Source document	Data entered in
No.	SDS	yes
type (symptom, diagnosis)	SDS	yes
start date and time	SDS	yes
end date and time (if ongoing and not “recovering”)	SDS	yes
seriousness	SDS	yes
each intensity	SDS	no
maximum intensity	SDS	yes
action taken	SDS	yes
Change-over to AE	SDS	yes
AEs observed, mentioned upon general questioning or spontaneously reported		
No.	SDS	yes
type (symptom, diagnosis)	SDS	yes
start date and time	SDS	yes
end date and time (if not “ongoing”, “unknown”, etc.)	SDS	yes
seriousness	SDS	yes
each intensity	SDS	yes
action taken to treat AE	SDS	yes
causality (relationship with the IMP)	SDS	yes
outcome including comment in case “not yet resolved”, “unknown”	SDS	yes
referral to the family doctor	SR	no

SocraTec R&D

Appendix II: Blood sampling instructions and analytical measures

1 Pharmacokinetic samples

1.1 Sample collection time

Please adapt blood volume in chapter 13.5.1 and update the relevant chapter. A cross link is used.

During all treatment periods, blood samples of approximately 4.9 ml volume will be taken. The plasma obtained hereof will be divided into two equal aliquots. However, the resulting plasma in the first aliquot should be at least 1 ml plasma. Blood samples will be taken at the following time points:

pre-dose samples	
sample no.	time point
1	within 1.0 h prior to 1st administration on study day 1
post-dose samples	
sample no.	time point
2	5 min
3	10 min
4	15 min
5	20 min
6	25 min
7	30 min
8	35 min
9	40 min
10	50 min
11	60 min
12	75 min
13	90 min
14	120 min
15	150 min
16	180 min
17	4 h
18	5 h
19	6 h
20	8 h
21	10 h
22	12 h
23	14 h
24	16 h
25	24 h

The clinical trial will generate approximately 4050 samples for analytical determination (75 samples per subject). For total blood volume taken for pharmacokinetic characterisation see chapter 13.5.1.

Blood sampling times should meet the planned schedule as accurately as possible.

For blood samples with a deviation of ≤ 5 min from the planned time schedule a reason will be not be recorded. These blood samples will not be listed as protocol deviation as this deviation is per se minor as real blood sampling time points will be used for PK evaluation.

Time deviations will be handled as follows:

- For blood samples with a deviation of more than 5 min from the planned time schedule a reason will be recorded and the deviation will be listed as protocol deviation.

For samples taken before administration of the IMPs, a variation from the scheduled time is without relevance and will not be considered as protocol deviation.

1.1 Labelling of blood and plasma samples

All blood and plasma tubes will be labelled with the study number, a running number for the samples of each subject, a subject number, aliquot number, study period.

1.2 Blood withdrawal material and procedures

Blood samples for concentration measurements of paracetamol will be collected in 4.9 ml tubes (CCI) from a vein using an indwelling cannula with switch valve or by direct venipuncture.

Observations regarding haemolysed or lipaemic samples will be documented.

1.3 Shipment of samples

At the end of the clinical part of the clinical trial one of the two generated batches of the frozen plasma samples will be sent to the analytical laboratory for analysis shipped on dry ice.

After shipment of first aliquots, acknowledgement of receipt has to be awaited before the second aliquots are shipped. Temperature loggers in each box per transport will be used during shipment in order to document that samples are kept at the prescribed temperature during the entire shipment.

2 Bioanalytical methods

Bioanalytical measurements will be carried out by Anapharm Bioanalytics.

Paracetamol in plasma samples will be analysed by use of a validated LC-MS/MS method. LLOQ of the method is intended as CCI ng/mL.

Plasma used for validation and quality control during routine analysis must have been obtained with the same anticoagulant as used for the clinical trial samples.

For the determination of plasma concentration profiles over time, the open-label design is adequate. Blinding is not necessary as primary target parameters cannot be influenced by neither the subject nor the investigator. The staff of the bioanalytical department involved in bioanalytical measurements will be blinded for the treatments, which are administered to the particular subjects and will not have access to the randomisation list.

2.1 Quality control of bioanalytical methods

Method validation will be performed prior to analysis of the clinical trial samples.

Method validation and analysis of study samples including quality control during routine drug analysis and its evaluation, documentation and reporting is to be performed in accordance with the requirements of the “Guideline on bioanalytical method validation” (CHMP, July 2011) and GLP principles. As pre-suppositions for an appropriately performed method validation and analysis of study samples including acceptance criteria are specified in detail in the “Guideline on bioanalytical method validation” (CHMP, July 2011), only specific or additional requirements not mentioned in the guideline are presented in the following.

Furthermore, implementation and specification of requirements of the guideline are to be defined in the analytical study plan or SOPs of the bioanalytical laboratory.

2.2 Method validation

If reference is made to a method validation used for an earlier clinical trial, the following prerequisites are to be observed.

- If the analytical method has been used continuously over the months prior to this clinical trial, no further validation is necessary.
- If the analytical method has not been used continuously but no changes of the analytical procedure have been performed, it will be acceptable to perform a short-term validation covering a one-day re-test of accuracy, precision and calibration curve considering the requirements of the “Guideline on bioanalytical method validation” (CHMP, July 2011).
- If changes of the analytical procedure have been performed, a full method validation has to be performed and the affiliated validation report has to be provided to SocraTec R&D GmbH. Particular parts of the validation can be omitted after permission by the sponsor.

Cases of unavoidable carry-over are to be discussed before study sample analysis with the scientific director of SocraTec R&D.

In this clinical trial co-administration of hormonal contraceptives, hormone replacement therapy and ibuprofen are allowed. Thus, a validation and/or an assessment with regard to potential interferences between comedication and paracetamol has to be performed.

Furthermore, the laboratory will be informed about actually administered concomitant medication (e.g. in order to overrule an AE) in order to perform a validation and/or an assessment with regard to potential interferences.

2.3 Analysis of study samples

Generally, samples will be analysed as single measurements.

All samples of an analytical run (blank sample, zero sample, calibration standards, QC samples and study samples) should be processed as one single batch.

Preferably, all samples of a subject should be analysed within one run (except repeat measurements).

Samples with concentrations above the ULOQ shall be reanalysed after dilution.

If a narrow or extended range of analysis values is observed during sample analysis, either the standard calibration range should be narrowed/extended (and validated), QC concentrations revised, or additional QC concentrations are to be added before continuing with the study sample analysis.

Decision upon manual / automatic re-integration and the acceptance of calculated data after re-integration is in the responsibility of the analytical laboratory. If chromatogram reintegration is performed, the rationale and methods for the reintegration should be previously described in an SOP. Documentation of information of the re-integration (original data, new data, method of integration, reason for re-integration, etc.) should be performed according to "ICH guideline M10 on bioanalytical method validation and study sample analysis" (EMA/CHMP/ICH/172948/2019, 25 July 2022) and to the "Guideline on bioanalytical method validation" (CHMP, July 2011).

The following procedures concerning manual / automatic re-integration shall be observed:

- changes in parameters for integration of complete runs which as a consequence avoid manual re-integration and lead to automatic re-integration should be favoured.
- manual re-integration of QCs and calibration samples during validation and measurement of the study samples must not be performed.
- manual re-integration in case of stability and recovery tests will be acceptable but only in single cases.

Manual re-integration of study samples is to be avoided in this clinical trial as far as possible. However, if the analytical method established requires manual re-integration, this will be accepted if changed as analytically necessary and comprehensible and not more than 5 % of the study samples with reportable values in each run are affected.

In the analytical report the information about the number of manually re-integrated samples per analyte and per run will be given (for samples with reportable values).

2.4 Outliers, reanalysis of study samples

Repeat measurements will be performed just once if necessary due to analytical reasons (e.g. equipment failure, poor chromatography, failed run, concentration above ULOQ), reanalysis result as the only valid value will be reported. Number of samples and percentage of total number of samples will be discussed in the analytical report. For definition of repeat measurements due to analytical reasons references will be made to the SOP of the bioanalytical laboratory.

Reanalysis because of pharmacokinetic reason is not acceptable.

Incurred samples will be provided according to the requirements of “Guideline on bioanalytical method validation” (CHMP, July 2011) and of “ICH guideline M10 on bioanalytical method validation and study sample analysis” (EMA/CHMP/ICH/172948/2019, 25 July 2022) and detailed specification will be given by the analytical laboratory.

Results of incurred sample re-analysis will be reported.

2.5 Bioanalytical data handling and documentation

All measured values will be set out in Excel charts (.xls file format)/ documented and transferred to the responsible department as signed printouts and electronic data files (.xls file format). Raw data from analytical measurements will be documented as electronic files in a way, which allows retrospective identification of individual measured values and identification of automatically and manually integrated values, respectively. When manual re-integration has been performed for determination of analytical values, the original values obtained by automatic integration are to be documented in the files at the analytical laboratory only. The type and programming of integration software used will also be documented in the analytical laboratory.

Documentation of the analytical method in an analytical validation report and of the results of routine drug analysis in the analytical report has to be done in accordance with the requirements of “Guideline on bioanalytical method validation” (CHMP, July 2011) and of “ICH guideline M10 on bioanalytical method validation and study sample analysis” (EMA/CHMP/ICH/172948/2019, 25 July 2022).

A table summarising name and date of all analytical runs shall also identify the study samples (subjects) within the analytical runs.

Copies of 100% chromatograms (all subjects) have to be submitted as appendix to the final analytical report including standards and QC samples from those analytical runs.

2.6 Quality assurance of analytical procedures

Quality assurance of analytical procedures will reflect relevant national and international guidelines with special focus on the current “Guideline on bioanalytical method validation” (CHMP, July 2011), on “ICH guideline M10 on bioanalytical method validation and study sample analysis” (EMA/CHMP/ICH/172948/2019, 25 July 2022) and the GLP-guidelines as well as the GCP principles (as outlined under chapter 10).

SocraTec R&D

Appendix III: Clinical laboratory parameters

1 Screening and end of study examination

At the screening and end of study examination the following clinical laboratory investigation will be performed

- blood analysis including haematology, haemostatic system, clinical chemistry, hormones, serology (only at screening examination), and urinalysis.

For parameters see TT 3.

TT 3: Standard clinical laboratory parameters

	screening examination	**Within study examination**	**end of study examination**
	-28 to -2	study day -1	
Haematology:			
Erythrocytes*	•		•
mean corpuscular haemoglobin (MCH)	•		•
mean corpuscular volume (MCV)	•		•
mean corpuscular haemoglobin concentration (MCHC)	•		•
haemoglobin	•		•
haematocrit	•		•
platelets*	•		•
leukocytes*	•		•
neutrophils	•		•
segmented neutrophile granulocytes[a]	•		•
rod-shaped neutrophile granulocytes[a]	•		•
eosinophils	•		•
basophils	•		•
lymphocytes	•		•
monocytes	•		•
Clinical chemistry:			
alkaline phosphatase (AP)	•		•
glutamic oxalacetic transaminase (GOT/ASAT)	•		•
glutamic pyruvic transaminase (GPT/ALAT)	•		•
gamma glutamyl transferase (GGT)	•		•
lactate dehydrogenase (LDH)	•		•
creatine kinase (CK)	•		•
creatine kinase muscle-brain (CK-MB)[b]	•		•
glucose	•		•
cholesterol	•		•
triglycerides	•		•
total bilirubin	•		•
uric acid	•		•
sodium	•		•
potassium	•		•
chloride	•		•

	screening examination	Within study examination	end of study examination
calcium	•		•
creatinine	•		•
urea	•		•
total protein	•		•
Hormones			
FSH[c]	•		
human chorionic gonadotropin (β-HCG)[c]	•	•	•
TSH	•		•
Haemostatic system:			
prothrombin time (PT, Quick test)	•		•
INR value (International Normalised Ratio)	•		•
activated partial thromboplastin time (APTT)	•		
Serology:			
markers of viral hepatitis (HBs-AG (hepatitis B virus surface antigen), anti-HBc IgM and anti HCV-AB (anti hepatitis C virus antibodies))	•		
HIV infection (anti-HIV-AB 1+2[d] (anti human immunodeficiency virus antibodies) including p24Ag)	•		
Urine:			
pH	•		•
specific gravity	•		•
semi quantitative analysis of leukocytes	•		•
protein	•		•
glucose	•		•
ketone bodies	•		•
bilirubin	•		•
nitrites	•		•
urobilinogen	•		•
blood and sediment[e]	•		•

[a] only in single cases if peculiarities in hemogram occur, statistics will only be given for segmented neutrophile granulocytes and rod-shaped neutrophile granulocytes and not for total neutrophils
[b] may be determined but is only mandatory if CK values are above 3.5 µmol/s/l
[c] for all female subjects with childbearing potential
[d] if positive to be verified by western blot
[e] only in single cases on demand
* if necessary, additional differentiation is possible

For blood volume withdrawn during screening and end of study examination see chapter 13.5.1.

Blood and urine sampling, sample work-up and labelling of tubes will be in accordance with the regulations of the clinical laboratory.

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