Clinical Study Protocol

AN OPEN-LABEL, RANDOMIZED, 4-PERIOD, 4-TREATMENT, CROSSOVER, SINGLE-CENTER, SINGLE-DOSE BIOAVAILABILITY STUDY WITH ALTERNATE METHODS OF ADMINISTRATION OF CRUSHED NALOXEGOL TABLETS, 25 mg AND OF A NALOXEGOL SOLUTION FORMULATION, 25 mg, COMPARED TO WHOLE NALOXEGOL TABLETS, 25 mg, IN HEALTHY SUBJECTS

PAREXEL STUDY NUMBER:	PXL220225
SPONSOR STUDY NUMBER:	D3820C00035
EudraCT No.:	2014-005002-38
NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	Naloxegol
THERAPEUTIC INDICATION:	Opioid induced constipation (OIC)
PHARMACOLOGICAL CLASS:	Peripheral μ-opioid antagonist
DEVELOPMENT PHASE:	Bioavailability Study (Phase I)
SPONSOR:	AstraZeneca AB [redacted]
STUDY CENTER:	PAREXEL Early Phase Clinical Unit Berlin [redacted]
VERSION AND DATE OF PROTOCOL:	Final 1.0 [redacted]

This clinical study will be conducted according to the clinical study protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki (Version 1996) and with other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Title of the study

An open-label, randomized, 4-period, 4-treatment, crossover, single-center, single-dose bioavailability study with alternate methods of administration of crushed naloxegol tablets, 25 mg and of a naloxegol solution formulation, 25 mg, compared to whole naloxegol tablets, 25 mg, in healthy subjects

Principal Investigator (PI)

Dr. med. Rainard Fuhr

Study center

This study will be conducted at a single study center.

PAREXEL Early Phase Clinical Unit Berlin

[redacted]

Study rationale

Alternative ways of administering a tablet may be useful to help patients who, for different reasons, have difficulties with swallowing a whole tablet. Administration of dispersed (crushed) tablets suspended in water is a common way of administering drugs to these patients. A useful method in patients whose condition prevents swallowing is administration of dispersed tablets through nasogastric tubes. Additionally a solution formulation may be an attractive option for some patients including the pediatric population.

The purpose of this study is to evaluate the relative bioavailability of naloxegol after three alternative methods of administering naloxegol compared to commercially available whole naloxegol tablets in healthy subjects. The results of this study will define the alternative ways of administration of naloxegol.

Number of subjects planned

Up to 44 subjects will be randomized to a 4 sequence Williams design for 4 periods and 4 treatments: ADBC, BACD, CBDA and DCAB, in order to ensure at least 36 evaluable subjects at the end of the last treatment period.

Study period

Estimate date of first subject enrolled:	TBD 2015 (signing of informed consent)
Estimate date of last subject completed:	TBD 2015

Study objectives

Primary objective:

- To determine the relative bioavailability of naloxegol when administered as each of three alternative methods of naloxegol administration compared to whole naloxegol tablets given orally, by assessment of the primary pharmacokinetic (PK) parameters of naloxegol

Secondary objective:

- To assess the safety and tolerability of single doses of naloxegol in healthy subjects

Exploratory objectives:

- To evaluate, by questionnaire, the perceived taste of the naloxegol liquid formulations (dispersed tablets orally and oral solution)
- To collect and store deoxyribonucleic acid (DNA) for possible future exploratory investigation of the influence of genotype on naloxegol disposition and safety

Outcomes variables

Pharmacokinetic parameters:

Where possible, the following PK parameters will be assessed for naloxegol:

- Primary PK parameters: AUC, $AUC_{(0-t)}$, C_{max}
- Secondary PK parameters: t_{max}, t_{last}, $t_{½\lambda z}$, MDT (whole tablet only), MRT, λ_z, CL/F, V_z/F

Additional PK parameters may be determined where appropriate.

Safety and tolerability variables:

Safety and tolerability variables will be assessed by collection of data on adverse events (AEs), vital signs (blood pressure [BP], pulse), 12-lead electrocardiogram (ECG), laboratory assessments (hematology, clinical chemistry, urinalysis), pregnancy testing (females only), physical examination findings, body weight, performance of the Columbia-Suicide Severity Rating Scale (C-SSRS) and use of concomitant medication.

Exploratory variables:

Taste test assessment.

Blood samples for pharmacogenetic testing will be collected to allow for potential future investigation of the influence of genotype on investigational medicinal product (IMP) disposition and safety.

Study design

This study will be an open-label, randomized, 4-way crossover study in healthy male and female (non-childbearing potential) subjects, performed at a single study center.

The study will comprise:

- A screening period of maximum 28 days;
- Four treatment periods during which subjects will be resident from one day before dosing (Day -1) until 48 hours after dosing; discharged on the morning of Day 3. Subjects will have to attend the clinical unit as required for collection of PK samples up to 72 hours after dosing;
- A final follow-up study visit within 72 hours after the last procedure of the last treatment period.

  For subjects who completed all the treatment periods, the final follow-up procedures (including adverse event [AE] data collection) may be performed at the last ambulatory visit of Treatment period 4 up to 72 hours after this visit. For subjects who discontinued the study, the final follow-up procedures may be performed at their last visit up to 72 hours after this visit, at the discretion of the investigator.

There will be a washout period of at least 7 calendar days between treatment periods.

Subjects will receive the IMP under fasted conditions.

The end of the study is defined as the last subject's last visit.

Target study population and reproductive restrictions

Healthy subjects, males and females (non-childbearing potential)

Women of childbearing potential are not allowed to participate in this study.

Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of signed and dated written informed consent prior to any study specific procedures.
2. Healthy male and female subjects aged 18 to 55 years with suitable veins for cannulation or repeated venipuncture.
3. Upon questioning, indicate willingness and ability to tolerate the insertion of a nasogastric tube and the administration of naloxegol crushed tablets dispersed in water through the nasogastric tube.
4. Females must have a negative pregnancy test at screening and on admission to the clinical unit, must not be lactating and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:
   - Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels in the post-menopausal range.

- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy; but not tubal ligation.

5. Have a body mass index (BMI) between 18.5 and 29.9 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg inclusive.
6. Able to understand, read and speak the German language.
7. Subjects willing to participate in genetic research: Provision of signed, written and dated informed consent for optional genetic research.

   If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this clinical study protocol.

Exclusion criteria

Persons who meet one or more of the exclusion criteria will not be considered eligible to participate in the study:

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the potential subject at risk because of participation in the study, or influences the results or the potential subject's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.
4. Any clinically significant abnormalities in hematology, clinical chemistry or urinalysis results, as judged by the investigator.
5. Any clinically significant abnormal findings in vital signs, as judged by the investigator.
6. Any clinically significant abnormalities on 12-lead ECG, as judged by the investigator.
7. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody, and human immunodeficiency virus (HIV) antibodies.
8. Known or suspected history of drug abuse, as judged by the investigator.
9. Received another new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of IMP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.

   Note: Subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.
10. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.
11. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to naloxegol.
12. Current smokers or those who have smoked or used nicotine products within the previous 3 months.
13. Positive screen for drugs of abuse or cotinine (cotinine level above 500 ng/mL) at screening or on each admission to the clinical unit, or positive screen for alcohol on each admission to the clinical unit.
14. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

    Drugs include known CYP3A4 and/or P-gp inhibitors and inducers, e.g., diltiazem, verapamil, and erythromycin
15. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life.

    For females, hormonal replacement therapy is not allowed.
16. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol, as judged by the investigator.
17. Involvement of any AstraZeneca or clinical unit employee or their close relatives.
18. Subjects who previously received naloxegol.
19. Consumption of poppy seeds within 7 days of first admission to the clinical unit.

20. Subject with a relevant history of a suicide attempt or suicidal behavior. Any recent suicidal ideation within the last 6 months (a level of 4 or 5), or who are at significant risk to commit suicide, as judged by the investigator using the C-SSRS.
21. Judgment by the investigator that the potential subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.
22. Applicable to subjects willing to participate in genetic research: Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection or previous bone marrow transplant.
23. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

Investigational medicinal product

Supplier:	AstraZeneca Mölndal, Sweden	
Test and reference products:	**Treatment A:** naloxegol tablet crushed, suspended in water, given orally	Test product
	Treatment B: naloxegol tablet crushed, suspended in water, given via nasogastric tube (total of 200 mL water)	Test product
	Treatment C: naloxegol oral solution	Test product
	Treatment D: naloxegol whole tablet, given orally	Reference product
Formulation:	Naloxegol film coated tablets 25 mg (as naloxegol oxalate 28.5 mg) Naloxegol oral solution 2.5 mg/mL (as naloxegol oxalate 2.8 mg/mL)	
Strength/Concentrations:	**Treatment A:** 25 mg naloxegol tablet **Treatment B:** 25 mg naloxegol tablet **Treatment C:** 2.5 mg/mL oral solution **Treatment D:** 25 mg naloxegol tablet	
Route of administration:	Oral	
Dose:	**Treatment A:** naloxegol 25 mg (1 tablet) **Treatment B:** naloxegol 25 mg (1 tablet) **Treatment C:** naloxegol 25 mg (10 mL oral solution) **Treatment D:** naloxegol 25 mg (1 tablet)	
Regimen:	Single dose	
Special handling requirements:	The IMP label specifies the appropriate storage conditions.	
Availability of IMP:	All IMPs will be available TBD 2015 and will be ready for delivery to the clinical site delivery upon regulatory approval.	

Study duration

Each subject will be involved in the study for approximately 9 weeks.

Pharmacokinetic sampling times and analysis

Blood samples for the determination of plasma concentrations of naloxegol will be collected for all treatment periods at the following time-points: pre-dose (0 hours [within 30 minutes prior to IMP administration]) and post-dose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours (18 samples per treatment period). Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Plasma samples will be analyzed for naloxegol using a validated assay.

Pharmacokinetic data analysis

The PK analysis set will be a subset of those subjects in the safety analysis set and will include subjects who received at least one dose of IMP and had at least one post-dose plasma concentration measurement at a scheduled time-point without important protocol deviations or violations thought to significantly affect the PK (e.g., subject vomited, wrong dose administered, prohibited concomitant medication taken).

Analyses will be performed using a linear analysis of variance (ANOVA) model with the natural logarithm of AUC, $AUC_{(0-t)}$ and C_{max} as the response variables and fixed effects of sequence, period, treatment and subject nested within sequence.

Transformed back from the logarithmic scale, geometric least squares means together with 2-sided 95% confidence intervals (CIs) and coefficient of variation (CV) for AUC, $AUC_{(0-t)}$ and C_{max} will be estimated and presented. Also, ratios of geometric means for AUC, $AUC_{(0-t)}$ and C_{max} (each test treatment compared to the reference naloxegol tablet formulation) together with CIs (2-sided 90%) will be estimated and presented.

The concentration data and PK parameter data for subjects excluded from the PK analysis set will be listed only.

Safety data analysis

The safety analysis set will include all subjects who received at least one dose of naloxegol and for whom any safety post-dose data are available.

Subject disposition will be listed and summarized including the number of withdrawals and the primary reason for withdrawal. Subjects excluded from any analysis sets will be listed including the reasons for exclusions.

All safety data will be listed for each subject and summarized appropriately. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term (PT) and system organ class (SOC). Additional summaries by severity and causality will be presented.

All clinical safety laboratory data and vital signs measurements will be listed and summarized by treatment or treatment sequence (as applicable) including changes from baseline. Any out of range laboratory measurements will be flagged in the listings. Other safety data including C-SSRS, physical examinations and ECG will be listed for each subject.

Exploratory data analysis

Results of the taste test assessment will be listed for each subject.

The date and time of the pharmacogenetic sampling will be listed.

Determination of sample size

Based on Study D3820C00018, the intra-subject CV = 15.7% for C_{max} and 31.9% for AUC. Thirty-six subjects (9 subjects per sequence) are needed to provide at least 80% power to show that the 90% CI of the ratio for a specific parameter (C_{max} and AUC) of each test formulation of naloxegol compared to the whole tablet (reference) formulation is within 0.80 and 1.25. This calculation is based on a CV of 31.9% and an expected mean ratio of 1.00.

No multiplicity adjustment is planned.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 12.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under plasma concentration- time curve from time zero extrapolated to infinity
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BBB	Blood-brain barrier
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	Body mass index
BLQ	Below limit of quantification
BP	Blood pressure
bpm	Beats per minute
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{last}	Last observed quantifiable concentration
CL/F	Apparent total body clearance after extravascular administration estimated as dose divided by AUC
ClinBase™	PAREXEL's electronic source data capturing and information management system
C_{max}	Observed maximum plasma concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale

CV%	Coefficient of variation percentage
DBP	Diastolic blood pressure
DCF	Data clarification form
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
ECG	Electrocardiogram
EMA	European Medicines Agency
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase (transferase)
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GRand	Global randomization system
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
ICH E3	ICH guideline for structure and content of clinical study reports
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
λ_z	Terminal elimination rate constant
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin

MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDT	Mean dissolution time
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
n	Number of subjects
NA	Not applicable
ND	Not determined
NR	No result
OAE	Other significant adverse event
OIC	Opioid-induced constipation
OTC	Over-the-counter
$\%AUC_{extr}$	Percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve to infinity from the time of the last quantifiable plasma concentration using λ_z
PAMORA	Peripherally-acting mu-opioid receptor antagonist
PDF	Portable Document Format
PDS	Protocol deviation specification (document)
PEG	Polyethylene glycol
PHL	Potential Hy's law
PI	Principal investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
QP	Qualified Person
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic

	concentration-time curve
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum plasma concentration
USA	United States of America
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WAD	Windows Allowance Document
WBC	White blood cell

3. ETHICAL AND REGULATORY REQUIREMENTS

3.1. Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Version 1996) and are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

3.2. Subject data protection

The Informed Consent Document (ICD) will incorporate wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in ClinBase™ and other documents by their subject number, not by name. Documents that identify the subject (e.g., signed ICD) will be maintained in confidence by the investigator.

Study data will be stored in accordance with local and global data protection laws.

3.3. Ethics and regulatory review

The study will be submitted to the national regulatory authority, Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]), Germany, for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Landesamt für Gesundheit und Soziales, Ethik-Kommission des Landes Berlin, Postfach 310929, 10639 Berlin, Germany, for ethical review and approval, by PAREXEL in accordance with local procedures.

AstraZeneca will provide the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and the national regulatory authority with safety updates and/or reports, according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

3.4. Insurance

The sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. T he name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

3.5. Informed consent

The subjects shall be informed of the nature, significance, implications and risks of the research study; and informed consent will be freely given and evidenced in writing, dated and signed, by the subject as evidence to indicate his/her free informed consent, prior to the start of the study.

The nature of the informed consent will comply with the Declaration of Helsinki (Version 1996), the current requirements of GCP (CPMP/ICH/135/95) and local regulation whichever affords the greater subject protection.

3.6. Changes to the clinical study protocol and Informed Consent Document

Study procedures will not be changed without the mutual agreement of the investigator and AstraZeneca.

If there are any substantial changes to the clinical study protocol, then these changes will be documented in a protocol amendment and where required in a new version of the clinical study protocol.

The amendment should be approved by the IEC/IRB and the national regulatory authority, before implementation. Local requirements should be followed for revised clinical study protocols.

If a protocol amendment requires a ch ange to the ICD the IEC/IRB should approve the revised ICD before the revised document is used.

Administrative changes will be communicated to the IEC/IRB, in accordance with local requirements.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor: AstraZeneca AB

[redacted]

Sponsor's Lead Physician:

[redacted]

Sponsor's Biostatistician:

[redacted]

Principal Investigator (PI):

[redacted]

Contract Research Organization (CRO): PAREXEL Early Phase Clinical Unit Berlin

[redacted]

Clinical Laboratory:	Synlab Clinical Trial GmbH [redacted]
Analytical Laboratory: (PK sample analysis)	Bioanalytical Chemistry Covance Laboratories, Inc. [redacted]
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site [redacted]

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating investigators will be provided in the clinical study report (CSR).

5. INTRODUCTION

5.1. Background information

Naloxegol is polyethylene glycol (PEG) naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-gp transporter, which substantially limits its ability to cross the blood-brain barrier (BBB). Naloxegol, by binding to μ-opioid receptors within the gastrointestinal (GI) tract, targets the underlying causes of opioid-induced constipation (OIC), i.e., the reduced GI motility, hypertonicity, and increased fluid absorption resulting from long-term opioid treatment. With its antagonist effects essentially restricted to the opioid receptors located outside the central nervous system (CNS), naloxegol is expected to alleviate OIC without reducing the central analgesic effects of opioids.

Patients receiving opioids for their pain may benefit from an oral therapy that directly addresses the underlying OIC GI pathophysiology and that provides a durable and consistent relief. The need is especially apparent for patients who continue to have constipation symptoms despite treatment with laxatives. Naloxegol has the potential to offer clinical benefits compared with existing therapies as an oral agent in the peripherally-acting μ-opioid receptor antagonist class developed for patients with OIC.

On 25 September 2014 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Moventig (naloxegol), 12.5 mg and 25 mg, film-coated tablet intended for the treatment of OIC in adult patients who have had an inadequate response to laxative(s). The applicant for this medicinal product was AstraZeneca AB [1]. Moventig was the first once-daily oral peripherally-acting mu-opioid receptor antagonist (PAMORA) to be approved in the European Union (EU) [2].

Applicable references are listed in the Investigator's Brochure [3].

5.2. Non-clinical studies with naloxegol

The primary pharmacological action of naloxegol was assessed in a number of *in vitro* and *in vivo* assays. The *in vitro* assays were performed to characterize the primary pharmacological action on opioid receptors and the aim of the *in vivo* studies was to determine the functional effect of naloxegol on central and peripheral morphine-induced effects. The pharmacological profile of naloxegol was characterized in *in vitro* binding assays demonstrating that naloxegol binds to μ-, δ- and κ- opioid receptors, with highest affinity at μ-opioid receptors. In [35S]GTPγS binding assays, naloxegol was shown to be a full and competitive antagonist at human μ-opioid receptors, with no significant agonist efficacy. In *in vivo* studies naloxegol reversed morphine-induced slowing of GI transit at doses lower than those that reverse

morphine analgesia, providing evidence of a separation between desired peripheral GI effect and undesired central CNS morphine antagonism in rats.

Details on non-clinical pharmacokinetic (PK) and other contributing studies are contained in the Investigator's Brochure [3].

5.3. Effects in humans

Clinical effects of naloxegol have been studied in fourteen Phase I, one Phase II and five Phase III trials.

Details are presented in the Investigator's Brochure [3].

5.4. Pharmacokinetics and drug metabolism in humans

Bioequivalence has been demonstrated across naloxegol formulations. The PK properties of naloxegol in solution and as tablets were investigated in healthy subjects and in patients with OIC. The PK properties of naloxegol appeared to be dose and time independent. Accumulation following daily repeated dosing was minimal at the dose level used in the Phase III studies. Current information suggests that the major plasma circulating species is naloxegol.

Details are presented in the Investigator's Brochure [3].

5.4.1. Absorption and food-effect

The investigational medicinal product (IMP) acts within the GI tract. Following oral administration, naloxegol is absorbed rapidly, with peak concentrations (C_{max}) achieved in less than 2 hours. In a majority of subjects, a secondary plasma concentration peak of naloxegol was observed approximately 0.4 to 3 hours after the first peak. Enterohepatic recirculation may be an explanation as extensive biliary excretion was seen in the rat [4, 5].

A high-fat meal increased the extent and rate of naloxegol absorption. The C_{max} and area under the plasma concentration-time curve (AUC) were increased by approximately 30% and 45%, respectively [5].

5.4.2. Distribution

The mean apparent volume of distribution during the terminal phase (V_z/F) in healthy subjects ranged from 968 to 2,140 L across dosing groups and studies. Protein binding of naloxegol in humans was low and the fraction unbound ranged from 80% to 100% [5].

5.4.3. Biotransformation

In a mass balance study in humans, a total of 6 metabolites were identified in plasma, urine and feces. These metabolites represented more than 32% of the administered dose and were formed via N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain. None of the metabolites were present in > 10% of the plasma concentrations of parent or total parent and metabolite-related material [5].

5.4.4. Elimination

Following oral administration of radiolabelled naloxegol, 68% and 16% of total administered dose were recovered in the feces and urine, respectively. Parent naloxegol excreted in the urine accounted for less than 6% of the total administered dose. Thus, the primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role [3, 4, 5].

In clinical pharmacology studies, the half-life of naloxegol at therapeutic dose ranged from 6 to 11 hours [5].

5.4.5. Special populations

There is no gender effect on the PK of naloxegol. The effect of race on the pharmacokinetics of naloxegol is small (approximately 20% decrease in the AUC of naloxegol when other groups are compared to Caucasian) and, therefore, no dos e adjustment is necessary. Naloxegol exposure was found to increase with increased weight, however, the differences in exposure were not considered clinically relevant [5].

5.5. Information on safety and potential risks in humans

No dose adjustment is required for patients with mild to moderate hepatic impairment. Safety and efficacy have not been established in patients with severe hepatic impairment. The dose for patients with moderate or severe renal impairment is 25 mg. If side effects affecting tolerability occur, naloxegol should be discontinued.

No dose adjustment is recommended for the elderly. Safety and efficacy of naloxegol have not been established in pediatric patients.

The dose should be decreased to 12.5 mg daily when co-administered with dual P-gp/moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and erythromycin).

Naloxegol is contraindicated in patients with known or suspected GI obstruction or in patients at increased risk of recurrent obstruction, due to the potential for GI perforation.

Naloxegol is contraindicated for use by any patient with a known serious hypersensitivity to this product, including its excipients, or any other opioid antagonist [4].

5.6. Study rationale

Alternative ways of administering a tablet may be useful to help patients who, for different reasons, have difficulties with swallowing a whole tablet. A dministration of dispersed (crushed) tablets suspended in water is a common way of administering drugs to these patients. A useful method in patients whose condition prevents swallowing is administration of dispersed tablets through nasogastric tubes. Additionally a solution formulation may be an attractive option for some patients including the pediatric population.

The purpose of this study is to evaluate the relative bioavailability of naloxegol after three alternative methods of administering naloxegol compared to commercially available whole naloxegol tablets [4] in healthy subjects. The results of this study will define the alternative ways of administration of naloxegol.

For evaluation of PK data, the following guidelines were considered:

- European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence. [6]
- United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. [7]

5.7. Risk-benefit assessment

The information contained in this protocol is consistent with current knowledge of the risks and benefits of the IMP. Subjects will be informed of the risks of the IMP and the clinical trial. Risks, responsibilities and benefits will be detailed in the ICD.

6. STUDY OBJECTIVES

6.1. Primary objective

- To determine the relative bioavailability of naloxegol when administered as each of three alternative methods of naloxegol administration compared to whole naloxegol tablets given orally, by assessment of the primary PK parameters of naloxegol

6.2. Secondary objective

- To assess the safety and tolerability of single doses of naloxegol in healthy subjects

6.3. Exploratory objectives

- To evaluate, by questionnaire, the perceived taste of the naloxegol liquid formulations (dispersed tablets orally and oral solution)
- To collect and store deoxyribonucleic acid (DNA) for possible future exploratory investigation of the influence of genotype on naloxegol disposition and safety

Outcome variables are described in Section 11.9.1 (PK parameters), Section 9.3 (safety measurements) and Section 9.4 (exploratory assessments).

7. INVESTIGATIONAL PLAN

7.1. Overall study design

This study will be an open-label, randomized, 4-way crossover study in healthy male and female (non-childbearing potential) subjects, performed at a single study center.

For details on randomization and flow of events, refer to Section 8.9.2 and Figure 1, respectively.

The study will comprise:

- A screening period of maximum 28 days;
- Four treatment periods during which subjects will be resident from one day before dosing (Day -1) until 48 hours after dosing; discharged on the morning of Day 3. Subjects will have to attend the clinical unit as required for collection of PK samples up to 72 hours after dosing;
- A final follow-up visit within 72 hours of the last procedure of the last treatment period.

  For subjects who completed all the treatment periods, the final follow-up procedures (including AE data collection) may be performed at the last ambulatory visit of Treatment period 4 up to 72 hours after this visit. For subjects who discontinued the study, the final follow-up procedures may be performed at their last visit up to 72 hours after this visit, at the discretion of the investigator.

There will be a washout period of at least 7 calendar days (minimum number of days based on half-life of naloxegol) between treatment periods.

Subjects will receive the IMP under fasted conditions.

7.1.1. End of study

The end of the study is defined as the last subject's last visit.

7.1.2. Interim analyses

No interim analyses will be performed in this study.

7.1.3. Expected duration of study

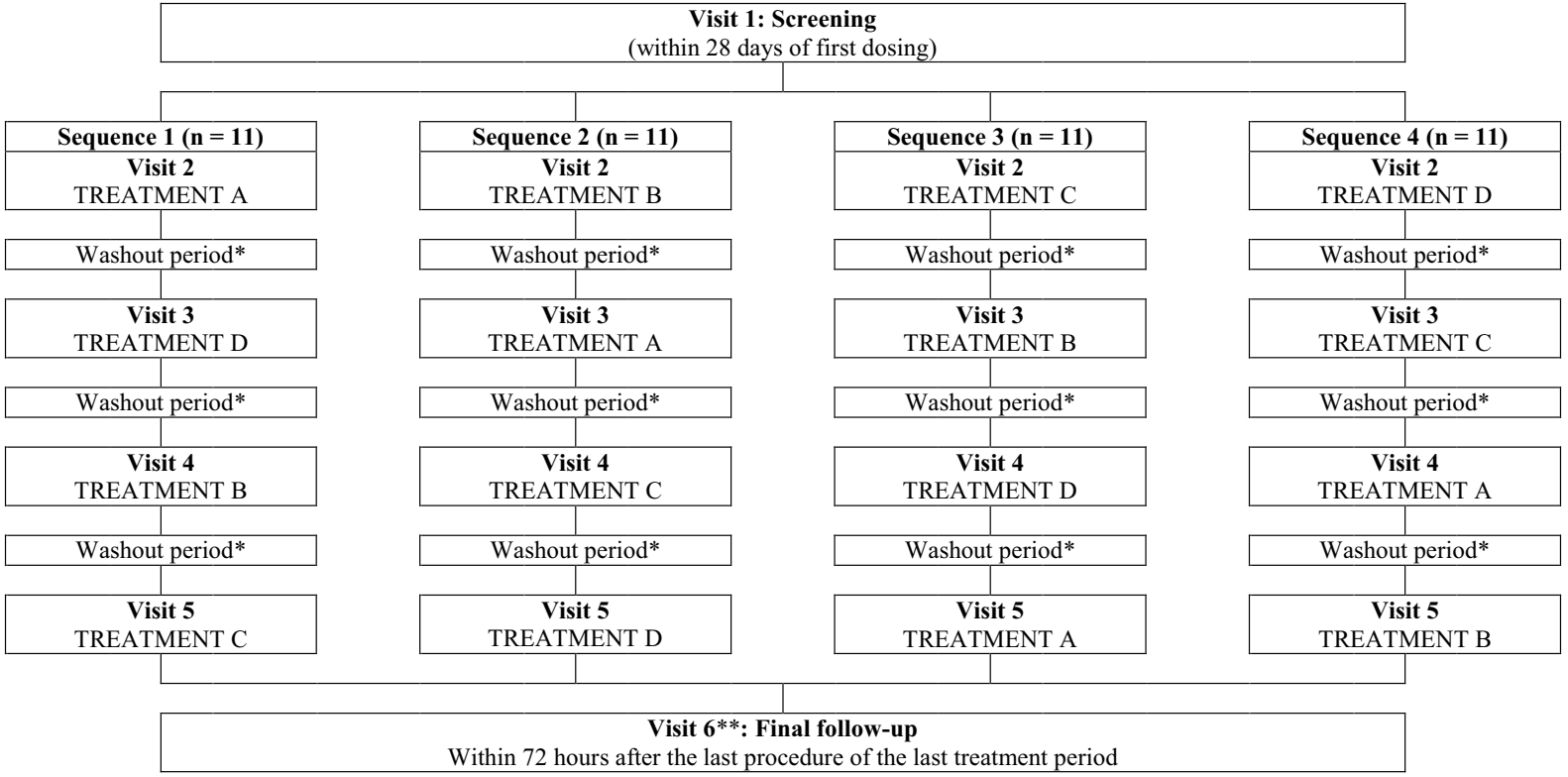
Each subject will be involved in the study for approximately 9 weeks.

7.2. Study flow chart and schedule of assessments

Figure 1 illustrates the flow of events for Treatment A, B, C and D.

Up to 44 subjects will be randomized to a 4 sequence Williams design for 4 periods and 4 treatments: ADBC, BACD, CBDA and DCAB, in order to ensure at least 36 evaluable subjects at the end of the last treatment period.

Figure 1 Study Flow Chart



* Washout period of at least 7 calendar days from last dose of naloxegol

** For subjects who completed all the treatment periods, the final follow-up procedures (including AE data collection) may be performed at the last ambulatory visit of Treatment period 4 up to 72 hours after this visit. For subjects who discontinued the study, the final follow-up procedures may be performed at their last visit up to 72 hours after this visit, at the discretion of the investigator.

Treatment A: naloxegol 25 mg (1 tablet) crushed, suspended in water, given orally

Treatment B: naloxegol 25 mg (1 tablet) crushed, suspended in water, given via nasogastric tube

Treatment C: naloxegol 25 mg (10 mL oral solution)

Treatment D: naloxegol 25 mg (1 tablet) whole tablet, given orally

The schedule of assessments displaying assessments/tasks and time-points is presented in Table 1.

Table 1 Schedule of Assessments

Assessment/Task	Screening	Admission	Treatment Periods	Final follow-up / Early termination
	From Day -28	Day -1	Days 1 to 4 for each period	
	Visit 1	Visit 2, 3, 4 and 5		Visit 6**
Signed informed consent	X			
Inclusion/exclusion criteria	X			
Eligibility check[1]		X		
Demographic data (including body height and BMI)	X			
Medical and surgical history	X			
Urine drugs of abuse, alcohol and cotinine testing	X	X		
Viral serology screening[2]	X			
Serum FSH (females only)	X			
Randomization[3]		X		
Study residency (in-house stay)[4]		X		
Non-residential visits (ambulatory visits)[5]	X		X	X
IMP administration[6]			X	
Safety and tolerability assessments				
Adverse events questioning[7]	←	X		→
Vital signs (blood pressure, pulse)[8]	X	X	X	X
12-Lead ECG[9]	X	X	X	X
Hematology, clinical chemistry, urinalysis (dipstick)[10]	X		X	X
Pregnancy testing (females only)[11]	X	X		X
Physical examination[12]	X	X	X	X
Body weight	X	X		X
Columbia-Suicide Severity Rating Scale (C-SSRS)[13]	X		X	
Prior and concomitant medication[14]	←	X		→
Pharmacokinetics				
Pharmacokinetic sampling[15]			X	
Exploratory assessments				
Taste test assessment[16]			X	
Pharmacogenetic sample[17]		X		

** For subjects who completed all the treatment periods, the final follow-up procedures (including AE data collection) may be performed at the last ambulatory visit of Treatment period 4 up to 72 hours after this visit. For subjects who discontinued the study, the final follow-up procedures may be performed at their last visit up to 72 hours after this visit, at the discretion of the investigator.

BMI = b ody mass index; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; IMP = investigational medicinal product.

[1] In addition to the eligibility check the recorded medical history will be updated if necessary on admission to Treatment period 1.

[2] Including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) screening.

[3] Randomization will be performed after confirmation of eligibility on admission to Treatment period 1 (on Day -1).

[4] Admission on Day -1 to each treatment period; discharged from the clinical unit 48 hours after dosing(morning of Day 3) to each treatment period.

[5] Ambulatory visits: Screening and Day 4 to each treatment period, and final follow-up/early termination (ET) visit**.

[6] IMP administration: On Day 1 at 0 hours to each treatment period.

[7] Questioning will be conducted spontaneously plus at the following scheduled time-points to each treatment period: pre-dose (0 hours) and post-dose at 3, 12, 24 and 48 hours. Serious adverse events (SAEs) will be recorded from the signing of informed consent and adverse events (AEs) will be recorded from randomization until the final follow-up/ET visit. Data to be collected for statistical analysis are described in Section 11.10.1.

[8] Blood pressure (BP) and pulse measurements (supine position) will be collected at screening and for each treatment period on admission, at pre-dose (0 hours) and post-dose at 24 and 48 hours, as well as at the final follow-up/ET visit.

[9] 12-Lead electrocardiogram (ECG) will be performed at screening, first admision to the clinical unit (Visit 2, Day -1), 1.25 hours after each dose (Visits 2-5, Day 1), as well as at the final follow-up/ET visit (total of 7 ECGs per subject who complete the study).

[10] Hematology, clinical chemistry and urinalysis will be performed at screening and at the final follow-up/ET visit; in addition, for the first and third treatment period at pre-dose.

[11] Serum pregnancy test at screening; urine pregnancy tests thereafter (females only).

[12] Full physical examination will be performed at screening and the final follow-up/ET visit. Abbreviated physical examination will be performed on admission and at 48-hours post-dose to each treatment period.

[13] C-SSRS will be performed at screening (version Baseline - Screening) and at the final follow-up/ET visit (version Since Last Visit) (see Appendix 15.5).

[14] Prior and concomitant medications are defined, and data to be collected for statistical analysis are described in Section 11.8.1.

[15] Blood samples for the determination of plasma concentrations of naloxegol will be collected for all treatment periods at the following time-points: pre-dose (0 hours [within 30 minutes prior to IMP administration]) and post-dose at 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours (18 samples per treatment period).

[16] Taste test assessment as soon as possible after dosing (Treatments A and C only).

[17] Pharmacogenetic sample: Subjects willing to participate in genetic research will sign a separate informed consent for this optional genetic research. If for any reason the blood sample is not drawn on Day -1 of the first treatment period, it may be taken at any time up until the last study visit. Refer to Section 9.4.2.

At the discretion of the investigator, vital signs and laboratory investigations of variables outside the reference ranges may be repeated up to three times during the screening period.

7.3. Order of assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time-point.

The sequence at a particular time-point is:

1. 12-lead electrocardiogram (ECG)

2. Vital signs (blood pressure [BP] and pulse)

3. Pharmacokinetic blood sample (will be drawn at the specified time-point)

4. Safety laboratory assessments

7.4. Dose rationale

The recommended dosage of naloxegol is 25 mg once daily in the morning [4, 5]. Naloxegol 25 mg will provide sufficient plasma exposure for the PK analysis of naloxegol.

7.5. Restrictions during the study

The following restrictions apply to the specified times during the study period:

1. On Day 1 of each treatment period, subjects will be fasted for at least 10 hours prior to IMP administration and until 4 hours after IMP administration. No fluids will be allowed apart from water which can be given until 1 hour prior to IMP administration and then from 2 hours after IMP administration (excluding water used in conjunction with IMP administration; see Section 8.6).

2. Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after IMP administration.

3. Subjects should not engage in any strenuous activity from 72 hours prior to IMP administration on Day 1 of the first treatment period until after their final follow-up visit.

4. Prior to each treatment period subjects should abstain from alcohol for 72 hours prior to admission until after their last PK sample was collected. Between treatment periods subjects should consume no more than 2 units of alcohol per day and completely abstain from 72 hours prior to their next admission. Subjects should also abstain from alcohol for 72 hours before their final follow-up visit.

5. Prior to each treatment period subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to dosing until discharge from the clinical unit. At other times, subjects should limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup = 360 mL soda, 180 mL coffee, or 240 mL tea) for the duration of the study.

6. Subjects should abstain from grapefruit or grapefruit juice, Seville oranges (also called bitter orange [a hybrid between a mandarin and pomelo], including marmalade), and quinine (e.g., tonic water) from 7 days prior to admission on Day -1 of the first treatment period until after their final follow-up visit.

7. During in-house stay subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed whilst in the clinical unit.

8. During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (e.g., Red Bull), and food containing poppy seeds and any over-the-counter (OTC) medication or herbal preparations until after their final follow-up visit has been completed.

9. Subjects will be required to abstain from blood or plasma donation until 3 months after their final follow-up visit.

10. Medication restrictions: Refer to Section 8.7.

11. Reproductive restrictions:

- Female subjects

  Women of childbearing potential are not allowed to participate in this study. Women of non-childbearing potential are defined in Section 7.6.1.

- Male subjects

  It is important that women of childbearing potential who are the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male subject has taken the last dose of IMP.

  As a precaution, all male subjects should avoid fathering a child by either true abstinence or the use of two effective means of contraception with their partner from the time of first IMP administration until 3 months after the last dose of IMP.

  Two or more of the following methods are acceptable and must include at least one barrier method:

  – Surgical sterilization (i.e., bilateral tubal ligation for females; vasectomy for male partners)
  – Placement of an intrauterine device or intrauterine system
  – Hormonal contraception (implantable, patch, oral)
  – Barrier methods including condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

  Male subjects who have been sterilized are required to use one barrier method of contraception (condom).

- Sperm donation

  Male subjects should not donate sperm for the duration of the study and for at least 3 months after the last day of IMP administration.

- Pregnancy

  Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

  A pregnancy notification form and follow-up will be completed.

7.6. Selection of study population

The investigator should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule. Subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

This study will be conducted in male and female (non-childbearing) subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

7.6.1. Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of signed and dated written informed consent prior to any study specific procedures.
2. Healthy male and female subjects aged 18 to 55 years with suitable veins for cannulation or repeated venipuncture.
3. Upon questioning, indicate willingness and ability to tolerate the insertion of a nasogastric tube and the administration of naloxegol crushed tablets dispersed in water through the nasogastric tube.

4. Females must have a negative pregnancy test at screening and on admission to the clinical unit, must not be lactating and must be of non-childbearing potential, confirmed at screening by fulfilling one of the following criteria:

   - Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels in the post-menopausal range.
   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy; but not tubal ligation.

5. Have a body mass index (BMI) between 18.5 and 29.9 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg inclusive.

6. Able to understand, read and speak the German language.

7. Subjects willing to participate in genetic research: Provision of signed, written and dated informed consent for optional genetic research.

   If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this clinical study protocol.

7.6.2. Exclusion criteria

Persons who meet one or more of the exclusion criteria will not be considered eligible to participate in the study:

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the potential subject at risk because of participation in the study, or influence the results or the potential subject's ability to participate in the study.

2. History or presence of GI, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.

4. Any clinically significant abnormalities in hematology, clinical chemistry or urinalysis results, as judged by the investigator.

5. Any clinically significant abnormal findings in vital signs, as judged by the investigator.

6. Any clinically significant abnormalities on 12-lead ECG, as judged by the investigator.

7. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody, and human immunodeficiency virus (HIV) antibodies.

8. Known or suspected history of drug abuse, as judged by the investigator.

9. Received another new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of IMP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.

   Note: Subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

10. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.

11. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to naloxegol.

12. Current smokers or those who have smoked or used nicotine products within the previous 3 months.

13. Positive screen for drugs of abuse or cotinine (cotinine level above 500 ng/mL) at screening or on each admission to the clinical unit or positive screen for alcohol on each admission to the clinical unit.

14. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

    Drugs include known CYP3A4 and/or P-gp inhibitors and inducers, e.g., diltiazem, verapamil, and erythromycin

15. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life.

    For females, hormonal replacement therapy is not allowed.

16. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol, as judged by the investigator.

17. Involvement of any AstraZeneca or clinical unit employee or their close relatives.

18. Subjects who previously received naloxegol.

19. Consumption of poppy seeds within 7 days of first admission to the clinical unit.

20. Subject with a relevant history of a suicide attempt or suicidal behavior. Any recent suicidal ideation within the last 6 months (a level of 4 or 5), or who are at significant risk to commit suicide, as judged by the investigator using the Columbia-Suicide Severity Rating Scale (C-SSRS).

21. Judgment by the investigator that the potential subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.

22. Applicable to subjects willing to participate in genetic research: Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection or previous bone marrow transplant.

23. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

7.6.3. Discontinuation of investigational medicinal product, individual stopping criteria and withdrawal from the study

Subjects may discontinue treatment or may be withdrawn from the study for the following reasons:

- Healthy subject decision: The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Withdrawal of consent: Subjects have the right to withdraw from the study at any time for any reason. If the withdrawal occurs following dosing with the study product, the subject will be asked to come for the follow-up examination.
- The subject will be withdrawn by the investigator,
  - If intercurrent illnesses occur, which, in the clinical judgment of the investigator or after discussion with the sponsor, may invalidate the study by interfering with the study product,
  - If it is discovered that the subject has entered the study in violation of the protocol,
  - If a significant protocol violation occurs during the study.

- Adverse event (AE), any significant and clinically relevant changes in the safety parameters which make continuation of IMP administration unjustified, at the discretion of the investigator. This includes but it is not limited to:
  - Any case of potential Hy's law (PHL) according to Appendix 15.3
  - Any case of a suspected severe gastrointestinal drug reaction
  - Any other severe or serious AE (SAE) that is judged as possibly related to the IMPs by the investigator
- Severe non-compliance to study protocol.

The reason(s) for withdrawal should be recorded on the appropriate page of the case report form (CRF) and the end of study form to be completed for each prematurely discontinued subject.

Subjects who discontinue the study will take part in a final follow-up examination including a physical examination, vital signs, ECG and standard safety laboratory tests, if possible. All subjects who drop from the study because of an AE or clinical laboratory abnormality will be followed-up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure reversibility or stabilization. The subsequent outcomes of these events will be recorded on the CRF.

7.6.4. Replacement of subjects

Subjects who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless a specific sample size is to be met for statistical purposes and if the sponsor's responsible physician and the PI agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the Sponsor.

Where a subject, who does not meet the selection criteria, is randomized in error and this is identified before IMP administration, the subject should be withdrawn from the study. If a subject is withdrawn prior to IMP administration, the subject will be replaced.

If a subject, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision will be made as to whether the subject should be replaced.

7.6.5. Premature termination of the study

The study may be terminated prematurely if:

- The PI and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance when there is at least 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered related by the investigator and the sponsor.
- The sponsor considers the applied doses of the study drug to be no longer relevant.
- The sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the PI and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

7.6.6. Total Blood Volume

The approximate total amount of blood to be collected from subjects in this study, excluding repeat samples, is summarized in Table 2.

Table 2 Total Blood Volume

Assessment	Sample volume	Number of samples				Total volume
		Screening	Admission	Treatment period	Final follow-up/ET	
Hematology	2.7 mL	1	0	2 x 1	1	10.8 mL
Clinical chemistry†	7.5 mL	1	2 x 1	0	1	30.0 mL
Pharmacogenetic sample (optional)	5.0 mL	0	1 x 1	0	0	5.0 mL
Pharmacokinetics*	3.0 mL	0	0	4 x 18	0	216.0 mL
Total						**261.8 mL**

ET = early termination

† At screening, viral serology, as well as serum pregnancy testing and serum FSH (females only) will be performed on the sample collected for clinical chemistry assessments.

* More details on pharmacogenetic and pharmacokinetic (PK) sampling will be provided in the Laboratory Manual.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

8. TREATMENTS

8.1. Identity of the investigational medicinal product

Supplier:	AstraZeneca [redacted]	
Test and reference products:	**Treatment A:** naloxegol tablet crushed, suspended in water, given orally	Test product
	Treatment B: naloxegol tablet crushed, suspended in water, given via nasogastric tube (total of 200 mL water)	Test product
	Treatment C: naloxegol oral solution	Test product
	Treatment D: naloxegol whole tablet, given orally	Reference product
Formulation:	Naloxegol film coated tablets 25 mg (as naloxegol oxalate 28.5 mg) Naloxegol oral solution 2.5 mg/mL (as naloxegol oxalate 2.8 mg/mL)	
Strength/Concentrations:	**Treatment A:** 25 mg naloxegol tablet **Treatment B:** 25 mg naloxegol tablet **Treatment C:** 2.5 mg/mL oral solution **Treatment D:** 25 mg naloxegol tablet	
Route of administration:	Oral	
Dose:	**Treatment A:** naloxegol 25 mg (1 tablet) **Treatment B:** naloxegol 25 mg (1 tablet) **Treatment C:** naloxegol 25 mg (10 mL oral solution) **Treatment D:** naloxegol 25 mg (1 tablet)	
Regimen:	Single dose	
Special handling requirements:	The IMP label specifies the appropriate storage conditions.	
Availability of IMP:	All IMPs will be available TBD 2015 and will be ready for delivery to the clinical site delivery upon regulatory approval.	

AstraZeneca will provide detailed handling instructions for each product and treatment. Details of the batch numbers will be included in the Trial Master File and the final CSR.

8.2. Supply of investigational medicinal product

The IMPs will be manufactured in accordance with Good Manufacturing Practice (GMP) and will be supplied by AstraZeneca.

The IMP will be provided in bulk labelled with a study specific label. Naloxegol 25 mg tablets will be provided as commercial blister strips and Naloxegol 2.5 mg/mL oral solution formulation will be supplied in 60 mL brown bottles with a screw cap. The IMP will be re-packaged into subject-specific containers by Hubertus Apotheke.

An agreement between PAREXEL and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMP at the clinical unit.

A release document signed by a legally authorized Qualified Person (QP) at Hubertus Apotheke will be placed in the appropriate section of the Trial Master File to document labelling.

The sponsor will retain reserve IMP samples in accordance with the EU Guidelines to GMP, Annex 13 – Investigational Medicinal Products, 03 February 2010.

8.3. Storage and handling procedures

Separate instructions for preparation and handling of the IMP will be provided for the study by the sponsor. The IMP will be stored in a secure facility under appropriate storage conditions. Details of storage conditions will be provided on the label of the IMP.

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

8.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements and medical device directive for labelling. Labels prepared by the clinical unit will be in the local language.

8.5. Accountability

The IMP provided for this clinical study will be used only as directed in the clinical study protocol. In accordance with GCP, the clinical unit will account for all supplies of the IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of the IMP will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

8.6. Doses and treatment regimen

Each subject will receive single dose treatments of naloxegol on four occasions in the fasted state. AstraZeneca will provide detailed dispensing and handling instructions for each product and treatment, including the amount of water to be taken with each treatment.

- **Treatment A:** Naloxegol 25 mg (1 tablet) crushed, suspended in water, given orally
- **Treatment B:** Naloxegol 25 mg (1 tablet) crushed, suspended in water, given via nasogastric tube (total of 200 mL water)
- **Treatment C:** Naloxegol 25 mg (10 mL oral solution)

- **Treatment D:** Naloxegol 25 mg (1 tablet) whole tablet, given orally

Non-carbonated water, 240 mL, at room temperature will be used, as applicable. Use of mineral water for dosing is not allowed.

Subjects will be required to be fasted for at least 10 hours before dosing.

Food and water restrictions, as well as posture control are described in Section 7.5.

8.7. Concomitant medication

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the investigator. For females, hormonal replacement therapy is not allowed.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator during the residential period. When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator must determine whether or not the subject should continue in the study.

8.8. Treatment compliance

Administration of IMP will take place at the PAREXEL Early Phase Clinical Unit. Data will be captured in ClinBase.

For Treatment A, C and D, the exact day and time of IMP administration will be recorded. A check of the subject's mouth and hands will be performed after dosing.

For Treatment B, the time at which the IMP is fully administered into the nasogastric tube will be taken as the time of dosing, for calculation of PK parameters. The exact day and time of IMP administration will be recorded.

Further data on dispensing and IMP administration to be captured in ClinBase, e.g., volume administered, will be detailed in the dispensing and handling instructions, which will be provided separately from this protocol.

8.9. Randomization

8.9.1. Subject Enrolment and Randomization

The PI will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.

- Each potential subject is assigned a unique enrolment number at screening upon signing the ICD.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomization code (subject number).

Randomization will be performed after confirmation of eligibility on admission to Treatment period 1 (on Day -1).

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization, starting from e.g., 101 (no leading zeroes). When using unique enrolment number, the specific format must be followed (i.e., reduced enrolment number, e.g., "1001" in ClinBase and on labels, full enrolment number, e.g., "E0001001" for outputs).

If a subject withdraws his/her participation in the study, then his/her enrolment/randomization code cannot be reused.

8.9.2. Procedures for Randomization

Upon completion of the randomization request form, the randomization will be produced by AstraZeneca using the global randomization system (GRand).

The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 44) (see Section 11.4) as well as providing sufficient randomization numbers for replacements. For this study, a total of 88 subject identifiers will be randomly assigned to four treatment sequences: ADBC, BACD, CBDA and DCAB.

Subjects will be assigned a randomization number for dosing in consecutive order per the randomization list.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the sponsor, then a new randomization number will be assigned. The replacement subjects will be assigned to the same treatment sequence as the discontinued subject using the next available randomization number that corresponds to the specific sequence.

8.10. Blinding

This is an open-label study.

9. PHARMACOKINETICS, SAFETY MEASUREMENTS AND EXPLORATORY ASSESSMENTS

9.1. Appropriateness of measurements

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of naloxegol planned to be given during this study, no safety issues are expected.

9.2. Pharmacokinetics

9.2.1. Sample collection and handling

Blood samples for the determination of plasma concentrations of naloxegol will be collected, using an indwelling catheter as appropriate, for all treatment periods at the following time-points: pre-dose (0 hours [within 30 minutes prior to IMP administration]) and post-dose at 0.25 (15 minutes), 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours (18 samples per treatment period).

Procedures for sample collection and handling will be detailed in the Laboratory Manual.

9.2.2. Labelling and shipment of biohazard samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (for International Airline Transportation Association [IATA] guidance, see Appendix 15.2 of this clinical study protocol).

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

9.2.3. Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the clinical unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca bio-bank system during the entire life cycle.

9.2.4. Pharmacokinetic drug assays

Blood samples for determination of naloxegol concentrations in plasma will be analyzed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca Research and Development, using a validated assay. Full details of the analytical method used will be described in a separate bioanalytical report.

9.2.5. Sample storage and destruction

Pharmacokinetic samples will be disposed of after finalization of the Bioanalytical Report or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported separately in a Bioanalytical Report, not in the CSR.

9.2.6. Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analyzed and the action documented. As collection of donated biological samples is an integral part of the study, consent withdrawal implies that the subject is withdrawn from further study participation. For pharmacogenetic sampling to this study, refer to Section 9.4.2.

AstraZeneca ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented and the signed document returned to the clinical unit.

9.3. Safety measurements

Safety and tolerability variables will be assessed by collection of data on AEs, vital signs, 12-lead ECG, laboratory assessments (hematology, clinical chemistry and urinalysis), pregnancy testing (females only), physical examination findings, body weight, performance of the Columbia-Suicide Severity Rating Scale (C-SSRS) and use of concomitant medication.

Viral serology, FSH (females only), and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility.

For timing of assessments refer to the Schedule of Assessments in Table 1.

9.3.1. Adverse events

Refer to Section 12.

9.3.2. Vital signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

- Systolic BP (SBP) (mmHg)
- Diastolic BP (DBP) (mmHg)
- Pulse (beats per minute [bpm])

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

9.3.3. Resting 12-lead electrocardiogram

A 12-lead ECG will be obtained after the subject rested in the supine position for at least 10 minutes. The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant and the reason for the abnormality will be recorded. The overall evaluation (normal/abnormal) will be reported in ClinBase.

The investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

9.3.4. Laboratory assessments

Laboratory variables include the following:

9.3.4.1. Hematology

White blood cell (WBC) count
Red blood cell (RBC) count
Hemoglobin (Hb)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Neutrophil absolute count
Lymphocyte absolute count
Monocyte absolute count
Eosinophil absolute count
Basophil absolute count
Platelet count
Reticulocyte absolute count

9.3.4.2. Serum clinical chemistry

Sodium
Potassium
Urea
Creatinine
Albumin
Calcium
Phosphate
Glucose (fasting)
Follicle stimulating hormone (FSH; females only)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transpeptidase (GGT)
Total bilirubin
Unconjugated bilirubin
Conjugated bilirubin
C-reactive protein (CRP)

9.3.4.3. Urinalysis

Glucose
Protein
Blood
Microscopy (if positive for blood or protein)

9.3.4.4. Viral serology

For each subject, HBsAg, hepatitis C virus antibody and HIV I and II antibodies will be assessed.

9.3.4.5. Urine drugs of abuse, alcohol and cotinine

Amphetamine / Ecstasy
Alcohol
Cannabinoids
Cocaine
Opiates
Tricyclic anti-depressants
Benzodiazepines
Methadone and methadone metabolites
Barbiturates
Phencyclidine
Cotinine
Urine creatinine

9.3.5. Pregnancy testing

Human beta chorionic gonadotropin will be measured in serum and urine samples as per schedule of assessments (female subjects only).

9.3.6. Physical examination

Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, mouth and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Abbreviated (Brief)

The abbreviated physical examinations will include an assessment of the general appearance, skin, abdomen, musculoskeletal, cardiovascular and respiratory systems.

9.3.7. Body weight

The measurement of body weight will be carried out according to the relevant PAREXEL SOPs.

9.3.8. Columbia-Suicide Severity Rating Scale

The C-SSRS [8] is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide. The C-SSRS will be performed to determine the presence of suicidality. T he scales for assessment at screening (version Baseline - Screening) and other visit(s) (version Since Last Visit) are located in Appendix 15.5.

For timing of assessments refer to Schedule of Assessments in Table 1.

9.3.9. Concomitant medication

Refer to Section 8.7.

9.4. Exploratory assessments

9.4.1. Taste test assessment

A standardized questionnaire will be provided to subjects as indicated in the Schedule of Assessments (Table 1). Subjects will be asked to complete the questionnaire for the liquid formulations tested, i.e., naloxegol crushed tablet, oral (Treatment A) and naloxegol oral

solution (Treatment C), without assistance or influence from site personnel. For each formulation, the questionnaire will be identical and will require the subject's opinion as indicated in Appendix 15.4.

9.4.2. Pharmacogenetic testing

Subjects will be offered the possibility to participate in optional genetic exploratory research. After signing a separate consent for optional genetic research, a blood sample will be collected in accordance with the inclusion criteria and study plan.

If for any reason the blood sample is not drawn on Day -1 according to the study plan (see Table 1), it may be taken at any time up until the last study visit. Although the genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis.

Only one sample should be collected per subject for genetic research during the study, to allow for potential future investigation of the influence of genotype on naloxegol disposition and safety.

A record of the date the subject consented to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF. Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual.

10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

10.1. Quality control and source data verification

Source data verification will be conducted with due regard to subject confidentiality.

The clinical unit will allow the study monitor and sponsor representative direct access to all study documents, medical files, and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the clinical unit.

10.2. Audit/Inspections

The clinical unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

10.3. Study monitoring

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.4. Data collection

PAREXEL's ClinBase system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based and/or transferred by external vendors, will be collected in ClinBase. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the clinical unit. The investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase.

10.4.1. Case report forms and source documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase. All source documents from which ClinBase entries are derived should be placed in the subject's personal records.

The original ClinBase entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

10.4.2. Access to source documents

During the course of the clinical study, a study monitor will make clinical unit visits to review protocol compliance, compare ClinBase entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs may wish to carry out source data inspections on-site, and the sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The investigator assures the sponsor of the necessary support at all times.

10.5. Data management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

11. STATISTICAL METHODS

11.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate statistical analysis plan (SAP) will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

11.2. General statistical methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarized by treatment sequence and overall. Pharmacokinetic data will be summarized by treatment. Safety and tolerability data will be summarized by treatment or by treatment sequence and overall, where applicable.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$.

The following rules will apply to any repeated safety assessments occurring within each treatment period:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 7.3.

For safety assessments performed at screening and the final follow-up, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at screening the last available value will be used in the summary statistics;
- If the repeated assessment occurs at the final follow-up visit the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.2 or later.

11.2.1. Missing Data

Missing dates and times in the AE data will be handled as described in Section 11.10.1. Concentrations that are below limit of quantification (BLQ) in the PK data will be handled as described in Section 11.9.2.

There will be no imputations of other missing data. All subjects will be included into the safety analyses as far as the data permit.

11.3. Study populations

11.3.1. Safety analysis set

The safety analysis set will include all subjects who received at least one dose of naloxegol and for whom any safety post-dose data are available.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP will also be presented using the safety analysis set.

11.3.2. Pharmacokinetic analysis set

The PK analysis set will be a subset of those subjects in the safety analysis set and will include subjects who received at least one dose of IMP and had at least one post-dose plasma concentration measurement at a scheduled time-point without important protocol deviations or violations thought to significantly affect the PK (e.g., subject vomited, wrong dose administered, prohibited concomitant medication taken).

Data from subjects may be excluded from the PK analysis set as a result of the following:

- Subjects who experienced vomiting at or before 2 x median t_{max} will be excluded for the affected treatment period

  Following oral administration, naloxegol is absorbed at less than 2 hours [4].

- Subjects whose pre-dose plasma naloxegol concentration is > 5% of the corresponding C_{max} will be excluded for the specific treatment period

A subject may be excluded from the analysis only for the specific treatment period in which the AE occurred.

The exclusion of any subjects or concentrations at certain time-points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The concentration data and PK parameter data for subjects excluded from the PK analysis set will be listed only.

11.4. Determination of sample size and statistical considerations

Based on Study D3820C00018, the intra-subject coefficient of variation percentage (CV%) = 15.7% for C_{max} and 31.9% for AUC. Thirty-six subjects (9 subjects per sequence) are needed to provide at least 80% power to show that the 90% confidence interval (CI) of the ratio for a specific parameter (C_{max} and AUC) of each test formulation of naloxegol compared to the whole tablet (reference) formulation is within 0.80 and 1.25. This calculation is based on a CV of 31.9% and an expected mean ratio of 1.00. No multiplicity adjustment is planned.

Up to 44 subjects will be randomized to a 4 sequence Williams design for 4 periods and 4 treatments: ADBC, BACD, CBDA and DCAB, in order to ensure at least 36 evaluable subjects at the end of the last treatment period.

11.5. Protocol deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, subject was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications

- Other procedural and study conduct deviations recorded by the clinical unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study-specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD) which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

11.6. Subject disposition

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarized by treatment sequence and overall, and will include the following information: number of subjects randomized and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented for all randomized subjects.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

11.7. Demographic and baseline data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarized separately by treatment sequence and for all subjects. The denominator for percentages will be the number of subjects in the safety analysis set for each treatment sequence or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable).

A summary of the number and percentage of subjects who had relevant medical histories will be presented by treatment sequence and for all subjects for the medical history PT.

11.8. Prior and concomitant medication and drug administration

11.8.1. Prior and concomitant medication

Prior medications are those that started and stopped prior to the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the sponsor's drug dictionary.

11.8.2. Drug administration

Drug administration dates and times, including volume administered (where applicable) will be listed for each subject and treatment period.

11.9. Pharmacokinetic analysis

11.9.1. Pharmacokinetic parameters

Where possible, the following PK parameters will be calculated for naloxegol.

Primary PK parameters

AUC	Area under plasma concentration-time curve from time zero extrapolated to infinity
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
C_{max}	Observed maximum plasma concentration

Secondary PK parameters

t_{max}	Time to reach maximum plasma concentration
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
MDT	Mean dissolution time (whole tablet only) (calculated as $MRT_{Treatment\ D\ [Reference]} - MRT_{Treatment\ C\ [Test]}$)
MRT	Mean residence time
λ_z	Terminal elimination rate constant

CL/F	Apparent total body clearance after extravascular administration estimated as dose divided by AUC
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

The following diagnostic parameters for plasma PK analysis will be listed, but not summarized:

λ_z upper and lower	The time interval (h) of the log-linear regression to determine $t_{½}$
λ_z, N	Number of data points included in the log-linear regression analysis
Rsq_adj	Regression coefficient adjusted for λ_z, N , Goodness of fit statistic for calculation of λ_z
$\%AUC_{extr}$	Percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve to infinity from the time of the last quantifiable plasma concentration using λ_z

Additional PK parameters may be determined where appropriate.

11.9.2. Derivation of Pharmacokinetic Parameters

The PK analyses of the plasma concentration data for naloxegol will be performed by Covance, on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca Research and Development.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher and/or SAS® Version 9.2, or higher. All descriptive and inferential statistical computations will be performed using SAS® Version 9.2, or higher.

PK analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used.

Plasma concentrations which are BLQ prior to the first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any BLQ plasma concentrations will be set to missing for all concentration profiles. W here two or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

Terminal elimination half-life is estimated as $(\ln 2)/\lambda_z$, where λ_z refers to the terminal elimination rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve. For the determination of λ_z, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log linear decline in plasma concentrations. A minimum of 3 data points will be used in calculating λ_z, and the duration of time over which PK blood samples were collected will be at least twice the subsequently estimated terminal half-life. Where an elimination half-life is estimated to be more than half of the PK collection interval, it will be flagged, commented upon in the study report and interpreted with caution. AUC is estimated by $AUC_{(0\text{-}t)} + C_{last}/\lambda_z$ where C_{last} is the observed last quantifiable drug concentration. AUC values where the percentage extrapolation is less than 20% will be reported. The AUC values where the percentage extrapolation is greater than 20% will be flagged in the data listings.

AUCs (including AUC and $AUC_{(0\text{-}t)}$) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

11.9.3. Presentation of pharmacokinetic data

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized by treatment (where treatments will be pooled across treatment periods) using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum and maximum. For t_{max}, only n, median, minimum and maximum will be presented.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the log-transformed data.

For concentration data the mean, geometric mean, SD, median, minimum and maximum values will be reported to three significant figures and CV% to one decimal place. Individual

PK parameters will be presented to three significant figures, with the exception of t_{max} which will be presented to two decimal places. Values >1000 in either the concentration data or PK parameter data will be presented to the nearest integer.

Plasma concentrations that are BLQ or if there are missing values (e.g., no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time-point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time-point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The max value will be reported from the individual data, and the min and median will be set to BLQ.
- If all values are BLQ at a time-point, no descriptive statistics will be calculated for that time-point. Not applicable (NA) will be written in the field for standard deviation and CV% and BLQ will be written in fields for mean, geometric mean, min, median, and max.
- The number of BLQ values (n below LLOQ) will be reported for each time-point.

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi logarithmic scale with all treatments overlaid on the same plot and separate plots for each subject.

Combined individual plasma concentration versus actual times will be plotted in linear and semi logarithmic scale. Plots will be grouped by treatment.

Arithmetic mean plasma concentration (±SD) versus nominal sampling time will be plotted in linear and semi logarithmic (no SD presented) scale with all treatments overlaid on the same figure.

For mean plots, BLQ values will be handled as described for the summary tabulations; for individual plots plasma concentrations which are BLQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any BLQ plasma concentrations will be regarded as missing. All individual and mean plots will be based on the PK analysis set.

11.9.4. Statistical analysis

Analyses will be performed using a linear analysis of variance (ANOVA) model using the natural logarithm of AUC, $AUC_{(0-t)}$ and C_{max} as the response variables and fixed effects of sequence, period, treatment and subject nested within sequence.

Transformed back from the logarithmic scale, geometric least squares means together with 2-sided 95% CIs along with CV for AUC, $AUC_{(0-t)}$ and C_{max} will be estimated and presented. Also, ratios of geometric means for AUC, $AUC_{(0-t)}$ and C_{max} (each test treatment compared to the reference naloxegol tablet formulation) together with CIs (2-sided 90%) will be estimated and presented.

Data from healthy subjects excluded from the PK analysis set will be included in the data listings, but not in the summaries or statistical analyses.

The statistical analysis will be conducted separately for the following:

- Treatment A versus Treatment D
- Treatment B versus Treatment D
- Treatment C versus Treatment D

Only the data for the comparison under investigation will be included in the statistical analysis i.e., when comparing Treatment A and Treatment D, the data for Treatment B and Treatment C will be removed from the dataset.

Subjects must have the specific PK parameter (i.e., AUC, $AUC_{(0-t)}$ or C_{max}) available for both treatments of naloxegol in order to be included in a specific relative bioavailability assessment; a subject may therefore be included in one, two or all comparisons for each of the PK parameters.

In this analysis no adjustments will be made for multiple comparisons.

11.10. Analysis of safety data

The analysis of the safety variables will be based on the safety analysis set.

11.10.1. Adverse events

All AEs will be coded using MedDRA, and will be listed for each subject. A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) after the first dose of IMP in Treatment period 1. Adverse events will be assigned to a treatment based on the start date/time of the AE:

- Screening: all AEs with start date/time prior to dosing in Treatment period 1.

- Treatment period 1: AEs with start date/time at the time of or after dosing in Treatment period 1 until the time of dosing in Treatment period 2.
- Treatment period 2: AEs with start date/time at the time of or after dosing in Treatment period 2 until the time of dosing in Treatment period 3.
- Treatment period 3: AEs with start date/time at the time of or after dosing in Treatment period 3 until the time of dosing in Treatment period 4,
- Treatment period 4: AEs with start date/time at the time of or after dosing in Treatment period 4 until the final follow-up visit.

Adverse events with missing start dates/times will be handled as follows:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing;
- If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;
- If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of Screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of Screening if this is later.
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

Adverse events will be summarized by treatment (where treatments will be pooled across the treatment periods) and overall, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who

had any AEs, SAEs and AEs that led to discontinuation will be summarized. The AEs that occur before (first) dosing will be excluded from the summary tables.

The following information will be included in the listings: verbatim term, MedDRA SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of subjects.

11.10.2. Vital signs

The results of the vital signs measurements will be listed by subject and time-point including the date/time of the assessment, flags for measurements that are outside the reference range (L or H, if applicable), changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be the pre-dose assessment on Day 1 in each treatment period. Descriptive statistics will be presented by treatment and time-point for both observed values and changes from baseline.

11.10.3. Resting 12-lead electrocardiogram

12-Lead ECG results will be listed for each subject.

11.10.4. Laboratory assessments

Hematology and clinical chemistry values will be listed by subject and time-point including changes from baseline and repeat/unscheduled measurements. Summary tabulations will be presented by treatment sequence and time-point for the safety analysis set. The baseline for the measurements will be the pre-dose assessment performed prior to dosing in Treatment period 1. Changes from baseline will be calculated and presented for all post-baseline time-points including pre-dose in Treatment period 3 and the follow up visit. Shift tables will also be presented.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (e.g., AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in the units provided by the clinical laboratory for the Safety Review Committee meeting (if applicable), and in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)

11.10.5. Physical examination and body weight

The results of the physical examination will be listed by body system for each subject.

Body weight will be listed by subject and time-point.

11.10.6. Columbia-Suicide Severity Rating Scale

Results of the C-SSRS will be listed for each subject and time-point.

11.11. Analysis of exploratory data

11.11.1. Taste test assessment

For Treatment A and C, palatability will be assessed as measured by taste scores. The results of the taste questionnaire will be listed for each subject and treatment, where applicable.

11.11.2. Pharmacogenetics

The date and time of the blood sample taken for pharmacogenetics will be listed.

12. ADVERSE EVENTS

12.1. Definitions

12.1.1. Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG).

In clinical studies an AE can include an undesirable medical condition occurring at any time after the subject/patient has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

12.1.2. Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix 15.1 of this clinical study protocol.

12.1.3. Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or AEs leading to withdrawal. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation

with the Global Safety Physician, be considered as other significant adverse events (OAEs) and reported as such in the CSR. A similar review of other data from vital signs, laboratory assessments and other safety assessments will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

12.2. Recording of adverse events

12.2.1. Time period for collection of adverse events

SAEs will be collected from the signing of informed consent and AEs from randomization until the final follow-up visit.

12.2.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in ClinBase.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP (yes or no)
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables (e.g., action taken with study drug) will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)

3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

12.2.4. Causality collection

The investigator will assess causal relationship between IMP and each AE, and answer "yes" or "no" to the question: "*Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"*

For SAEs causal relationship will also be assessed for study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix 15.1 of this clinical study protocol.

12.2.5. Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in ClinBase.

When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of symptoms and signs. However, if a diagnosis is known and there are other symptoms or signs that are not generally part of the diagnosis, the diagnosis and each symptom or sign will be recorded separately.

12.2.6. Adverse events based on examinations and tests

The results from protocol mandated safety assessments will be summarized in the CSR.

Deterioration as compared to baseline in protocol mandated safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria.

If deterioration in a vital sign or laboratory value is associated with clinical symptoms and signs, the symptom or sign will be reported as an AE and the associated vital sign or laboratory result will be considered as additional information.

Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

In the absence of clinical symptoms or signs, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

12.3. Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IMP, or to the study procedure(s). All SAEs will be recorded in ClinBase.

If any SAE occurs in the course of the study, then investigators or other clinical unit personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety Data Entry Site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

Investigators or other clinical unit personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

In addition to recording of SAEs in ClinBase, the AstraZeneca Serious Adverse Event Report – Clinical Study form for reporting an SAE to the Data Entry Site (DES) will also be used.

All information provided for the SAE sent into the DES will be in English.

The following CRF modules will be completed for each SAE report:

- Demography
- Dosing
- AE (including start and stop date/time for the AE, the investigator's causality assessment to study drug, action taken with study drug, severity and outcome)

- SAE (including serious criteria, causality assessment to study procedure any investigations, the symptoms and course of the event and any treatments given)
- Medical History
- Concomitant Medications
- LIVERRF (risk factors), LIVERSS (signs and symptoms) and LIVERDI (additional diagnostic with results) for all SAEs with a reported term of 'potential Hy's Law' or 'Hy's Law' will be provided in a narrative form by the PI
- Any additional supporting information e.g., laboratory test results, vital signs, ECG assessments

The 'AstraZeneca first aware date' for all SAEs reported is the date that any member of the Provider or AstraZeneca first become aware of the SAE and for regulatory reporting purposes this is the 'clock start date'.

Each SAE (as Portable Document Format [PDF]) should be sent to the DES Tata Consultancy Services (TCS) preferably via secure e-mail using the mailbox e-mail address: AEMailboxClinicalTrialTCS@astrazeneca.com

The e-mail should contain the following information in the e-mail header:
Subject Title: New SAE; <study code>, <SAE text>, <Country>, <Centre No>, <Enrolment code>, <Randomization code>

The message in the e-mail itself should contain the following:

A NEW serious adverse event has been reported for the following subject:

Study Code:

Country: <country>

Centre No: <study site number>

Enrolment Code: <SUBJECT>

Randomization Code: <SUBJECT>

SAE Description:

Seriousness Criteria:

Study Drug Causality/Additional Med Causality/other Med Causality/Study Procedure Causality

Date SAE met criteria for serious:

AZ (= PAREXEL investigator) first aware date:

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of study documentation

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

Investigator specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents could be retained for a longer period however, if required by the regulatory requirements or by an agreement with AstraZeneca. It is the responsibility of AstraZeneca to inform the investigator as to when these documents no longer need to be retained.

Study documentation will be archived by the CRO for 15 years.

13.2. Publication of study results

If a publication (e.g., in a scientific journal) based on the results of this study is envisaged, approval from AstraZeneca will be obtained and a draft manuscript will be submitted to AstraZeneca for scrutiny and comment. The choice of conduit will be mutually agreed on by the PI and AstraZeneca.

13.3. Clinical study report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IEC/IRB and the national regulatory authority in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCES

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7. United States Department of Health and Human Services, Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Center for Drug Evaluation and Research (CDER) March 2003 BP.

8. C-SSRS Columbia University Medical Center. Columbia-Suicide Severity Rating Scale (2008).http://www.cssrs.columbia.edu/. Accessed on 02 November 2014.

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15. APPENDICES

15.1. Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious adverse event (SAE), although the reasons for it may be (e.g., bronchospasm, laryngeal edema). H ospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.

- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational medicinal product (IMP).

- **Time Course / Exposure to suspect drug**

  Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- **Consistency with known drug profile**

  Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR, could the AE be anticipated from its pharmacological properties?

- **Dechallenge experience**

  Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- **No alternative cause**

  The AE cannot be reasonably explained by other aetiology such as the underlying disease, other drugs, other host or environmental factors.

- **Rechallenge experience**

  Did the AE reoccur if the suspected drug was reintroduced after having been stopped?

  Note: AstraZeneca would not normally recommend or support a rechallenge.

- **Laboratory tests**

  A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship, unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

15.2. International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

CATEGORY A

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are for example, Ebola and Lassa Fever viruses. Category A pathogens:

- are to be packed and shipped in accordance with IATA Instruction 602.

CATEGORY B

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D, and E viruses, and human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

Category B pathogens:

- are to be packed in accordance with UN3373 and IATA Instruction 650.

EXEMPT

Exempt refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)

- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times.

  The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver clinical chemistry. The investigator is responsible for determining whether a subject/patient meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug Induced Liver Injury (DILI) caused by the investigational medicinal product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥ 2x ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP)
- The elevations do not have to occur at the same time or within a specified time frame

Hy's Law (HL)

- AST or ALT ≥ 3x ULN **and** TBL ≥ 2x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug
- The elevations do not have to occur at the same time or within a specified time frame

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject/patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN

- TBL ≥ 2x ULN

The investigator will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject/patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory case report form (CRF)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the subject/patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject/patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

4.2 Potential Hy's Law Criteria met

If the subject/patient does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.

  The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects'/patients' follow-up and the continuous review of data.

Subsequent to this contact the investigator will:

- Monitor the subject/patient until liver clinical chemistry variables and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- Complete the three Liver CRF Modules as information becomes available.

If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria were met. No later than 3 weeks after the clinical chemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate. According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would clarify the ALT or AST and TBL elevations other than IMP causality:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review [9].

15.4. Taste Test Assessment

Document included:

- TASTE version 1.1 Eng. Used by permission, © AstraZeneca

TASTE

ID: ☐☐☐☐☐☐

Age: ☐☐

Sex: ☐ male ☐ female

Treatment Period: ☐

Below are questions about the taste of the medicine you received. Answer each question by ticking the box, please mark only one alternative.

1. Sweet

0	1	2	3	4	5	6	7	8	9	10
Not at all sweet										Extremely sweet

2. Salty

0	1	2	3	4	5	6	7	8	9	10
Not at all salt										Extremely salt

3. Sour

0	1	2	3	4	5	6	7	8	9	10
Not at all sour										Extremely sour

4. Bitter

0	1	2	3	4	5	6	7	8	9	10
Not at all bitter										Extremely bitter

5. Metallic

0	1	2	3	4	5	6	7	8	9	10
Not at all metallic										Extremely metallic

6. Hot/spicy

0	1	2	3	4	5	6	7	8	9	10

Not at all hot/spicy — Extremely hot/spicy

7. Overall, how would you rate the taste of this medicine?

0	1	2	3	4	5	6	7	8	9	10

I dislike it extremely much — I like it extremely much

8. Do you think this medicine smells?

Yes No

9. If Yes, how does it smell?

0	1	2	3	4	5	6	7	8	9	10

Extremely bad — Extremely nice

10. Would you consider taking this medicine again?

0 1 2 3 4 5 6 7 8 9 10

Never – under no circumstances — Yes, definitely

11. Please add any additional comments you have regarding the taste and/or smell of this medicine.

15.5. Columbia-Suicide Severity Rating Scale

Documents included:

- C-SSRS used at screening (version Baseline - Screening)
- C-SSRS used for other visit(s) (version Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal	Past __ Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

	Most Severe	Most Severe
Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

16.2. Declaration of Sponsor or Responsible Medical Expert (Biostatistician)

Protocol Title: An open-label, randomized, 4-period, 4-treatment, crossover, single-center, single-dose bioavailability study with alternate methods of administration of crushed naloxegol tablets, 25 mg and of a naloxegol solution formulation, 25 mg, compared to whole naloxegol tablets, 25mg, in healthy subjects.

This clinical study protocol was subjected to critical review and has been released by AstraZeneca. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 1996) and the guidelines on GCP and other regulatory requirements, applicable to this clinical study. This clinical study involves research.

Sponsor Signatories/Responsible Medical Expert

[redacted]

[redacted]

Date of Signature

[redacted]

16.3. Declaration of the Principal Investigator

Protocol Title: An open-label, randomized, 4-period, 4-treatment, crossover, single-center, single-dose bioavailability study with alternate methods of administration of crushed naloxegol tablets, 25 mg and of a naloxegol solution formulation, 25 mg, compared to whole naloxegol tablets, 25mg, in healthy subjects.

This clinical study protocol was subjected to critical review and has been released by AstraZeneca. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 1996) and the guidelines on GCP and other regulatory requirements, applicable to this clinical study. This clinical study involves research.

Principal Investigator

[redacted]

Signature

[redacted]

Date of Signature

[redacted]

Principal Investigator
PAREXEL Early Phase Clinical Unit