Quotient Sciences

NCT #: NCT06612255

CLINICAL STUDY PROTOCOL

A Phase 1, Single Part, Partially Randomised, Open-Label Study to Evaluate the Relative Bioavailability of a Taste-Masked Delafloxacin Powder for Oral Suspension with Oral Delafloxacin Tablet Reference in Healthy Subjects

Short Study Title: Evaluation of the Relative Bioavailability of a Taste-Masked Delafloxacin Powder for Oral Suspension with Oral Delafloxacin Tablet Reference

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3 Synopsis

Sponsor:	Drug Substance:	IRAS ID:
Melinta Therapeutics, LLC	Baxdela® (delafloxacin)	1009679

Title of Study:

A Phase 1, Single Part, Partially Randomised, Open-Label Study to Evaluate the Relative Bioavailability of a Taste-Masked Delafloxacin Powder for Oral Suspension with Oral Delafloxacin Tablet Reference in Healthy Subjects

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Objectives and Endpoints:

Objectives	Endpoints
Primary To determine the relative bioavailability of delafloxacin Powder for Oral Suspension compared to that of oral delafloxacin Tablet reference	Results of the formal statistical analysis of overall exposure (AUC) for delafloxacin Powder for Oral Suspension, compared to oral delafloxacin Tablet reference
Secondary To determine the PK of delafloxacin Powder for Oral Suspension formulation	PK parameters for delafloxacin: Tlag, Tmax, Cmax, AUC(0-24), AUC(0-last), AUC(0-inf), lambda-z, Frel,T1/2, CL/F, Vz/F, and MRT, as applicable
To determine the relative bioavailability of delafloxacin Powder for Oral Suspension in the fed and fasted state	Results of the formal statistical analysis of overall exposure (AUC) for delafloxacin Powder for Oral Suspension in the fed state compared to the fasted state
To provide additional safety and tolerability information for orally administered delafloxacin	Assessment of adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests
Exploratory To evaluate the taste/palatability attributes (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste) and overall acceptability of delafloxacin Powder for Oral Suspension	Results of the taste questionnaire

Methodology:

This is a Phase 1, single centre, single part, partially randomised, open-label, relative bioavailability study in healthy subjects.

It is planned to enrol approximately 16 healthy male and healthy non-pregnant, non-lactating female subjects.

It is planned to administer up to four regimens:

Period	Regimen	Investigational Medicinal Product	Dose	Route of Administration
1 and 2	A	delafloxacin Tablet (reference)	450 mg	Oral, Fasted
	B	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	450 mg	Oral, Fasted
3	C	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	450 mg or XX mg	Oral, Fed or Oral, Fasted
4 (optional)	D	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	XX mg or YY mg	Oral, Fed or Oral, Fasted

The order in which regimens are dosed may be subject to change due to logistical reasons

The effect of food on the PK of a novel delafloxacin Powder for Oral Suspension formulation may be explored in Period 3 or optional Period 4, by administering investigational medicinal product (IMP) after a high-fat breakfast. The effect of increasing or decreasing the dose level may also be explored.

There will be an interim decision meeting after Periods 2 and 3 to review the PK and safety data for up to 48 hours post-dose from preceding periods, in order to determine the dose and prandial state for Regimen C and Regimen D (if applicable).

There will be a minimum washout of 4 days between dosing in Periods 1 and 2. The intervals between Periods 2 and 3, and Period 3 and optional Period 4, will require a minimum of 14 days, to permit the interim decision process and IMP manufactures.

Study Design:

Subjects will undergo preliminary screening procedures for the study at the screening visit (Day -28 to Day -2).

Periods 1 and 2

Subjects will be admitted in the morning on the day before dosing (Day -1) in Period 1. Subjects will receive a snack in the evening, after which they will fast overnight from all food and drink (except water) for a minimum of 10 hours. Subjects will be administered IMP on the morning of Day 1 in the fasted state. Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration (Regimen B only).

Subjects will be randomised in a 1:1 ratio to one of two sequences (AB or BA) immediately prior to dosing in Period 1, for allocation of regimens across Periods 1 and 2.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose during each period. Subjects will remain resident in the clinical unit during the washout period (minimum 4 days) between Periods 1 and 2. Subjects will be discharged from the clinical unit at 48 hours post-dose (Day 3) in Period 2.

Following dosing of Regimens A and B, there will be an interim decision meeting to review available PK and safety data to decide the dose level and prandial state for Regimen C. The Investigator and Sponsor will decide whether to continue to evaluate a 450 mg dose level of delafloxacin Powder for Oral Suspension following a high-fat breakfast, or to evaluate an alternative dose level in the fasted state.

Period 3

Subjects will be admitted in the evening on the day before dosing (Day -1). Subjects will fast overnight from all food and drink (except water) for a minimum of 10 hours, and will

be administered IMP on the morning of Day 1 in the fasted state (if a different dose level is selected), or approximately 30 minutes after a high-fat breakfast (if a change to prandial state is selected). Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose (Day 3), at which time subjects will be discharged from the clinical unit.

Following dosing of Regimen C, there will be an interim decision meeting to review available PK and safety data, to decide whether to proceed with optional Period 4 or whether to end the study. If it is decided to end the study, a follow-up phone call will take place on Day 6 ± 1 to ensure the ongoing wellbeing of subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit. End of study is defined as completion of the last follow-up phone call or unscheduled follow-up visit. If it is decided to proceed with optional Period 4, the dose level and prandial state for Regimen D will be determined; the Investigator and Sponsor will decide whether to continue to evaluate the dose level selected for Regimen C following a high-fat breakfast, or to evaluate an alternative dose level in the fasted state.

Optional Period 4

Subjects will be admitted in the evening on the day before dosing (Day -1). Subjects will fast overnight from all food and drink (except water) for a minimum of 10 hours, and may be administered IMP on the morning of Day 1 in the fasted state (if a different dose level is selected), or approximately 30 minutes after a high-fat breakfast (if a change to prandial state is selected). Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose (Day 3), at which time subjects will be discharged from the clinical unit. A follow-up phone call will take place on Day 6 ± 1 to ensure the ongoing wellbeing of subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit; completion of the last follow-up phone call or unscheduled follow-up visit will be considered the end of the study.

Number of Subjects Planned:

The study is exploratory, and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a sample size of 16 subjects and a minimum of 12 evaluable subjects is considered sufficient to meet the objectives of the study.

An evaluable subject for the relative bioavailability assessment will have received delafloxacin Powder for Oral Suspension (test) and the oral delafloxacin Tablet (reference) at the same dose level, in the fasted state, and have evaluable PK and safety data to 48 hours post-dose.

An evaluable subject for the food effect assessment will have received delafloxacin Powder for Oral Suspension in the fed and fasted state, at the same dose level, and have evaluable PK and safety data to 48 hours post-dose.

Subjects withdrawn due to an IMP-related AE will not be replaced.

Subjects who are withdrawn for other reasons may be replaced as required, by agreement between the Investigator and the Sponsor, to ensure sufficient evaluable subjects. Up to 4 replacement subjects may be enrolled into the study. The maximum number of subjects that may be dosed is 20.

Duration of Study:

Subjects will receive single administrations of delafloxacin on up to 4 separate occasions. The estimated time from screening until the follow-up phone call is approximately 14 weeks.

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMPs will be used in this clinical study:

IMP Name	Dose	Route of Administration
delafloxacin Tablet, 450 mg (reference)	450 mg[a]	Oral, Fasted
delafloxacin Powder for Oral Suspension, 300 – 600 mg[b]	300 mg – 600 mg[c]	Oral, Fasted or Fed

[a] Each oral delafloxacin Tablet contains 649.35 mg delafloxacin meglumine (salt form) equivalent of 450 mg free acid

[b] Delafloxacin Powder for Oral Suspension will be reconstituted with orange flavoured vehicle

[c] Delafloxacin Powder for Oral Suspension contains 439.5 mg to 878.9 mg delafloxacin meglumine (salt form) equivalent to 300 mg to 600 mg free form

Oral tablets will be administered with a total of 240 mL of water. If required, additional water may be given with the IMP in 50 mL aliquots.

Immediately after administration of delafloxacin Powder for Oral Suspension, the dosing vessel will be rinsed with water and subjects will consume the rinse solution. Subjects will then consume further water to a total volume of 240 mL (including the dosing volume and volume used to rinse the dosing vessel). If required, additional water may be given with the IMP in 50 mL aliquots.

Study Assessments:

The following blood and urine samples will be collected, and assessments performed, at specified time points:

- Delafloxacin in plasma for PK analysis.
- Taste/palatability questionnaire (following delafloxacin Powder for Oral Suspension [i.e., test] regimens only).
- Safety assessments comprising AE monitoring, clinical laboratory tests (clinical chemistry, haematology and urinalysis), physical examinations, single 12-lead ECGs and vital signs.

Statistical Analysis:

PK parameters will be calculated using standard non-compartmental analysis to obtain at a minimum: Tlag, Tmax, Cmax, AUC(0-24), AUC(0-last), AUC(0-inf), Lambda-z, Frel, T1/2, CL/F, Vz/F, and MRT for delafloxacin in plasma, as applicable.

Descriptive summaries for all PK, safety, and taste data by regimen, as applicable, will be provided (including changes from baseline as required).

Formal statistical analysis will be performed on the PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess relative bioavailability. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model, with terms for sequence and regimen as fixed effects, and subject within sequence as a random effect.

Formal statistical analysis will also be performed on the PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess for the effects of food on delafloxacin Powder for Oral Suspension regimens administered at the same dose level. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model, with terms for regimen as fixed effect, and subject as a random effect.

Additionally, formal statistical analysis may be performed on the log-transformed, dose-corrected PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess dose

proportionality, if two dose levels of delafloxacin Powder for Oral Suspension are administered in the same prandial state, using a mixed effect model, with terms for regimen as a fixed effect and subject as a random effect.

4 List of Abbreviations

Abbreviation	Definition
ABSSSI	acute bacterial skin and skin structure infections
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
BID	twice daily
BMI	body mass index
CABP	community acquired bacterial pneumonia
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CSPM	Clinical Sample Processing Manual
CV%	coefficient of variation
CYP	cytochrome P450
DMP	data management plan
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GMR	geometric mean ratios
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
ISF	Investigator Site File

IV	intravenous
MRSA	methicillin resistant *Staphylococcus aureus*
MHRA	Medicines and Healthcare products Regulatory Agency
PIS	Participant Information Sheet
PK	pharmacokinetic(s)
QA	quality assurance
QC	quality control
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	safety advisory committee
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

The pharmacokinetic definitions used in this study are presented in Section 15.3.

5 Background Information

5.1 Introduction

Delafloxacin (also noted as RX-3341, ABT-492, ABT-319492, or WQ-3034, and currently marketed in multiple countries, including in the US as Baxdela® [1], and in the EU as Quofenix® [2]) is an approved, broad-spectrum anionic fluoroquinolone antibiotic for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Melinta Therapeutics, LLC (Melinta; formerly Rib-X Pharmaceuticals) licensed Baxdela® from Wakunaga Pharmaceutical Company in Japan. Prior to its licensing by Melinta, the compound was developed by Abbott Laboratories as an oral formulation (ABT-492) for use in the treatment of community-acquired infections.

Throughout the world, the incidence of antimicrobial resistance has increased for bacterial infections in hospital and community settings. *Staphylococcus aureus*, especially methicillin resistant *S. aureus* (MRSA), ranks as the most frequently isolated pathogen in hospital intensive care units in the US. The Centers for Disease Control and Prevention estimates that MRSA is responsible for more than 300,000 infections, resulting in more than 10000 deaths per year in the US [3]. The risk factors for MRSA are constantly evolving, and the distinction between community-acquired MRSA and hospital-acquired MRSA is becoming less clear from a therapeutic standpoint because of overlapping susceptibility patterns.

Whilst gram-positive pathogens, including *streptococci* and *staphylococci*, are the most common bacteria associated with ABSSSI, gram-negative pathogens must also be considered as causative when selecting initial empiric therapy, particularly in patients with certain comorbid conditions such as diabetes, surgical site infections, anal and perianal region infections, and compromised vascular perfusion [4]. Drug-resistant bacteria are demonstrating alarming trends as causative pathogens in skin and soft tissue infections. Delafloxacin exhibits a concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro [1].

Baxdela® is indicated in adults for the treatment of ABSSSIs and CABP, and can be administered as an intravenous (IV) infusion or as an oral tablet [1]. Melinta is developing an oral suspension formulation as a potential therapeutic for CABP in paediatric patients (target age group 2 months to 18 years). Safety and effectiveness in paediatric patients below the age of 18 years have not been established [5].

This study will evaluate the relative bioavailability of a novel powder for oral suspension formulation of Baxdela®, intended for weight-based paediatric dosing, relative to that of the licensed Baxdela® oral tablet, in approximately 16 healthy adults. Food effect and effect of a change in dose level on bioavailability of the novel powder for oral suspension will also be evaluated.

5.2 Investigational Medicinal Products

The investigational medicinal products (IMPs) that will be used in this clinical study are presented in Table 1.

Table 1 Investigational Medicinal Products

IMP Name	Dose	Route of Administration
delafloxacin Tablet, 450 mg (reference)	450 mg[a]	Oral, Fasted
delafloxacin Powder for Oral Suspension, 300 – 600 mg[b]	300 mg – 600 mg[c]	Oral, Fasted or Fed

[a] Each oral delafloxacin Tablet contains 649.35 mg delafloxacin meglumine (salt form) equivalent of 450 mg free acid
[b] Delafloxacin Powder for Oral Suspension will be reconstituted with orange flavoured vehicle
[c] Delafloxacin Powder for Oral Suspension contains 439.5 mg to 878.9 mg delafloxacin meglumine (salt form) equivalent to 300 mg to 600 mg free form

Delafloxacin Powder for Oral Suspension is an un-licensed medicinal product for use only in the proposed clinical trial.

The oral delafloxacin Tablets to be used in this study are marketed in the US (as Baxdela®). They are to be used in the clinical trial within the terms of the marketing authorisation, other than being administered to healthy volunteers.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments will be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

Where Quotient Sciences is manufacturing the IMPs, suitability of the manufacturing process will be documented in a Pharmaceutical Development and Control Strategy Report.

IMPs will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

5.3 Previous Study Findings

Full details of previous study findings can be found in the Investigator's Brochure (IB) [5]. A summary of the non-clinical and clinical findings is provided below.

5.3.1 Non-clinical Findings

Delafloxacin was demonstrated to have a favourable pharmacokinetic (PK) profile in non-clinical studies, with rapid absorption from the gastrointestinal (GI) tract following oral administration, and extensive distribution into tissues, but with essentially no retention of drug in tissues. The absorption, distribution, metabolism, and excretion study program demonstrated the rat and dog to be acceptable models for studying the non-clinical safety of delafloxacin.

The non-clinical safety assessment of delafloxacin comprised studies of oral and IV acute and repeat-dose toxicology in mice (single dose only), rats, and dogs, and in vitro and in vivo genotoxicity tests and reproductive and developmental toxicity in rats and rabbits. Genotoxicity tests demonstrated a favourable safety margin for clastogenicity in vivo, and a single positive clastogenic finding in vitro. In addition, other evaluations were conducted to evaluate dose formulations and local tolerance and to qualify impurities. The order and timing of studies followed appropriate guidelines and regulatory feedback to allow testing in humans, including women of childbearing potential. Registration non-clinical studies of up to 3 months duration support the clinical treatment duration of

12-hour intervals (i.e., twice daily [BID]) for 5 to 14 days. Primary findings were related to GI effects and included abnormal stool, dilated caecum, decreased food consumption and/or body weights in rats, and emesis, salivation, and abnormal stool/diarrhoea in dogs. Additionally, in dog studies of ≥4-weeks duration, elevations in liver serum enzymes (primarily alanine aminotransferase [ALT] and alkaline phosphatase) without microscopic changes were seen in some dogs. Toxicokinetic measurements were done extensively throughout the programme. Designs for pivotal studies complied with US Food and Drug Administration (FDA) Good Laboratory Practice and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines applicable at the time the studies were conducted.

The primary pharmacology of delafloxacin has been studied in vitro and in vivo with established models to define antimicrobial effects. Delafloxacin was demonstrated to have a favourable PK profile in non-clinical studies, with rapid absorption and extensive distribution into tissues, but with essentially no retention of drug in tissues. The non-clinical pharmacology results with delafloxacin support the use of this drug for the treatment of ABSSSI and other indications.

An extensive core battery of central nervous system (CNS), cardiovascular, and respiratory evaluations was conducted with delafloxacin, including supplemental GI evaluations. These studies did not indicate a risk to human safety, with most effects restricted to high doses/concentrations, associated with delafloxacin plasma concentrations exceeding those observed in clinical studies.

Further details of the non-clinical studies conducted can be found in the IB for delafloxacin [5].

5.3.2 Clinical Findings

Delafloxacin is a broad-spectrum anionic fluoroquinolone antibiotic, approved for administration in adults as IV infusion and oral tablet formulations, and has been marketed for the treatment of adults with ABSSSI and CABP as Baxdela® [1] since 2017 and 2019, respectively, in the US, and as Quofenix® [2] since 2019 and 2021, respectively, in the EU. A total of 32 clinical studies have been completed with oral and IV delafloxacin, including twenty-four Phase 1, four Phase 2 and four Phase 3 studies. In total, approximately 3117 subjects and patients have received delafloxacin in completed trials.

Following oral tablet administration, peak plasma concentrations of delafloxacin occur at a median of 0.8 hours (range 0.5 hours to 4 hours). Delafloxacin maximum mean plasma concentration measured after dosing (Cmax) and area under the mean concentration time curve (AUC) increase proportionally to dose over the range of 50 mg to 1600 mg and 200 mg to 1600 mg, respectively. The absolute bioavailability of oral delafloxacin Tablet is 58.8%. The administration of delafloxacin with food delays absorption and reduces Cmax, but does not alter total absorption (AUC). Thus, delafloxacin can be given without regard to food. The 450 mg delafloxacin commercial tablet and 300 mg IV Captisol® lyophilised formulations are bioequivalent with regard to total exposure (AUC). Multiple oral BID dosing of delafloxacin 450 mg tablets to steady-state results in 1.35-fold higher concentrations of delafloxacin. Delafloxacin is well distributed after IV and oral tablet administration, with a mean volume of distribution at steady state of 34.2 L, which is just below total body water (42 L). Plasma protein binding is approximately 84%.

Delafloxacin is primarily metabolised by glucuronidation, with oxidative metabolism representing <1% of the dose. The glucuronidation of delafloxacin is primarily mediated by UGT1A1 and UGT1A3. Unchanged parent drug is the predominant component in plasma; no single metabolite represents ≥ 20% of circulating components. Delafloxacin is eliminated primarily by renal excretion, but biliary clearance and transintestinal elimination may also play a role. Metabolism accounts for about 20% of the elimination of delafloxacin.

Ten Phase 1 studies have been conducted examining the safety, tolerability, and PK of various oral formulations in single and multiple doses over a range of 50 mg to 1600 mg. The treatment-emergent adverse events (TEAEs) experienced by ≥2% of the subjects in the oral Phase 1 studies were mostly GI related, including diarrhoea (13.5%), headache (8.7%), nausea (5.2%), and abdominal pain (2.8%). These were also the most frequently occurring (≥2%) TEAEs with possible, probable, or definite relatedness to delafloxacin (diarrhoea [12.3%], headache [5%], nausea [4.2%], and abdominal pain [2.8%]). There were no serious adverse events (SAEs) in these trials. Aggregate data suggest a dose response, with a greater frequency and severity of diarrhoea at higher dose levels.

Electrocardiogram (ECG) tracings were routinely collected in all clinical trials conducted; no remarkable effects were noted, and delafloxacin has shown minimal potential to cause corrected QT interval (QTc) prolongation after once daily oral administration at doses of 200 mg, 800 mg, and 1200 mg.

Delafloxacin does not inhibit cytochrome P450 (CYP) enzymes or transporters to any significant degree. In vitro, delafloxacin has been shown to be a mild inducer of CYP3A4; however, an in vivo clinical drug-drug interaction study demonstrated no interactions with midazolam, a sensitive CYP3A4 substrate. Hence, clinically significant drug-drug interactions due to inhibition of CYP-mediated biotransformation of co-administered drugs by delafloxacin are unlikely in humans.

Delafloxacin, at 200 mg/day and 400 mg/day for 6 days, did not demonstrate clinically significant phototoxic potential at any wavelengths tested (295 nm to 430 nm). In particular, the classical pattern of fluoroquinolone phototoxicity as detected in previous phototoxicity studies (i.e., a UVA phenomenon maximal at 24 hours) was not seen.

6 Rationale

6.1 Study Rationale

This study will evaluate the relative bioavailability of a novel powder for oral suspension formulation of Baxdela® (delafloxacin), intended for weight-based paediatric dosing to treat CABP, relative to that of the licensed Baxdela® (delafloxacin) oral tablet, in approximately 16 healthy adults. The novel delafloxacin Powder for Oral Suspension in this study will be reconstituted with a sweetened, flavoured vehicle, selected from a previous basic science study (assessing the taste of an oral suspension with vehicles containing different sweeteners and sweetener/flavour combinations), which demonstrated the most promising taste/palatability profile.

A Phase 1 study exploring food effect of a 900 mg oral delafloxacin tablet administered after a 10 hour fast, or after a high-fat meal, demonstrated no clinically significant food effect [5]. It is planned to explore food effect in this study to determine whether there is a food effect on bioavailability of the novel delafloxacin Powder for Oral Suspension formulation.

As PK and relative bioavailability of a novel formulation of delafloxacin Powder for Oral Suspension compared with the oral delafloxacin Tablet (reference) will be assessed, the study will be open-label.

Randomisation will be used in Periods 1 and 2 to minimise bias in the assignment of subjects to regimens, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across regimens, and to enhance the validity of comparisons. As a single formulation/unit dose will be administered in Period 3 and optional Period 4, no randomisation is required for these periods.

6.2 Dose Rationale

Oral delafloxacin is currently licensed for use at a dose of 450 mg BID [1]. Therefore, a single 450 mg dose has been selected for the relative bioavailability assessment in Periods 1 and 2.

Single oral doses of up to 1600 mg and multiple oral doses of up to 1200 mg have been safely administered to healthy volunteers in previous Phase 1 clinical trials. Single oral doses of delafloxacin Powder for Oral Suspension administered to healthy subjects in either the fasted or fed state will not exceed the highest dose previously administered in healthy subjects (1600 mg), are expected to be safe and well tolerated, and will allow for the development of a dosing regimen for this prototype formulation with similar exposure to the 450 mg oral delafloxacin Tablet (reference) formulation. A food effect study has been conducted using the 900 mg oral delafloxacin Tablet formulation, and the results indicated no clinically significant food effect.

6.3 Population Rationale

As this is a Phase 1 study assessing the PK, relative bioavailability, safety, and taste of delafloxacin, the most relevant population is healthy volunteers, as recommended by the US FDA [6] and the European Medicines Agency (EMA) [7]. Subjects who are non-smokers without a history of alcohol or drug abuse or regular co-medication (except hormonal contraception and hormone replacement therapy [HRT]) are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

Oral delafloxacin Tablet is currently licensed for use in both males and females [1]. Additionally, delafloxacin did not affect the fertility of male and female rats up to the highest IV dose tested (120 mg/kg/day) [8], which is approximately 5-fold the estimated human plasma exposure based on AUC. In embryo-foetal studies in rats and rabbits, orally administered delafloxacin demonstrated no teratogenic effects up to the highest doses tested (1600 mg/kg/day and 1.6 mg/kg/day, respectively). There was also no evidence of differences in tissue accumulation, distribution, or elimination of delafloxacin between repeat orally and intravenously administered delafloxacin in pregnant rats. However, the potential for delafloxacin to be excreted in human milk has not been studied. Therefore, females of childbearing potential will be allowed to participate in the study, as long as they comply with the contraception requirements detailed in Section 9.4; male subjects must also comply with these requirements. Additionally, pregnant or lactating females, or male subjects with pregnant or lactating female partners, will not be permitted take part in the study.

Based on the above considerations and the target population, healthy male and healthy non-pregnant, non-lactating female subjects aged 18 to 55 years, inclusive, are considered suitable for this study.

6.4 Risks and Benefits

6.4.1 Risks Associated with Delafloxacin Administration

Delafloxacin is a fluoroquinolone; this class of antibacterial drugs have been associated with disabling and potentially irreversible serious adverse reactions (SARs) from different body systems that can occur together in the same patient. Commonly seen adverse reactions to fluroquinolones include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and CNS effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving fluoroquinolone therapy, including delafloxacin. Clostridium difficile-associated diarrhoea has also been reported in users of nearly all systemic antibacterial drugs, including delafloxacin, with severity ranging from mild diarrhoea to fatal colitis. Subjects will not be permitted to participate in the study if they experience SARs or serious hypersensitivity to any drug or formulation excipients, or any previous hypersensitivity to fluoroquinolones, including delafloxacin, or if they have acute diarrhoea or constipation in the 7 days before the predicted first study day.

Fluoroquinolones have also been associated with disturbances of blood glucose, including symptomatic hyperglycaemia and hypoglycaemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glyburide) or with insulin. Epidemiologic studies report an increased risk of aortic aneurysm and dissection within two months following use of fluoroquinolones, particularly in elderly patients. The cause for the increased risk has not been identified; therefore, only healthy subjects aged 18 to 55 years, inclusive, will be eligible to take part in the study.

Unlike some other fluoroquinolones, in pre-clinical studies, delafloxacin does not prolong QTc, alter glucose levels, induce convulsions, cause phototoxicity, or lead to microscopic changes in the liver, kidney, bone marrow, or eye. Phase 1 clinical trials with delafloxacin have also demonstrated no effect on QTc, and no phototoxicity. Compared to other fluoroquinolones, the structural attributes of delafloxacin are unique, thereby potentially reducing the risk of adverse events (AEs) common to other fluoroquinolones. For example, delafloxacin does not bind melanin and was designed structurally to minimise the potential for phototoxicity. Delafloxacin has not shown an increase in AEs of special interest that have been associated with the quinolone class when compared to non-quinolone comparators. The safety/general pharmacology and toxicology studies support the use of delafloxacin in the clinic and it is approved for the treatment of ABSSSI and CABP in patients. However, subjects participating in this study will undergo extensive safety assessments to monitor any potential risks associated with fluroquinolones, including the following: AE monitoring, physical examinations, vital signs, ECGs, and clinical laboratory tests (clinical chemistry, haematology and urinalysis).

Due to its shape and anionic nature, delafloxacin at clinically relevant concentrations does not inhibit GABA/N-methyl-D-aspartate and muscarinic receptors, which have been associated with CNS events and/or tendinopathies. Therefore, CNS assessments, such as the Columbia-Suicide Severity Rating Scale assessment, are not considered necessary for this Phase 1 study in healthy subjects.

Based on clinical trials previously conducted with delafloxacin, the expected adverse drug reactions (ADRs) occurring in >2% of subjects are nausea, vomiting, diarrhoea, transaminase elevation, and headache. Subjects will be monitored for TEAEs while resident in the clinical unit, until the end of the study, and will be treated symptomatically

(if required). Any subject experiencing significant increases in transaminases e.g., ALT concentration >3 × the upper limit of the reference range, will be withdrawn from further dosing (see Section 8.3 for further details).

The potential effects of delafloxacin on the reproductive capacity of animals has been investigated in a number of non-clinical studies; additionally, oral delafloxacin Tablet (Baxdela®) is currently licensed for use in males and females [1]. Female subjects of childbearing potential who are not pregnant or lactating will be allowed to participate in the study, and all subjects will be required to comply with the contraception requirements in Section 9.4.

6.4.2 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the time in which the study is conducted during the Coronavirus Disease 2019 (COVID-19) pandemic.

6.4.2.1 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a subject developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP – as a fluoroquinolone antibacterial – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a subject would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy subjects enrolled in the study.

6.4.2.2 General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient Sciences' monitoring and prevention control measures.

COVID-19 testing may be performed based on current infection rates and availability of tests. If required, testing will comprise an antigen test performed at screening and/or on Day -1 of each treatment period, prior to admission to the clinical unit, and discharge or the day before discharge from each treatment period. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick-Off Meeting minutes or in a file note if the study is ongoing.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

6.4.2.3 COVID-19 Vaccine-Related Risk

Based on the mechanism of action of the IMP – as a fluoroquinolone antibacterial – there is no perceived impact on the safety of the study subjects, or on the study objectives, for subjects who may receive these vaccines. It is also very unlikely that administration of the IMP would interfere with COVID-19 vaccination response; however, no specific pre-clinical or clinical investigations have been conducted at this point with delafloxacin. Therefore, subjects will not be permitted to receive a COVID-19 vaccination within 2 days (48 hours) prior to admission and for the duration of the study.

6.4.3 General Risks and Overall Risk-Benefit Assessment

Collecting a blood sample from a vein may cause pain, swelling, bruising, light-headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

ECG stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

There is no benefit to the subjects from taking part in this study. The development of a product to treat CABP in paediatric patients will be of benefit to paediatric patients with CABP.

The overall risk benefit balance is therefore considered to be acceptable.

7 Objectives and Endpoints

Objectives	Endpoints
Primary To determine the relative bioavailability of delafloxacin Powder for Oral Suspension compared to that of oral delafloxacin Tablet reference	Results of the formal statistical analysis of overall exposure (AUC) for delafloxacin Powder for Oral Suspension, compared to oral delafloxacin Tablet reference
Secondary To determine the PK of delafloxacin Powder for Oral Suspension formulation	PK parameters for delafloxacin: Tlag, Tmax, Cmax, AUC(0-24), AUC(0-last), AUC(0-inf), lambda-z, Frel,T1/2, CL/F, Vz/F, and MRT, as applicable
To determine the relative bioavailability of delafloxacin Powder for Oral Suspension in the fed and fasted state	Results of the formal statistical analysis of overall exposure (AUC) for delafloxacin Powder for Oral Suspension in the fed state compared to the fasted state
To provide additional safety and tolerability information for orally administered delafloxacin	Assessment of AEs, vital signs, ECGs, physical examinations, and clinical laboratory tests
Exploratory To evaluate the taste/palatability attributes (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste) and overall acceptability of delafloxacin Powder for Oral Suspension	Results of the taste questionnaire

8 Study Design

8.1 Study Plan

This is a Phase 1, single centre, single part, partially randomised, open-label, relative bioavailability study in healthy subjects.

It is planned to enrol approximately 16 healthy male and healthy non-pregnant, non-lactating female subjects.

An evaluable subject for the relative bioavailability assessment will have received delafloxacin Powder for Oral Suspension (test) and the oral delafloxacin Tablet

(reference) at the same dose level, in the fasted state, and have evaluable PK and safety data to 48 hours post-dose.

An evaluable subject for the food effect assessment will have received delafloxacin Powder for Oral Suspension in the fed and fasted state, at the same dose level, and have evaluable PK and safety data to 48 hours post-dose.

It is planned to administer up to four regimens (Table 2).

Table 2 Description of Regimens

Period	Regimen	Investigational Medicinal Product	Dose	Route of Administration
1 and 2	A	delafloxacin Tablet (reference)	450 mg	Oral, Fasted
	B	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	450 mg	Oral, Fasted
3	C	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	450 mg or XX mg	Oral, Fed or Oral, Fasted
4 (optional)	D	delafloxacin Powder for Oral Suspension, reconstituted with orange flavoured vehicle	XX mg or YY mg	Oral, Fed or Oral, Fasted

Details of the IMPs are provided in Section 5.2. The order in which regimens are dosed may be subject to change due to logistical reasons

The effect of food on the PK of a novel delafloxacin Powder for Oral Suspension formulation may be explored in Period 3 or optional Period 4, by administering IMP after a high-fat breakfast. The effect of increasing or decreasing the dose level may also be explored.

There will be an interim decision meeting after Periods 2 and 3 to review the PK and safety data for up to 48 hours post-dose from preceding periods, in order to determine the dose and prandial state for Regimen C and Regimen D (if applicable).

There will be a minimum washout of 4 days between dosing in Periods 1 and 2. The intervals between Periods 2 and 3, and Period 3 and optional Period 4, will require a minimum of 14 days, to permit the interim decision process and IMP manufactures.

The study will follow the design in Figure 1.

Subjects will undergo preliminary screening procedures for the study at the screening visit (Day -28 to Day -2).

Periods 1 and 2

Subjects will be admitted in the morning on the day before dosing (Day -1) in Period 1. Subjects will receive a snack in the evening, after which they will fast overnight from all food and drink (except water) for a minimum of 10 hours. Subjects will be administered IMP on the morning of Day 1 in the fasted state. Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration (Regimen B only).

Subjects will be randomised in a 1:1 ratio to one of two sequences (AB or BA) immediately prior to dosing in Period 1, for allocation of regimens across Periods 1 and 2.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose during each period. Subjects will remain resident in the clinical unit during the washout period (minimum 4 days) between Periods 1 and 2. Subjects will be discharged from the clinical unit at 48 hours post-dose (Day 3) in Period 2.

Following dosing of Regimens A and B, there will be an interim decision meeting to review available PK and safety data to decide the dose level and prandial state for Regimen C. The Investigator and Sponsor will decide whether to continue to evaluate a 450 mg dose level of delafloxacin Powder for Oral Suspension following a high-fat breakfast, or to evaluate an alternative dose level in the fasted state.

Period 3

Subjects will be admitted in the evening on the day before dosing (Day -1). Subjects will fast overnight from all food and drink (except water) for a minimum of 10 hours, and will be administered IMP on the morning of Day 1 in the fasted state (if a different dose level is selected), or approximately 30 minutes after a high-fat breakfast (if a change to prandial state is selected). Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose (Day 3), at which time subjects will be discharged from the clinical unit.

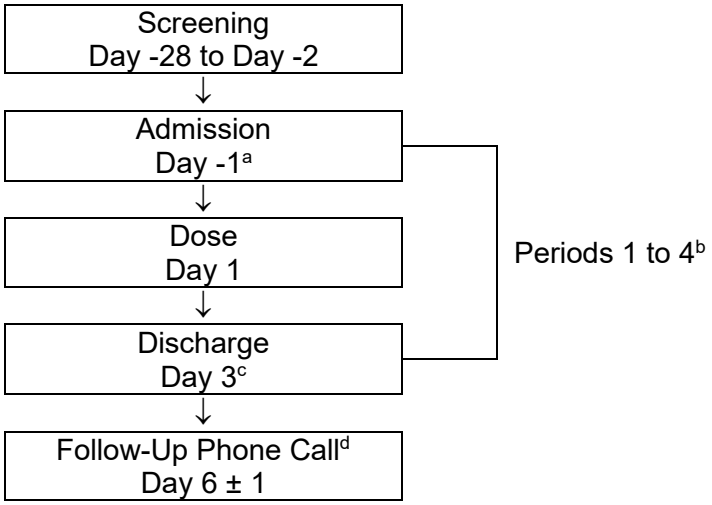
Following dosing of Regimen C, there will be an interim decision meeting to review available PK and safety data, to decide whether to proceed with optional Period 4 or whether to end the study. If it is decided to end the study, a follow-up phone call will take place on Day 6 ± 1 to ensure the ongoing wellbeing of subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit. End of study is defined as completion of the last follow-up phone call or unscheduled follow-up visit. If it is decided to proceed with optional Period 4, the dose level and prandial state for Regimen D will be determined; the Investigator and Sponsor will decide whether to continue to evaluate the dose level selected for Regimen C following a high-fat breakfast, or to evaluate an alternative dose level in the fasted state.

Optional Period 4

Subjects will be admitted in the evening on the day before dosing (Day -1). Subjects will fast overnight from all food and drink (except water) for a minimum of 10 hours, and may be administered IMP on the morning of Day 1 in the fasted state (if a different dose level is selected), or approximately 30 minutes after a high-fat breakfast (if a change to prandial state is selected). Subjects will complete a written taste/palatability questionnaire individually and privately following IMP administration.

Blood and urine samples will be collected at regular intervals for PK and safety analysis, as applicable, from admission until 48 hours post-dose (Day 3), at which time subjects will be discharged from the clinical unit. A follow-up phone call will take place on Day 6 ± 1 to ensure the ongoing wellbeing of subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit; completion of the last follow-up phone call or unscheduled follow-up visit will be considered the end of the study.

Figure 1 Study Sequence



[a] Subjects will be admitted to the clinical unit in the morning on the day before dosing (Day -1) in Period 1, and in the evening on the day before dosing (Day -1) in Period 3 and optional Period 4. Subjects will remain resident in the clinical unit between Periods 1 and 2; therefore, no admission procedures will be conducted for Period 2

[b] Period 4 is optional

[c] Periods 2 to 4 only. Subjects will remain resident in the clinical unit between Periods 1 and 2; there will be a minimum washout of 4 days between dosing in Periods 1 and 2

[d] A follow-up phone call will take place on Day 6 ± 1 of the final treatment period, to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit

8.2 Criteria for In-Study Decisions

In-study decisions will be made by the safety advisory committee (SAC), which will always comprise the Investigator, the Sponsor's representative medical monitor or the Sponsor's medically qualified designee who is familiar with the study protocol and IB, and a PK expert where appropriate.

8.2.1 Decision Points

The following in-study decisions will be made during this study:

- Dose level and prandial status selection for Regimen C.
- Whether to proceed with optional Period 4.
- Dose level and prandial status selection for Regimen D (if applicable).

8.2.2 Criteria for Dose Level and Prandial Status Selection

Dose level and prandial status selection for Regimen C and Regimen D (if applicable) will only be made after a complete review of all data collected from the previous dose period(s). For dose level and prandial status selection to occur, data must be available from a minimum of 12 subjects who have completed the planned PK and safety assessments up to 48 hours after dosing. If data are not available for 12 subjects, the Investigator, Scientific Lead, and Sponsor will take a decision as to whether the data available are sufficient to support the dose level and prandial status selection decision. If data in fewer subjects are used in the decision process, additional subjects will not be dosed to increase the number of subjects in the completed regimen; however, additional subjects may be enrolled to achieve the target number of subjects for subsequent regimens.

Regimens C and D will only be administered in the fed state if the selected dose level has previously been administered in the fasted state.

The following data are required:

- AEs.
- Vital signs.
- ECGs.
- Safety laboratory tests.
- Plasma concentrations of delafloxacin.
- PK parameter estimates (Cmax, Tmax, AUC(0-last), AUC(0-inf) and Frel comparisons) up to 48 hours post-dose.

The dose(s) selected for Regimen C or Regimen D (if applicable) will only be selected from the design space of 300 mg to 600 mg.

The decisions on dose level and prandial status will be made by the SAC. The decision will be documented and signed by the Investigator as per Quotient Sciences' current standard operating procedure (SOP). Evidence of the decision will be retained in the ISF.

8.3 Subject Withdrawal

If a subject wishes to leave the study at any time, they will be permitted to do so. Every reasonable effort will be made by Quotient Sciences to complete a final assessment/discharge procedures. Quotient Sciences will advise the Sponsor of the withdrawal of any subject from the study.

Early withdrawal is defined as the date of the decision to withdraw the subject from the study. Subject completion is defined as the date of the last procedure conducted or last contact (e.g., follow-up phone call or unscheduled follow-up visit) for that subject.

If a subject requests to leave the clinical unit earlier than the planned discharge time e.g., due to unforeseen personal circumstances, but aims to return to the clinical unit to complete the study, this will be documented as a subject self-discharge and a protocol deviation. The subject must complete the planned assessments/discharge procedures before discharge from the clinical unit, and may return for the next study period/assessments, as planned following agreement between the Sponsor and the Investigator.

Subjects will be withdrawn from the study drug(s) for the following reasons:

- Experiencing a serious or severe AE including but not limited to:
  - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG).
  - ALT concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test).
- Pregnancy.
- Termination of the study.
- Upon the subject's request (withdrawal of consent).
- Significant deviation from the protocol.
- Concurrent illness that would adversely affect subject safety or data integrity or requirement for prohibited medication.

- At the discretion of the Investigator.

For the purpose of withdrawal criteria, baseline will be considered as the last available assessment prior to dosing in Period 1.

For a subject who withdraws because of an IMP-related AE, every effort will be made to ensure the subject completes follow-up procedures.

Early withdrawal of consent by the subject to participate in any further activities will be distinguished from withdrawal for any of the other above reasons.

8.4 Subject Replacement

Withdrawn subjects may be replaced, at the discretion of the Investigator and Sponsor, with the aim of ensuring that the objectives of the trial can be met.

Replacement subjects enrolled will be dosed with the next planned regimen of the withdrawn subject, and they will not receive any regimen that the withdrawn subject has already received, with the exception of the need to increase subject numbers to obtain the minimum number of evaluable subjects required for interim decisions, and to obtain data in any other regimen that is required for a valid comparison e.g., test vs reference, fed vs fasted.

Any subject withdrawn due to an IMP-related AE will not be replaced.

Subjects withdrawing for other reasons may be replaced.

Up to 4 replacement subjects may be enrolled into the study. The maximum number of subjects that may be dosed is 20.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A SAR (i.e., a SAE considered at least possibly related to the IMP administration) in 1 subject.
- Severe non-serious adverse reactions (i.e., severe non-serious AE considered as at least possibly related to the IMP administration) in 2 subjects in the same cohort, independent of within or not within the same system organ class.

Relatedness to IMP will be determined by the Investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

8.6 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor and Investigator without consultation with the MHRA and EC. Notification of early termination must be provided to the MHRA and EC

immediately, and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow-up measures taken for safety reasons, if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the Investigator or Sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

8.7 Lost to Follow-up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and cannot be contacted by the clinical unit.

If a subject fails to return to the clinical unit for a required study visit:

- The clinical unit must attempt to contact the subject and reschedule the missed visit as soon as possible.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (e.g., three telephone calls on three separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented in the subject's source.
- If the subject cannot be contacted, they will be considered lost to follow-up.

8.8 Treatment Assignment and Randomisation

Periods 1 and 2 are randomised; therefore, a randomisation schedule will be produced for these periods.

Instructions to dispense and dose will be produced prior to dosing using the randomisation schedule and will be retained in the ISF.

The original randomisation schedule and proof of quality control (QC) procedures will be held by the Data Sciences department at Quotient Sciences until the study is archived, at which time the randomisation materials will be retained in the ISF.

Using a computer-generated randomisation schedule, subject numbers will be allocated to one of two sequences in a 1:1 ratio (AB or BA [see Table 2 for regimen details]). The allocation will be balanced, with 8 subjects receiving each sequence.

Subjects will be randomised immediately prior to dosing in Period 1.

Period 3 and optional Period 4 are non-randomised; therefore, a randomisation schedule will not be produced for these periods. Instructions to dispense and dose will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The instructions to dispense and dose will be retained in the ISF.

8.8.1 Subject Numbers

Subject numbers will be allocated on the morning of dosing according to the code [redacted] to [redacted] using the lowest number available. Replacement subjects will be allocated subject numbers [redacted] to [redacted] where the last two digits are the same as those of the original subject (e.g., if Subject [redacted] withdraws, the replacement will have the Subject

Number [redacted] and will receive any regimens which Subject [redacted] did not receive, in addition to any regimens which are required to make the required comparison of interest).

8.8.2 Blinding

This is an open-label study and therefore blinding is not required.

9 Selection of Subjects

Subjects will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not been dosed in a study within 90 days of the planned first dose date of this study, or less than 5 elimination half-lives prior to the planned first dose date of this study, whichever is longer.

9.1 Informed Consent

Subjects will be provided with a written explanation of the study at least the day before the screening visit. Additionally, subjects may be provided with an information video before the screening visit that introduces them to the study. In the video and/or during the screening visit, a physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies nationally. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an informed consent form (ICF). Until written consent has been obtained from the subject no study specific procedure or investigation will be performed. If an amendment is made to the participant information sheet (PIS), participants will be re-consented to the most current version of the ICF(s) where appropriate.

9.2 Inclusion Criteria

Informed Consent and Compliance

1. Must provide written informed consent.
2. Must be willing and able to communicate and participate in the whole study.

Demographics and Contraception

3. Aged 18 to 55 years inclusive at the time of signing informed consent.
4. Must agree to adhere to the contraception requirements defined in Section 9.4.

Baseline Characteristics

5. Healthy males or non-pregnant, non-lactating healthy females.
6. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 as measured at screening.
7. Weight ≥50 kg at screening.

Inclusion criteria 2, 4 and 5 from the list above will be re-assessed at admission/pre-dose of Period 1.

9.3 Exclusion Criteria

Medical/Surgical History and Mental Health

1. SAR (severe adverse reaction) or serious hypersensitivity to any drug or formulation excipients.
2. Any history of hypersensitivity to delafloxacin or any other fluroquinolones or previous history of tendon disorders related to fluroquinolone administration.
3. Presence or history of clinically significant allergy requiring treatment, as judged by the Investigator. Hay fever is allowed unless it is active.
4. History of clinically significant cardiovascular, renal, hepatic, respiratory, particularly GI disease, especially peptic ulceration, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome, and neurological or psychiatric disorders.
5. Subjects with a history of cholecystectomy or gallstones.
6. Acute diarrhoea or constipation in the 7 days before the predicted Day 1. If screening occurs >7 days before the Day 1, this criterion will be determined on Day 1. Diarrhoea will be defined as the passage of liquid faeces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as a failure to open the bowels more frequently than every other day.
7. Subject has a medical condition that may adversely affect taste or smell activity including but not limited to mouth ulcers, significant gum disease, and respiratory and/or sinus infection or cold.
8. Subject does not agree to the consumption of, or has any known allergies to, the formulation excipients.

Physical Examination

9. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the Investigator or delegate at screening or admission.

Diagnostic Assessments

10. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the Investigator (laboratory parameters are listed in Appendix 1). Subjects with Gilbert's Syndrome are not allowed.
11. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), or human immunodeficiency virus (HIV) 1 and 2 antibody results.
12. Females who are pregnant or lactating (all female subjects must have a negative highly sensitive urine or serum pregnancy test).

Prior Study Participation

13. Subjects who have received any IMP in a clinical research study within the 90 days of the planned first dose date, or less than 5 elimination half-lives prior to the planned first dose date, whichever is longer.
14. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood.

Prior and Concomitant Medication

15. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day, hormonal contraception, or HRT) in the 14 days before the first dose of IMP (see Section 11.4). Exceptions may apply, as determined by the Investigator, if each of the following criteria are met: medication with a short half-life if the washout is such that no pharmacodynamic activity is expected by the time of dosing with IMP; and if the use

of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study.
16. Subjects who are taking, or have taken, any antibacterial medications, antacids, medications containing multivalent cations or metal cations, multivitamin preparations containing zinc or iron, or didanosine buffered tablets within 14 days prior to the first dose of IMP.
17. Subjects who have had a COVID-19 vaccine within 2 days (48 hours) prior to admission.

Lifestyle Characteristics

18. History of any drug or alcohol abuse in the past 2 years.
19. Regular alcohol consumption in males >21 units per week and in females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
20. A confirmed positive alcohol breath test at screening or admission.
21. Current smokers and those who have smoked within the last 12 months.
22. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months.
23. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
24. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1) at screening or admission.

Other

25. Male subjects with pregnant or lactating partners.
26. Subjects who are, or are immediate family members of, a study site or Sponsor employee.
27. Subjects who do not agree to eat a high-fat breakfast.
28. Failure to satisfy the Investigator of fitness to participate for any other reason.

Exclusion criteria 3, 6, 7, 9, 10, 12, 14, 15, 16, 17, 20, 23, 24, 25 and 28 from the list above will be re-assessed at admission/pre-dose in Period 1.

Healthy subjects who do not meet the inclusion/exclusion criteria for the study will not be enrolled.

9.4 Contraception and Restrictions

Male Subjects with Partners of Childbearing Potential

Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 93 days after last IMP administration. This has been calculated based on 90 days (one cycle of spermatogenesis) plus 5 half-lives of the IMP. Five half-lives has been calculated as 3 days.

The following methods are acceptable:

- Partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

- Partner's use of progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system
- Partner's use of intrauterine device.
- Vasectomised.
- Partner's bilateral tubal occlusion.

These contraception requirements are considered to be more conservative than the guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [9].

Males with Partners of Non-childbearing Potential

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to sexual partners. Therefore, even if a male is sexually active with a partner of non-childbearing potential they will be required to use a condom from first administration of IMP until the follow-up phone call.

Female Subjects of Childbearing Potential

Female subjects who are sexually active and of childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until 33 days after last IMP administration. This has been calculated based on 30 days (one female menstrual cycle) plus 5 half-lives of the IMP. Five half-lives has been calculated as 3 days.

The following highly effective methods are acceptable:

- Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation.
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system
- Intrauterine device.
- Vasectomised partner.
- Bilateral tubal occlusion.

Female subjects are not required to use any of the above contraceptive methods if their sexual partner is female.

These contraception requirements are considered to be more conservative than the guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [9].

All Male Subjects and Female Subjects of Childbearing Potential

Alternatively, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Females of Non-Childbearing Potential

Female subjects who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential unless post-menopausal or permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a follicle stimulating hormone (FSH) result of ≥40 IU/L.

9.4.1 Sperm Donation

Male subjects should not donate sperm for the duration of the study and for 93 days after last IMP administration.

9.4.2 Egg Donation

Female subjects should not participate in egg donation from dosing, for the duration of the study and for at least 33 days after last IMP administration.

9.5 Pregnancy

Subjects will be instructed that if they/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/subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the subject/subject's partner and, if granted, any pregnancy will be followed and the status of mother and/or child(ren) will be reported to the Sponsor after delivery. Any subject reporting a pregnancy during the study will be discontinued from the study treatment and every reasonable effort will be made by Quotient Sciences to follow up the pregnancy until delivery.

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

9.6 Additional Study Restrictions

The following additional restrictions will be in place for the duration of the study:

1. Subjects must not eat anything likely to disturb GI transit (e.g., spicy or high-fat meals such as curry or fish and chips, or foods of a high-fibre content, such as All-Bran) for 24 hours prior to each admission until discharge from the clinical unit.
2. Subjects must abstain from alcohol during the 24 hours prior to screening and the 24 hours prior to each admission until discharge from the clinical unit.
3. Subjects must not drink liquids or eat food containing grapefruit, cranberry, caffeine or other xanthines from 24 hours prior to each admission until discharge from the clinical unit.

4. Subjects should refrain from eating food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to each admission until discharge from the clinical unit.
5. Subjects must not take part in any unaccustomed or strenuous exercise from the 72 hours before the screening visit and then from 72 hours prior to each admission until discharge from the clinical unit.
6. Must not donate blood or plasma (outside of this study), from clinical unit admission, from screening, throughout the study duration, and for at least 90 days following last dose of study medication.

The additional restrictions above are not exclusion criteria; if non-compliance occurs, a protocol deviation will be completed.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments in Appendix 2, and in accordance with Quotient Sciences' SOPs unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose, all subjects will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the schedule of assessments.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures will be repeated at the discretion of the Investigator.

Screening safety procedures such as clinical laboratory tests, ECGs, vital signs, alcohol breath tests, carbon monoxide breath tests and urinalysis can be repeated as clinically indicated under the discretion of the Investigator or Sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the trial.

10.1.1 Subject Re-Screening

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e., subject has not been dosed with IMP); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

10.2 Admission and Pre-dose Procedures

The identity of the subjects will be confirmed at each admission and pre-dose.

In addition, the ongoing eligibility of subjects will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

Admission/pre-dose safety procedures such as clinical laboratory tests, ECGs, vital signs, urinalysis and drugs of abuse tests can be repeated as clinically indicated under the discretion of Investigator or Sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the clinical trial.

Reserve subjects for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days.

If dosing is delayed, subjects who have completed admission procedures do not need admission procedures to be repeated if dosing is within 2 days and the subjects have remained resident in the clinical unit.

The subjects will be admitted to the clinical unit in the morning on the day before dosing (Day -1) in Period 1, and in the evening on the day before dosing (Day -1) in Period 3 and optional Period 4. Subjects will remain resident in the clinical unit between Periods 1 and 2; therefore, no admission procedures will be conducted for Period 2.

In addition, subjects may be required to visit the clinical unit on Day -1 of Periods 1, 3, and optional Period 4, prior to admission to the clinical unit, for SARS-CoV-2 antigen tests (if required; see Sections 6.4.2.2 and 14.5.8).

The admission and pre-dose procedures are presented in the schedule of assessments.

10.3 Study Day Procedures

10.3.1 Blood Volume

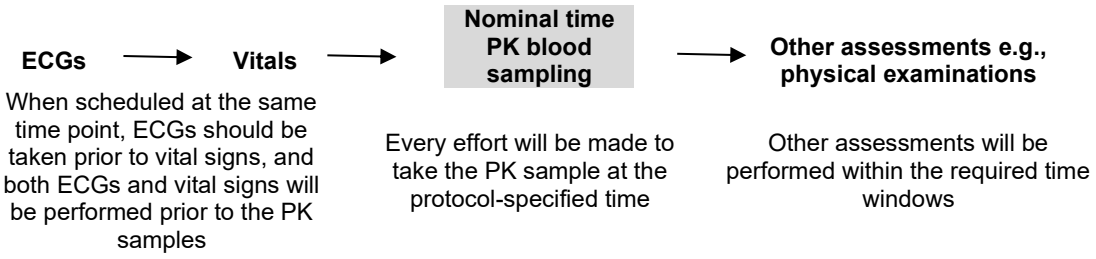
The number and timing of samples may be amended following any interim PK parameter estimations. However, in this case, the total blood volume for each subject will not exceed 550 mL in a 4-week period.

The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point.

As guidance, the preferred order of assessments is:



All safety assessments will be timed and performed relative to the start of dosing.

10.3.3 Discharge from the Clinical Unit

A subject will be allowed to leave the premises without additional Investigator or Sub-investigator review, following completion of study-specific procedures providing that:

- No AEs have been reported during the study visit
- The subject responds in the affirmative when asked if they are feeling well

Refer to Section 8.1 for further details, and the schedule of assessments for study-specific procedures at subject discharge. As subjects will remain resident in the clinical unit between Periods 1 and 2, discharge procedures will apply to Periods 2 to 4 only.

If any of these conditions are not met, then the subject will only be allowed to leave the clinical unit with the authorisation of the Investigator or Sub-investigator.

There will be no continued provision of the study intervention or treatment for subjects, as this study involves healthy volunteers only.

10.3.4 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines [10], each subject will receive a card stating the telephone number of the Investigator and the 24/7 contact details of the Quotient Sciences' on-call physician.

10.3.5 Follow-up

A follow-up phone call will take place on Day 6 ± 1 of the final treatment period, to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for an (unscheduled) follow-up visit; assessments may be performed at the unscheduled follow-up visit, as detailed in the schedule of assessments. Completion of the last follow-up phone call or unscheduled follow-up visit will be considered the end of the study.

11 Dosing of Subjects

Dosing will be performed at the time points detailed in the study schedule of assessments in Appendix 2.

11.1 Food and Fluid Intake

Subjects will be allowed water up to 1 hour before the scheduled dosing time and will be provided with 240 mL of water at 1 hour post-dose (to ensure adequate hydration) and thereafter, water will be allowed ad libitum after 1 hour post-dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

If, for technical reasons, dosing is delayed for more than 2 hours beyond the expected dosing time, subjects will receive 200 mL of an electrolyte drink (e.g., Lucozade Sport) at the originally scheduled dosing time, or earlier if possible.

Fasted Dosing

Fasted dosing will apply to regimens in Periods 1 and 2, and may apply to regimens in Period 3 or optional Period 4, unless fed dosing is selected during the relevant interim decision meeting, based on available PK and safety data.

The calorie/fat content of meals are not required to be controlled. Subjects will be provided with a standardised menu.

Subjects will be provided with a snack and then fast from all food and drink (except water) for a minimum of 10 hours on the day prior to dosing until approximately 4 hours post-dose, at which time lunch will be provided. An evening meal will be provided at approximately 10 hours post-dose and an evening snack at approximately 14 hours post-dose. On subsequent days, meals will be provided at appropriate times.

Fed Dosing

Fed dosing may be selected for regimens in Period 3 or optional Period 4.

The calorie/fat content of breakfast will be controlled on Day 1 (refer to Appendix 4 for breakfast content). Subjects will be provided with a standardised menu for all other meals.

For fed regimens, a high-fat breakfast will be given approximately 30 minutes before dosing.

Subjects will be provided with a snack and will fast for a minimum of 10 hours from all food and drink (except water) until the following morning, when they will be provided with a high-fat breakfast.

The breakfast should be consumed over a maximum period of 25 minutes, with dosing occurring 30 ± 5 minutes after the start of breakfast. Subjects should be encouraged to eat their meal evenly over the 25 minute period. It is acknowledged that some subjects will take less time to eat, but dosing should still occur 30 ± 5 minutes after the start of breakfast. Subjects must consume at least 90% of the pre-dose breakfast in order to be eligible for dosing. The start and stop time and percentage of the breakfast consumed must be recorded in the source.

Lunch will be provided at approximately 4 hours post-dose, an evening meal at approximately 10 hours post-dose and an evening snack at approximately 14 hours post-dose. On subsequent days, meals will be provided at appropriate times.

11.2 Administration of Test Preparations

Specific details of IMPs, and doses to be administered, are provided in Section 5.2 and Section 8.1, respectively. Subjects will be dosed on the morning of Day 1 of each study period.

The exact time of dosing will be decided based on logistics and will be documented in the source. The order in which regimens are dosed may be subject to change due to logistical reasons.

The minimum washout period between regimens may be changed, if data collected during the study support the change. However, the minimum washout period will not be reduced to less than 5 half-lives of the IMP.

Subjects will receive single administrations of delafloxacin on up to 4 separate occasions.

Oral tablets will be administered with a total of 240 mL of water. If required, additional water may be given with the IMP in 50 mL aliquots and will be recorded in the source but will not be classed as a protocol deviation.

Immediately after administration of delafloxacin Powder for Oral Suspension, the dosing vessel will be rinsed with water and subjects will consume the rinse solution. Subjects will then consume further water to a total volume of 240 mL (including the dosing volume and volume used to rinse the dosing vessel). If required, additional water may be given with the IMP in 50 mL aliquots and will be recorded in the source but will not be classed as a protocol deviation.

11.3 Dosing Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration.

Mouth and hand checks will be conducted after dosing, as applicable, to ensure that the IMP has been swallowed.

The date and time that each subject is dosed will be recorded in the subject's source data. Any violation of compliance will require evaluation by the Investigator and Sponsor to determine if the subject can continue in the study.

11.4 Prior and Concomitant Medications

No prescribed, over-the-counter medication or herbal remedies will be permitted from 14 days before the first dose of IMP until the follow-up phone call, except up to 4 g of paracetamol per day, hormonal contraception, or HRT, and those deemed necessary by the Investigator to treat AEs (see also Section 9.3). Any medications used will be recorded in the source.

Subjects are not permitted to receive antibacterial medications, antacids, medications containing multivalent cations or metal cations, multivitamin preparations containing zinc or iron, or didanosine buffered tablets in the 14 days before the first dose of IMP until the follow-up phone call.

Subjects are not permitted to receive a COVID-19 vaccine within 2 days (48 hours) prior to each admission, so that by the time of dosing, any effects of the vaccine (e.g., pyrexia, fatigue, pain/stiffness at site of injection) are likely to have abated. Additionally, COVID-19 vaccines will not be accepted concomitant medications for the duration of the study.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

Medication taken within 14 days of informed consent will be recorded in the source.

12 Assessment of Efficacy

Not applicable for this Phase 1 study.

13 Assessment of Pharmacokinetics, Taste/Palatability and Pharmacodynamics

PK assessments will be performed as detailed in the study schedule of assessments in Appendix 2.

13.1 Assessment of Pharmacokinetics

13.1.1 Pharmacokinetic Blood Sampling

Venous blood samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study. Samples will be processed to isolate plasma and PK analysis will be carried out on plasma samples.

Plasma samples will be sent for laboratory testing in linked anonymised form (subject number only). This information is able to be linked directly to the volunteer by the Quotient Sciences research team and study monitor, however not by the laboratory staff or Sponsor.

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture at the time points detailed in the schedule of assessments.

All PK windows will be timed relative to the start of dosing for each period.

The acceptable deviations from the nominal blood sampling times are as follows:

- Day 1: The pre-dose sample will be taken ≤1 hour before dosing.
- 0 to 1 hour post-dose samples will be taken within ± 2 minutes of the nominal post-dose sampling time.
- 1.5 hours to 12 hours post-dose samples will be taken within ± 10 minutes of the nominal post-dose sampling time.
- 14 hours to 48 hours post-dose samples will be taken within ± 30 minutes of the nominal post-dose sampling time.

The timing and number of the samples may be amended following any interim PK parameter estimations, including collection over a longer duration. Any changes to blood sampling time points would be documented in the interim dose decision report and retained in the ISF.

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the Clinical Sample Processing Manual (CSPM).

Samples will be shipped to PPD, Inc. for the analysis of delafloxacin.

13.2 Assessment of Pharmacodynamics

Not applicable for this Phase 1 study.

13.3 Taste/Palatability Evaluation

Taste/palatability will be assessed using a questionnaire (example provided in Appendix 3) at the time points detailed in the schedule of assessments. The questionnaire will ask subjects to rate the overall acceptability of taste/palatability of each of the delafloxacin Powder for Oral Suspension (i.e., test) regimens, with additional questions asked on specific taste/palatability attributes (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness, and aftertaste), on a 9-point scale [11]. The clinical staff will provide definitions and examples of each aspect that is being rated if required. Subjects will be asked to rate each test regimen independently of any previous taste/palatability questionnaires.

Each subject will complete the questionnaire individually and privately following each test IMP administration.

The questionnaire will be started within 10 minutes of test IMP administration.

14 Assessment of Safety

Safety assessments will be performed as detailed in the study schedule of assessments in Appendix 2.

14.1 Definition and Classification of Adverse Events

An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An ADR is any AE where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related).

AEs will be monitored from the time that the subject signs the ICF until after the follow-up phone call/unscheduled follow-up visit. The severity of AEs should be assessed as follows:

Mild An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.

Moderate An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe An AE that prevents normal everyday activities; treatment or other intervention usually needed.

14.2 Assessment of Causality

Every effort should be made by the Investigator to try to explain each AE and assess its relationship, if any, to the IMP. The temporal relationship of the event to IMP administration should be considered in the causality assessment (i.e., if the event starts soon after IMP administration and resolves when the IMP is stopped).

Causality should be assessed using the following categories:

Unrelated: Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP.

Possibly related: Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Related: Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals.

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, e.g., natural history of the underlying disease, concomitant therapy) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the IMP.
- Reactions of a similar nature have been previously observed with the IMP or this class of drug.
- The experience being related by time to IMP administration, terminating with IMP withdrawal or recurring on re-challenge.
- Alternative cause.

14.3 Recording Adverse Events

AEs (including SAEs) will be recorded from the time of providing written informed consent until discharge from the study at the follow-up phone call/unscheduled follow-up visit. During each study visit, the subject will be questioned directly regarding the occurrence of any adverse medical event according to the schedule in the source. All AEs, whether ascribed to study procedures or not, will be documented immediately in the subject's source. This will include the date and time of onset, a description of the AE, severity, seriousness, duration, actions taken, outcome and an Investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the Investigator.

Any subject who withdraws from the study due to an AE will be followed up until the outcome is determined and written reports are provided by the Investigator.

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Consists of a congenital anomaly or birth defect.
- An important medical event as recognised by the Investigator.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to an IMP and are both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and serious. SUSARs are subject to expedited reporting to the MHRA (see Section 16.3.2 for details on reporting SUSARs).

14.5 Laboratory Measurements

Venous blood and urine samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study.

Blood and urine samples are sent for laboratory testing in linked anonymised form (subject number, gender and date of birth for analytical reasons). This information is able to be linked directly to the volunteer by the Quotient Sciences research team and study monitor; however, not by the laboratory staff or Sponsor.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. The research will not involve analysis or use of human DNA.

Blood and urine samples results will be reviewed by a physician and acted upon before the subject is dosed or receives their next dose, or is released from the study, as is appropriate. A list of the laboratory parameters measured is presented in Appendix 1.

14.5.1 Haematology and Clinical Chemistry

Laboratory tests will be performed by The Doctors Laboratory at the time points detailed in the schedule of assessments. Blood samples will be collected and processed as detailed in the CSPM. Scheduled blood samples will be taken following an 8 hour fast.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- The pre-dose blood sample will be taken ≤2 hours before dosing.
- Post-dose blood samples will be taken ± 1 hour from the nominal blood sampling time.

14.5.2 Virology

HBsAg, HCV Ab, and HIV 1 and 2 tests will be performed from the clinical chemistry sample (see Section 14.5.1 for sample collection and processing information).

14.5.3 Urinalysis

Urinalysis will be performed on-site using a dipstick at the time points detailed in the schedule of assessments. Urine samples will be collected and processed as detailed in the CSPM. If microscopy is required, a urine sample will be sent to The Doctors Laboratory.

The acceptable deviations from the nominal blood sampling time points for urinalysis are:

- The pre-dose urine sample will be the first void of the day or a sample collected ≤3 hours before dosing.
- Post-dose urine samples will be taken ± 2 hours from the nominal urine sampling time.

14.5.4 Pregnancy Test

Serum and urine highly sensitive pregnancy tests will be performed at the time points detailed in the schedule of assessments. The samples will be collected and processed as detailed in the CSPM.

14.5.5 Follicle-Stimulating Hormone Test

Serum FSH tests will be performed at the time points detailed in the schedule of assessments. The samples will be collected and processed as detailed in the CSPM.

14.5.6 Drug Screen

A urine drug screen will be performed on-site using a point of care testing method (e.g., Alere Drug Screen Test Cup) at the time points detailed in the schedule of assessments. The sample will be collected and processed as detailed in the CSPM. Subjects will be screened for the drugs of abuse listed in Appendix 1.

14.5.7 Alcohol Breath Test

An alcohol breath test will be performed at the time points detailed in the schedule of assessments. A confirmed positive result will exclude the subject from dosing during that admission.

14.5.8 Carbon Monoxide Breath Test

A carbon monoxide breath test will be performed at the time points detailed in the schedule of assessments. A confirmed result of greater than 10 ppm will exclude the subject from the study.

14.5.9 SARS-CoV-2 Tests (If Required)

Testing for the SARS-CoV-2 virus may be performed based on current infection rates and availability of tests. If required, the samples will be collected and processed as detailed in the Screening Sample Processing Manual and CSPM, as applicable.

Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes or in a file note if the study is ongoing.

14.5.10 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the Investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken, e.g., the subject will not be entered into the study, or the subject may be withdrawn from the study. The subject will be referred to their general practitioner or other appropriate provider for further care if necessary. The same will apply if the results of the HBsAg, HCV Ab, or HIV test are positive and, in addition, the Investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the Investigator believes the results may be of clinical significance.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the Investigator or Sub-investigator.

14.6 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the subject has been in a supine position for a minimum of 5 minutes, and oral temperature and respiratory rate will be measured at the time points detailed in the schedule of assessments. The acceptable deviations from the nominal vital signs measurement time points are:

- The pre-dose vital signs measurements will be taken ≤2 hours before dosing.
- Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points.
- Discharge vital signs measurements will be taken ± 1 hour from the nominal time point.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator or Sub-investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

14.7 ECG Measurements

Single 12-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min at the time points detailed in the schedule of assessments. The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken ≤2 hours before dosing.
- Post-dose ECG measurements will be taken ± 15 minutes from the nominal post-dose time point.
- Discharge ECG measurements will be taken ± 1 hour from the nominal time point.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator or Sub-investigator.

Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

14.8 Body Weight, Height and BMI

The subject's body weight and height will be measured, and their BMI will be calculated at the time points detailed in the schedule of assessments.

14.9 Physical Examination

Subjects will undergo a physical examination at the time points detailed in the schedule of assessments.

In the targeted (symptom driven) physical examination, a physician will assess the subject; if the subject reports feeling unwell or has ongoing AEs, then the physician will examine the appropriate body system(s) if required.

14.10 Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed, if it is believed that an important effect of the IMP(s) is occurring or may occur at a time when no measurements are scheduled, or if extra procedures are needed in the interests of safety.

Additional blood samples for safety assessments may be taken if required by the Investigator or Sub-investigator at any point.

15 Statistics and Data Analysis

15.1 Sample Size Justification

The study is exploratory, and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a sample size of 16 subjects and a minimum of 12 evaluable subjects is considered sufficient to meet the objectives of the study.

15.2 Data Management

Data management will be performed by Quotient Sciences.

Study data will be managed using a validated electronic case report form (eCRF) database system and subjected to data consistency and validation checks. Data queries will be raised within the study eCRF database by data management staff and resolved with the assistance of clinical staff.

AEs, medical histories and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version to be specified in the Data Management Plan [DMP]) and the World Health Organization (WHO) Drug Dictionary Global Drug Reference (version to be specified in the DMP), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and haematology data (and other safety laboratory data) will be collected by a central laboratory (The Doctors Laboratory) and stored electronically in their clinical pathology system. The data will be transferred electronically to Quotient Sciences, and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the DMP are met.

Further details are addressed in the DMP.

15.3 Pharmacokinetic Data Analysis

The plasma concentration data for delafloxacin provided by PPD, Inc. will be analysed by Quotient Sciences, using Phoenix WinNonlin v8.3 or a more recent version (Certara USA, Inc., USA).

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the PK parameters presented in Table 3, where possible and appropriate.

Table 3 Plasma Pharmacokinetic Parameters

Parameter	Definition
Tlag	Time prior to the first measurable concentration
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-24)	Area under the curve from time 0 to 24 h post-dose
AUC(0-last)	Area under the curve from time 0 to the time of last measurable concentration
AUC(0-inf)	Area under the curve from time 0 extrapolated to infinity
AUCextrap	Area under the curve from time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity
T1/2	Terminal elimination half-life
Lambda-z	First order rate constant associated with the terminal (log-linear) portion of the curve
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
Vz/F	Apparent volume of distribution based on the terminal phase calculated using AUC(0-inf) after a single extravascular administration where F (fraction of dose bioavailable) is unknown
MRT(0-last)	Mean residence time from time 0 to time of the last measurable concentration
MRT(0-inf)	Mean residence time from time 0 extrapolated to infinity
Frel Cmax	Relative bioavailability based on Cmax
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last)
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf)

Interim PK parameter estimations will be provided for dose level and prandial state selection purposes, as described in Section 8.2.

Further details of the PK data analysis will be included in the reporting and analysis plan (RAP).

15.4 Statistical Data Analysis

Statistical analysis and production of summary tables, figures, and listings for this study will be performed by Quotient Sciences using the statistical package SAS (v9.4 or more recent version).

In general terms, categorical data (including TEAEs) will be presented using counts and percentages, while continuous variables will be presented using the mean, median, standard deviation, minimum, and maximum. Additional statistics will be provided for PK-related data including coefficient of variation (CV%), geometric mean, and geometric CV%.

Descriptive summaries for all safety data (AEs, vital signs, ECGs, and safety laboratory assessments) by regimen will be provided (including changes from baseline as required).

Descriptive summaries for all PK and taste data by regimen, as applicable, will be provided.

All PK, safety, and taste data will be listed.

Formal statistical analysis will be performed on the PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess relative bioavailability. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model, with terms for sequence and regimen as fixed effects, and subject within sequence as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the adjusted GMRs for the relevant comparison (i.e., Regimen A [reference] and Regimen B [test]) will be provided, where the ratios are defined as test/reference.

Formal statistical analysis will also be performed on the PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess for the effects of food on delafloxacin Powder for Oral Suspension regimens administered at the same dose level. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model, with terms for regimen as fixed effect, and subject as a random effect. Adjusted GMRs and 90% CIs for the adjusted GMRs for the comparison between fed and fasted regimens will be provided, where the ratios are defined as fed/fasted.

Additionally, formal statistical analysis may be performed on log-transformed, dose-corrected PK parameters Cmax, AUC(0-last), and AUC(0-inf) to assess dose proportionality, if two dose levels of delafloxacin Powder for Oral Suspension are administered in the same prandial state, using a mixed effect model, with terms for regimen as a fixed effect and subject as a random effect.

No formal hypothesis will be tested, and the results will be interpreted from GMRs and corresponding 90% CIs.

Populations and analysis sets will be determined for PK, safety, and taste data after database lock, when the relevant data are available, using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

Further details relating to the statistical analysis will be included in the RAP including the following:

- Criteria to be used to define each of the population and analysis sets.
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data.
- Handling of missing data, unused or spurious data.
- Handling of data from withdrawn subjects.

15.5 Interim Analysis

No formal interim analyses are planned for this study. Interim data reviews will be performed as detailed in Section 8.2.

16 Safety Reporting to Regulatory Authorities and Ethics Committees

16.1 Events Requiring Expedited Reporting

SUSARs (as defined in Section 14.4.2) are subject to expedited reporting to the appropriate regulatory authority.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would

be sufficient to consider changes in the IMPs' administration or in the overall conduct of the study, for instance:

- An increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important.
- SAEs that occur after the subject has completed the clinical study, where the Sponsor considers them to be a SUSAR.
- New events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects, such as:
    - An SAE which could be associated with the study procedures, and which could modify the conduct of the study.
    - A major safety finding from a newly completed animal study (such as carcinogenicity).
    - Any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same Sponsor.

16.2 Urgent Safety Measures

If Quotient Sciences, or any of its staff or contractors, becomes aware of an actual or potential urgent safety issue, then the Sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions, or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

The Sponsor is responsible for informing the appropriate regulatory authorities, and the EC; the task of reporting urgent safety measures will be delegated to Quotient Sciences.

16.3 Reporting

16.3.1 Reporting Serious Adverse Events

The Investigator must notify the study Sponsor and pharmacovigilance provider of any SAE or SAR immediately, and in all cases within 24 hours of becoming aware of the event or reaction. A copy of the written report of the event should promptly be sent to the study Sponsor for information purposes, in accordance with ICH guidelines for Good Clinical Practice (GCP) [12].

16.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the Investigator of their decision as soon as possible.

16.3.3 Expedited Reporting of Events

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the Investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the MHRA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. The task of reporting fatal or life-threatening SUSARs may be delegated to the pharmacovigilance provider. A separate notification to the EC is not required.

Other SUSARs

It is the responsibility of the Sponsor to report other SUSARs to the MHRA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. The task of reporting other SUSARs may be delegated to the pharmacovigilance provider. A separate notification to the EC is not required.

16.3.4 Reporting of Urgent Safety Measures

Quotient Sciences is required to notify the MHRA and the EC of an urgent safety measure immediately by telephone and follow-up in writing within 3 calendar days from the date the measures are taken.

16.3.5 Reporting of COVID-19 Vaccine-Related Adverse Events

AEs considered by the Investigator to be related to COVID-19 vaccines will be reported to the MHRA via the Yellow Card system.

16.4 Serious Breaches

It is the responsibility of the Sponsor to notify the MHRA of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

17 Protocol Amendments and Deviations

17.1 Amendments

After the protocol has been submitted to the MHRA and EC, any amendment must be agreed by the Investigator after discussion with the Sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for approval and/or an opinion, respectively, as required by current regulations.

If the PIS and ICF are updated as a result of the substantial amendment, the new approved versions will be used to re-consent currently enrolled subjects and must be provided to newly enrolled subjects prior to their entry into the study.

17.2 Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source as noted by the clinical staff. If necessary, the Sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the Sponsor in order to determine if the withdrawal criteria stated in Section 8.3 have been met.

18 Regulatory

18.1 Compliance

This study will be conducted in accordance with the protocol and with the following legislation:

- ICH GCP Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 [12].
- ICH E8 (R1) General Considerations for Clinical Studies, dated Oct 2021 [13].
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [14].
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [15].
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [16].
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [17].
- The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations. Statutory Instruments 2019 No. 744 [18].

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [19].

18.2 MHRA and Ethical Approval

Prior to the initiation of the study, the clinical trial of an investigational medicinal product (CTIMP) application, the protocol and associated documentation must be approved by the MHRA and given a favourable opinion by an EC. A copy of this written approval and any correspondence with the MHRA and EC will be available at the clinical site and will be provided to the Sponsor.

18.3 Source Data

A study-specific source document identification list will be finalised with the Sponsor prior to the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

For this study, electronic data capture will be used where possible, and data will be automatically recorded into an eCRF. In instances where paper source documents are used, data to be transcribed into the eCRF will be identified using a Source Document Identification List, as governed by Quotient Sciences' SOPs.

18.4 Declaration of the End of the Study

The end of the study is defined as the point at which the Sponsor determines that any remaining optional groups are not required to meet the objectives of the trial i.e., signed dose decision document or the completion of the last follow-up phone call/unscheduled follow-up visit for the final period, whichever occurs later. If the optional group is utilised, completion of the last follow-up phone call/unscheduled follow-up visit will be considered the end of the study. Any changes to this definition will be notified as a substantial amendment (see Section 17.1).

The EC and MHRA should be notified of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

18.5 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters, etc.) will be kept in accordance with the ICH guidelines for GCP 1996, updated 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 (ICH GCP Section 4.9.5) [12], The Medicines for Human Use (Clinical Trials) Regulations 2004 [14], The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [15][16] and The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations [18].

All study related documents will be retained for a minimum period of 25 years. After this time, the Sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

18.6 Protection of Personal Data and Confidentiality

Personal data are securely stored to prevent unauthorised access, disclosure, dissemination, alteration or loss of information and unauthorised personal data processing. Access to personal information is restricted so that only personnel who are required to access personal data as part of their job role can do so. All personnel who access personal information are bound by a duty of confidentiality.

Technical arrangements surrounding the electronic storage and use of data are as follows:

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls.
- Off-site personnel can only access networked computers through a virtual private network.
- Electronic access of data is limited according to user roles.
- All data are stored on password protected computers.

Organisational arrangements are as follows:

- All buildings are secured by key-card access.

- Manual files of personal data are stored within locked cabinets/restricted areas of the clinical unit that can only be accessed by authorised personnel.
- Data security and/or confidentiality provisions are utilised in agreements with third parties.
- Documented back-up and disaster recovery procedures are in place.
- Internal audit and compliance functions provide regulatory oversight.

The personal data of volunteers will be pseudonymised in that they will only include health, initials, date of birth and demographics (gender and ethnicity) and cannot be linked back to the individual by the recipient. The Sponsor shall be the data controller in respect of the personal data of the study subjects collected in connection with the study, and shall act in accordance with the relevant data protection laws in relation to the collection and processing of those personal data. The study subjects' pseudonymised personal data shall be collected and processed for the purposes of the study, and may also be added to research databases and used in the future by the Sponsor and its affiliates for certain additional clinical research, for product regulation and safety reporting purposes and for ensuring compliance with legal requirements. The study subjects' pseudonymised personal data may be processed for such purposes by other parties including: the Sponsor's affiliates and licensing partners, its business partners, regulatory agencies and other health authorities, and ECs. The study subjects' authorisation for such use and disclosure shall be obtained by the study subjects signing the ICF for the study.

Additionally, Quotient Sciences personnel are contractually bound by a duty of confidentiality and receive training on this matter.

18.7 Data Security Breach

Quotient Sciences has a comprehensive process in place for identifying, assessing, resolving and reporting any potential data security breach. All staff are trained in the identification of potential data security breaches. Potential breaches are managed by appropriately trained quality assurance (QA) personnel in accordance with Quotient Sciences' SOPs. After robust assessment of data breaches, those deemed serious will be reported to the Sponsor and Information Commissioner's Office, as applicable.

19 Quality Control and Quality Assurance

QC of all data collected from this study will be performed in accordance with Quotient Sciences' SOPs. This study (or elements thereof) may be subject to Quotient Sciences QA audit, in line with current internal auditing procedures. Similarly, the study (or elements thereof) may be subject to Sponsor QA audit.

19.1 Monitoring

GCP requires that studies are adequately monitored. The Sponsor should determine the appropriate extent and nature of monitoring. A study monitor, independent of Quotient Sciences, will be appointed to verify that the study is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The Investigator agrees to receive visits from a study monitor and provide assistance to verify protocol implementation, source completion and transcription of data into the eCRF, document storage and AE reporting.

Quotient Sciences will extend the professional privilege of access to the subjects' clinical source documents to the study monitor, EC, regulatory bodies or other authorised personnel (e.g., auditor) for the purposes of source data verification.

Following completion of the study both study related documents and subject data may be sent to the Sponsor at a location outside of the UK where data protection laws differ. In the interests of confidentiality, subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained.

20 Finance and Insurance

The Sponsor (Melinta Therapeutics, LLC) has funded this study. A no-fault clinical trials insurance has been obtained by the Sponsor. The Sponsor insurance will compensate subjects in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2018 edition [10].

21 Publication

Please refer to the Master Services Agreement for information on publication.

Quotient Sciences shall have the right to publish the results of the research, subject to the Sponsor's (Melinta and the Biomedical Advanced Research and Development Authority) prior written consent, which shall not be unreasonably withheld or delayed. Following the receipt of such consent, Quotient Sciences shall submit a copy of the proposed publication to the Sponsor, who shall have 45 calendar days for manuscripts and 30 calendar days for abstracts in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, Quotient Sciences shall be obliged to incorporate prior to such publication.

The Sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning the research, it will submit a copy of such publication to Quotient Sciences, who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendment are reasonable, the Sponsor shall be obliged to incorporate prior to such publication. All such publications shall acknowledge contract support as follows: "This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority, under Prime Contract No. 75A50123C00022".

22 References

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[4] Dryden MS. Skin and soft tissue infection: microbiology and epidemiology. *Int J Antimicrob Agents*. 2009; 34 Suppl1:S2-7.

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[13] ICH E8 (R1) General Considerations for Clinical Studies, dated Oct 2021.

[14] The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031.

[15] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928.

[16] The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984.

[17] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941.

[18] The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations. Statutory Instruments 2019 No. 744.

[19] World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (and all subsequent amendments).

Appendix 1 Clinical Laboratory Parameters

Haematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Haemoglobin Haematocrit (HCT; packed cell volume [PCV]) Red blood cell (RBC; erythrocyte) count Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) Platelet count White blood cell (WBC; leukocytes) count Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Sodium Potassium Chloride Bicarbonate Urea Creatinine Bilirubin (total) Bilirubin (direct; only if total is elevated) Alkaline phosphatase Aspartate aminotransferase (AST) ALT Creatine kinase (CK) Gamma glutamyl transferase (GGT) Protein (Total) Albumin Calcium Corrected calcium Glucose (fasting) Glucose FSH (post-menopausal female subjects only) Beta human chorionic gonadotropin (β-hCG) (all female subjects)	Hepatitis B surface antigen Hepatitis C virus antibody HIV 1 & 2 antibodies **If Required:** SARS-CoV-2 antigen	Bilirubin Urobilinogen Ketones Glucose Protein Blood Nitrites pH Specific gravity Leukocytes **At discretion of Investigator based on urinalysis results** Microbiology Urine microscopy **Urine Pregnancy** Human chorionic gonadotropin (hCG) (all female subjects)	Amphetamines Barbiturates Benzodiazepines Cocaine Marijuana/cannabis Methadone Methamphetamine/ ecstasy Morphine/opiates Phencyclidine Tricyclic antidepressants

Appendix 2 Schedule of Assessments

Study Day	-28 to -2	-1	1															2	3	6 ± 1 FUP Phone Call or Unscheduled FUP Visit[c]
			Times After Dosing (h)																	
	S	A[a]	P	0	0.5	1	1.5	2	3	4	6	8	10	12	14	16	20	24	48[b]	
General Assessments																				
Informed Consent	X																			
Medical History	X	X[d]																		
Weight, Height and BMI	X	X[e]																		
Vein Assessment	X	X[f]																		
Drug Screen	X	X																		
Alcohol Breath Test	X	X																		
Carbon Monoxide Breath Test	X	X																		
Randomisation[g]			X																	
IMP Administration				X																
Safety Assessments																				
Physical Examination	X																			
Targeted (symptom driven) Physical Examination[h]		X[f]	X[i]															X		X
Clinical Laboratory Tests[j]	X	X[f]	X[i]																X	X
Urinalysis	X	X[f]	X[i]																X	
Serum Pregnancy Test[k]	X																			
Urine Pregnancy Test[k]		X																	X	X
Single 12-Lead ECGs	X	X	X			X												X	X	X
Vital Signs[l]	X	X	X			X												X	X	X
Adverse Events	< ----------X---------- >																			
Prior and Concomitant Medication	< ----------X---------- >																			
PK Assessments																				
Plasma Samples for Delafloxacin			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Taste/Palatability Assessments																				
Taste/Palatability Questionnaire[m]				X																

A = admission, FUP = follow-up, P = pre-dose, S = screening
If replacement subjects are required, they will undergo screening assessments as detailed above
All assessments/procedures to be completed for every period unless specified otherwise

[a] Subjects will be admitted to the clinical unit in the morning on the day before dosing (Day -1) in Period 1, and in the evening on the day before dosing (Day -1) in Period 3 and optional Period 4. Subjects will remain resident in the clinical unit between Periods 1 and 2; therefore, no admission procedures will be conducted for Period 2
[b] Discharge from the clinical unit (Periods 2 to 4 only). There will be a minimum washout of 4 days between dosing in Periods 1 and 2. In the event of early withdrawal, discharge assessments should be completed
[c] A follow-up phone call will take place on Day 6 ± 1 of the final treatment period, to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs that present a cause for concern, they will be required to attend the clinical unit for a (unscheduled) follow-up visit. Assessments may be performed at the unscheduled follow-up visit as indicated
[d] Update only
[e] Weight only
[f] Period 1 only
[g] Subjects will be randomised immediately prior to dosing in Period 1, for allocation of regimens across Periods 1 and 2
[h] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the Investigator's judgement
[i] Periods 2 to 4 only
[j] Haematology and clinical chemistry at each time point including virology and FSH (post-menopausal female subjects only) at screening
[k] All female subjects
[l] Blood pressure, heart rate, oral temperature and respiratory rate will be measured at each time point
[m] The taste/palatability questionnaire will be started within 10 minutes of each delafloxacin Powder for Oral Suspension (i.e., test) regimen administration. See Appendix 3 for details of the taste/palatability questionnaire

Appendix 3 Example Taste/Palatability Questionnaire

QSC300553 (ML-DEL-101-3727-1) Taste Questionnaire

Study Period: | **Regimen:** | **Subject Number:**

Subject Initials:

Start time:
(to be started within 10 minutes of dosing)

Date:

Question 1
All aspects considered (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste), how would you rate your overall liking of this product:

NOTE: Tick 1 box below in blue or black pen

Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely

Question 2
We want to know how much you like certain aspects of the product: smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste. Please rate each test product independently of any previous taste questionnaires. **NOTE: Tick 1 box in the row for each aspect**

	Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely	Not detectable
Smell										
Sweetness										
Bitterness										
Flavour										
Mouthfeel/texture										
Grittiness										
Aftertaste										

Entered into eCRF by (initials): _____ Date: _____ QC checked by (initials): _____ Date: _____

Appendix 4 Breakfast Content

Meal Description	Total Energy (kcal)	Energy from Fat (%)	Composition
High-Fat Breakfast (FDA approved)[a]	950	58	1 (40 g) hash brown, 2 (80 g) Unsmoked Rind less Streaky Bacon, 1 medium (45 g) egg fried in 10 g of unsalted butter, 2 slices (95 g) of white sliced bread with 20 g of unsalted butter, 240 mL of full fat milk

Values/content are approximate. Every effort will be made to include the items described above; however, items may be replaced as long as they contain the equivalent nutritional content as the item it has replaced

[a] For FDA high-fat breakfast, if a replacement item is required it will be of comparable content, volume and viscosity

Appendix 5 Protocol Amendment Summary of Changes

This is the original protocol; no amendments have been performed to date.

Signatures for Quotient Sciences

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 (R2) GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 16.3 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the Sponsor.

[redacted]

Principal Investigator

[redacted], UK

See electronic signature at the end of the document

Signature

Date

Signatures for Sponsor

[redacted]

[redacted]

Date

Document Approvals

Approved Date: 22 Mar 2024

Approval Task Verdict: Approve	[redacted] Approval 22-Mar-2024 16:34:46 GMT+0000

Document Author(s): [redacted]