BenevolentAI Cambridge Ltd

Trial Protocol

Confidential

Trial title	A randomised, double-blind, placebo-controlled, phase 1 first-in-human study to investigate the safety, tolerability, pharmacokinetics, and food effect of single- and multiple-ascending doses of BEN8744 in healthy subjects
Short title	Safety, PK, and food effect of BEN8744
Version and date of protocol	Version 3, dated 11 December 2023
HMR code	22-014
Sponsor code	BB-8744-1001
IRAS number	1006884
EudraCT no	2022-003721-22
Trial medication	BEN8744
Phase of trial	Phase 1
Place of trial	HMR Cumberland Avenue London NW10 7EW UK Tel: 020 8961 4130 Fax: 020 8961 8665
Principal investigator	Denisa Wilkes MD HMR
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Planned dates of trial	JUN 2023 to APR 2024

Version control history

Version	Reason for change
1, dated 16 December 2022	N/A
2, dated 03 February 2023	Updates made to the protocol in response to GNA remarks from the MHRA
3, dated 11 December 2023	The pharmacokinetic exposure threshold has been updated to allow dosing to a higher level in Part A, based on emerging safety and pharmacokinetic data from completed Cohorts A1–A4. (Substantial) Implemented non-substantial administrative and file note changes

Protocol amendment summary

Substantial amendment 2 (Protocol version 3)

This amendment incorporates emerging safety and pharmacokinetic (PK) data from completed Cohorts A1–A4 to support the sponsor's proposal to update the PK exposure threshold to allow dosing to a higher level in Part A. Clarifications or non-substantial changes which were previously documented in file notes have also been implemented.

The protocol was updated from version 2 (dated 03 February 2023) to version 3 (dated 11 December 2023). The following changes were made.

Section(s), table(s) and figure(s) affected	Change
Section 2.5, 2.6.1, 6.2.3, 6.2.4, 6.5, 6.5.1, 6.5.2, 8.1.1, 8.4.2, 8.5.2, 8.5.5, 9.1, and Table 1–4, 6, and 8 and Figures 1–4	The PK exposure threshold has updated to the NOAEL in the most sensitive species (dog). The rationale for increasing the PK exposure threshold has been added, including safety and PK data from Cohorts A1–A4. The planned dose in Cohort A5 has been updated to 100 mg QD. The dose given in completed Cohort A4 (60 mg) has been updated throughout. Cohort A6 has been made optional.

Section(s), table(s) and figure(s) affected	Change
Section 2.5	Added 'significant suicidality history or suicidality risk (assessed by C-SSRS); history of seizures' to the main exclusion criteria.
Section 4	Updated the abbreviations list.
Section 5, 14.3, 14.5	Updated contact details for the pharmacovigilance provider and sponsor's representative.
Section 9.3	Updated exclusion criterion 23 for consistency with Table 13.
Section 11	Updated contraception requirements to list only low user dependent, highly effective methods for women of childbearing potential.
Table 8	Updated subject and sentinel numbers so that Cohorts A7 and A8 are consecutive.
Section 2.7.1, 12, 12.1	Updates to the schedules of procedures, as follows. *All study parts:* - urine drug screen and alcohol and cotinine tests have been removed from follow-up visits. - the OAAS and VAS have been removed from the 12, 16 and 36 h timepoints. Text has been updated in section 2.7.1 and 12 to reflect this. *Parts A and B:* Correction to footnote 9. *Part C:* - urine drug screen, alcohol and cotinine tests will be done on Day −1 (admission). - OAAS/S and VAS assessments will not be done at 12, 12.5, 13, 14, 15, 16, 20 and 36 h postdose for twice-daily dosing. - weight measurements will be done at follow-up. - for twice-daily dosing, vital signs and ECGs will be done before the morning dose only. When vital signs and ECGs are to be taken on Day 1, 24 h *and* Day 2 predose, only a Day 2 predose measurement will be taken.

Section(s), table(s) and figure(s) affected	Change
Section 12.4, 12.5	Updated blood collection tube sizes and the volume of blood taken for laboratory safety tests.
Section 12.4	Removed subsections on processing of blood samples, urine collection, and faecal sample collection for PK analysis. Details are provided in the study procedures manual.
Table 10	Updated the acceptable deviation time for 'all other procedures' on Days 1 and 14 to include procedures up to 24 h.
Section 12.1.3, 12.5 (Tables 14–16)	Removed PK sampling timepoints at 12.5, 13, 14, 15, 16 and 20 h on Day 14 for twice daily dosing, and 16 h on Days 1 and 14 for once daily dosing, in Part C. As a result, the total volume of blood in Part C has also been updated. The total volume of blood for all study parts has been updated to account for discard (when using a cannula) up to 24 h postdose.
Section 8.5.3	Corrected the PK data requirements for dose selection in Part B.

Previous protocol amendments

Amendment to address the MHRA's notice of grounds for non-acceptance.

1 Signatures

The investigator and the sponsor have discussed this protocol. The investigator agrees to perform the investigation and to abide by this protocol and any future agreed amendments, except in case of medical emergency.

Principal investigator

Dr Denisa Wilkes
HMR

Denisa Wilkes — Electronically signed by: Denisa Wilkes
Reason: I agree to this
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11-Dec-2023

Signature Date

Statistician

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2 Summary

2.1 Trial medication

BEN8744 is a potent, and selective small molecule inhibitor of phosphodiesterase 10A (PDE10A). It is being developed as an orally administered treatment for inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD).

2.2 Objectives

2.2.1 Primary objectives

Part A: To assess the safety and tolerability of single ascending oral doses of BEN8744 in healthy subjects

Part B: To characterise the effect of food on the pharmacokinetic (PK) profile of at least 1 oral dose of BEN8744

Part C: To assess the safety and tolerability of multiple ascending oral doses of BEN8744 in healthy subjects

2.2.2 Secondary objectives

Part A: To assess the PK profile of BEN8744 after single oral doses in healthy subjects

Part B: To assess the safety and tolerability of a single dose of BEN8744 following high-fat food intake relative to fasting conditions in healthy subjects

Part C: To assess the PK profile of BEN8744 after repeated oral doses in healthy subjects

2.2.3 Exploratory objectives

Part B (and optional in Part C):

To measure BEN8744 in urine and determine renal clearance in healthy subjects[*]

Exploratory characterisation of BEN8744 and its metabolites in plasma, urine, and faeces[†]

[*]If significant amounts of the parent compound are detected in Part B, the parent compound may be measured in Part C (in urine at 2 dose levels [low and high]).

[†]Faeces will be analysed in Part B only. If significant amounts of metabolites are detected in Part B, exploratory metabolite analyses may be conducted in Part C (in plasma and urine at 2 dose levels [low and high] on Day 1 and Day 14).

2.3 Endpoints

2.3.1 Primary endpoints

Safety and tolerability (Parts A and C): vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead electrocardiogram (ECG), cardiac telemetry (Part A only), physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), adverse events (AEs), and Observer's Assessment of Alertness/Sedation scale (OAAS/S), visual analogue scale (VAS) to monitor sedation, and Columbia-Suicide Severity Rating Scale (C-SSRS; Part C only).

PK (Part B): C_{max}, t_{max}, AUC_{24}, AUC_{72}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL/F, V_Z/F

2.3.2 Secondary endpoints

PK (Part A): C_{max}, t_{max}, AUC_{24}, AUC_{72}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL/F, V_Z/F

Safety and tolerability (Part B): vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead ECG, physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), AEs, and OAAS/S and VAS to monitor sedation.

PK (Part C): C_{max}, t_{max}, C_{trough}, AUC_{tau}, AUC_{last}, AUC_{72}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL_{SS}/F, V_Z/F, $R_{ac(AUC)}$, $R_{ac(Cmax)}$, $SR_{(AUC)}$

2.3.3 Exploratory endpoints

PK (Part B and optional in Part C): Ae_{72}, $f_e \cdot F$, CL_R

2.4 Type of trial

This is a Phase 1, single-centre trial to assess the safety, tolerability, PK and food effect of BEN8744 in healthy volunteers.

This trial will be in 3 parts, as follows:

Part A will test single doses of BEN8744 in a double-blind, randomised, placebo-controlled and dose-escalating design.

Part B will test the effect of food on the PK of BEN8744 in an open-label, randomised, 2-way crossover design.

Part C will test repeated doses of BEN8744 (once or twice daily for 14 days) in a double-blind, randomised, placebo-controlled and dose-escalating design.

2.5 Trial population

a **Total** Up to 108 healthy volunteers, excluding replacements: up to 64 in Part A (including 3 optional groups); up to 12 in Part B; and up to 32 in Part C (including 1 optional group).

b **Age** 18–65 years

c **Main inclusion criteria**

Healthy male or female volunteers, with a body mass index (BMI) of 18.0–30.9 kg/m^2; deemed healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine; agree to follow the contraception requirements of the trial; able to give fully informed written consent.

d **Main exclusion criteria**

Positive tests for hepatitis B & C, HIV; severe adverse reaction to any drug; sensitivity to trial medication or excipients; drug or alcohol abuse; habitual users of tobacco and/or nicotine containing products, as defined in the protocol; use of non-prescription or over-the-counter medication (with the exception of up to 2 g paracetamol [acetaminophen]) during the 7 days before and up to 24 h before the first dose of trial medication, or prescribed medication during the 28 days before first dose of trial medication; participation in other clinical trials of investigational medical products, or loss of more than 400 mL blood, within the previous 3 months; clinically relevant abnormal findings at the screening assessment; acute or chronic illness; clinically relevant abnormal medical history or concurrent medical condition; significant suicidality history or suicidality risk (assessed by C-SSRS); history of seizures; possibility that volunteer will not cooperate; pre-menopausal females who are pregnant or lactating, or who are sexually active and not using a reliable method of contraception.

2.6 Trial design and methods

The trial will be in 3 parts (Parts A, B, and C), as described below. In each part, subjects will be screened within 28 days before their (first) dose of trial medication.

Part A will test single ascending oral doses of BEN8744; Part B is a 2-way crossover assessment of the effect of food on the PK of BEN8744; and Part C will test multiple ascending oral doses of BEN8744.

2.6.1 Part A

Part A will test single oral doses of BEN8744 in a double-blind, randomised, placebo-controlled and dose-escalating design.

Up to 5 groups of 8 subjects will be enrolled in Part A (Groups A1–A5). Each subject will have 1 study session, in which they will receive a single dose of BEN8744 or placebo, by mouth in the fasted state. The planned dose levels are: 2 mg (Group A1), 6 mg (Group A2), 20 mg (Group A3), 60 mg (Group A4), and 100 mg (Group A5). Additional intermediate or higher dose levels may be explored in 3 optional groups (Groups A6–A8), as detailed in section 8.5.2. At each dose level, 6 subjects will receive BEN8744 and 2 will receive matching placebo.

The dose will be escalated only if the safety and tolerability of the previous highest dose are acceptable, and the plasma concentrations of BEN8744 are predicted to remain below the exposure limit, as determined by the Safety Review Group (SRG). A dose level may be repeated or decreased, as required, based on emerging results.

Each new ascending dose will be staggered, such that 2 sentinel subjects will be dosed first, and randomised such that 1 subject receives BEN8744 and the other receives placebo. The remaining 6 subjects will be dosed at least 23 h later, at intervals of at least 10 min. If the planned dose escalation is changed such that a selected dose is no higher than a dose previously shown to cause no safety concerns, then sentinel subjects will not be required.

Subjects will be resident on the ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4). They will return for a follow-up visit 7 (±2) days after their inpatient stay (Day 11 ±2 days).

2.6.2 Part B

Part B will test the effect of food on the PK of BEN8744 in an open-label, randomised, two-way crossover design.

Up to 2 groups of 6 subjects will be enrolled in Part B (Groups B1 and B2). Each subject will have 2 study sessions, in which they will receive at least 1 dose of BEN8744, by mouth after either an overnight fast in one session or a high-fat breakfast in the other session. A subject's doses will be separated by a washout of at least 7 days (or 5 half-lives as determined in Part A, whichever is longer).

The dose to be tested in Group B1 will be decided following review of the interim safety, tolerability, and PK data from at least 3 dose levels in Part A. Group B2 is optional and may be required if the Sponsor decides to test the effect of food at an additional dose level, or under different conditions (eg different fasting conditions or after a different meal such as a standard breakfast).

In each Session, subjects will be resident on ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4). They will return for a follow-up visit 7 (±2) days after their inpatient stay in Session 2 (Day 11 ±2 days).

2.6.3 Part C

Part C will assess the safety, tolerability, and PK of multiple ascending doses of BEN8744 in a double-blind, placebo-controlled, parallel-group design.

Up to 3 cohorts of 8 subjects will be enrolled in Part C (Groups C1–C3). Each subject will have 1 study session, in which they will receive daily doses of BEN8744 or placebo, by mouth for 14 days. At each dose level, 6 subjects will receive BEN8744 and 2 will receive matching placebo. An additional intermediate or higher dose level may be explored in 1 optional group (Group C4), as detailed in section 8.5.4.

Doses will be taken once or twice daily in the fasted state, unless emerging data indicate they should be taken in the fed state. The dose, dosing regimen (once or twice daily), and whether the dose is taken fed or fasted, will be determined based on review of the available safety, tolerability and PK results from Parts A and B, and previous groups in Part C.

Subjects will be resident on ward from the day before their dose (Day –1) until up to 72 h after their final dose (Day 17). They will return for a follow-up visit 7 (±2) days after their inpatient stay (Day 24 ±2 days).

2.7 Assessments

The following assessments will be made.

2.7.1 Safety and tolerability

Laboratory assessments (routine haematology, clinical chemistry, and urinalysis), physical examinations, 12-lead ECGs, and vital signs (blood pressure, pulse rate, respiratory rate, and tympanic temperature) and C-SSRS (in Part C) will be done during dosing and frequently until the subject's last visit. Cardiac telemetry (Part A only) will be done from 1 h before until 24 h after dosing. The OAAS/S and VAS will be done frequently at specific timepoints immediately before PK blood samples, up to 72 h after dosing in Parts A and B, and up to 72 h after dosing on Day 1 in Part C, to monitor sedation. AEs will be recorded from time of consent until the subject's last visit.

2.7.2 Pharmacokinetics

Blood samples for assay of BEN8744 will be taken before, and frequently up to 72 h after dosing in Parts A and B, and up to 72 h after dosing on Day 1 and Day 14 in Part C.

Urine will be collected continuously for up to 72 h after dosing in Part B, and may be collected for up to 72 h after dosing on Days 1 and 14 in Part C, for assay of BEN8744 and its metabolites.

A predose faecal sample will be collected from Day –2 to predose on Day 1 in Part B Session 1. Faecal samples will be collected continuously for up to 72 h after dosing in Part B for the exploratory characterisation of BEN8744 and its metabolites.

3 Contents

3.1 Table of Figures

3.2 Table of Tables

4 List of abbreviations

ABPI	Association of the British Pharmaceutical Industry
AE	adverse event
Ae_{72}	cumulative amount of unchanged drug excreted into urine at 72 h
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
$\%AUC_{extrap}$	percentage of AUC that was extrapolated
AUC	area under the curve
AUC_{24}	area under the concentration–time curve from time zero to time 24 h
AUC_{inf}	area under the concentration–time curve extrapolated to infinite time
AUC_{last}	area under the concentration–time curve to last measurable concentration
AUC_{tau}	area under the concentration–time curve during the dosing interval
BID	twice-daily
BLQ	below the limit of quantification
BMI	body mass index
BSA-CF	body surface area conversion factor
cAMP	cyclic adenosine monophosphate
CD	Crohn's disease
cGMP	cyclic guanosine monophosphate
C_{avg}	average plasma concentration during multiple-dose administration
CI	confidence interval
CL/F	apparent total clearance from plasma after oral administration
CL_R	renal clearance from plasma
CL_{SS}/F	apparent total clearance from plasma at steady state after non-intravenous administration
C_{max}	maximum plasma concentration
C_{min}	minimum measured concentration
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	clinical trial authorisation
C_{trough}	trough plasma concentration
CYP	cytochrome P450

CV	coefficient of variation
CYP3A4	cytochrome p450 3A4
D	decreased by more than predetermined amount
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EU	European Union
fe F	fraction of non-intravenously administered drug excreted into the urine
FDA	United States Food and Drug Administration
FTIH	first time in human
FSH	follicle-stimulating hormone
g	gram(s)
G	G force
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
h	hour(s)
Hb	haemoglobin
HED	human equivalent dose
HIV	human immunodeficiency virus
HMR	Hammersmith Medicines Research
HRA	Health Research Authority
IB	investigator's brochure
IBD	inflammatory bowel diseases
$IC_{50/90}$	concentration required for 50%/90% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMPD	investigational medicinal product dossier
INR	international normalised ratio
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
kg	kilogram(s)
LIMS	laboratory information management system
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MIA(IMP)	manufacturing authorisation for investigational medicinal products
min	minute(s)
mm Hg	millimetres of mercury
MRSD	maximum recommended starting dose
NOAEL	no observed adverse effect level
OAAS/S	Observer's Assessment of Alertness/Sedation scale
PAD	pharmacologically active dose
PDE	phosphodiesterase
PDE10A	phosphodiesterase 10A
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QTc	QT interval corrected for pulse rate
QTcF	QT interval corrected according to Fridericia's formula
R_{ac}	accumulation ratio
RBC	red blood cells
REC	research ethics committee
RES	Research Ethics Service
SAE	serious adverse event
SD	standard deviation
SOP(s)	standard operating procedure(s)
SRG	safety review group
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	time
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum plasma concentration
TNF-α	tumour necrosis factor α
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
USA	United States of America
VAS	visual analogue scale
V_Z/F	apparent volume of distribution/fraction of dose absorbed
WBC	white blood cells
WHO	World Health Organization

WHO DDE	WHO Drug Dictionary Enhanced
λ_z	terminal rate constant

5 Trial personnel

Principal investigator	Denisa Wilkes MD HMR Cumberland Avenue London NW10 7EW Tel: 020 8961 4130 Email: dwilkes@hmrlondon.com
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Derivation of pharmacokinetic (PK) parameters	Nick Jackson BSc HMR
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6 Introduction

6.1 Background

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic immune-mediated diseases collectively referred to as inflammatory bowel diseases (IBDs). UC is the most common form of IBD, currently estimated to affect 5–500 in every 100,000 people worldwide, with the incidence increasing [1,2] and higher prevalence in industrialised areas like Western Europe and the United States [3,4,5]. IBDs are characterised by dysregulated, aberrant immune responses of the intestinal mucosa[6]; in UC, diffuse mucosal inflammation originates in the rectum and extends to the proximal colon. Symptoms include bloody diarrhoea, abdominal pain, faecal urgency, and incontinence; some patients may present with extra-intestinal manifestations, and patients with more extensive disease may also have fever, weight loss, malaise, and fatigue[7,8,9].

Current therapies for IBDs focus on symptom control, clinical remission, and preventing flare-ups or disease progression by eliminating or controlling inflammatory burden[10]. Treatment is based on disease activity and severity; however, as there is no single method for determining severity, treatment options vary considerably between patients[11,12]. There are numerous approved treatments for IBDs, such as 5-aminosalicylates, corticosteroids, immunomodulatory agents, and monoclonal antibodies directed against tumour necrosis factor α (TNF-α). However, these therapies have multiple limitations, including: low remission rates (eg after treatment with 5-aminosalicylates, 30% of UC patients do not reach remission after 8 weeks[13] and 50% do not maintain complete remission after 12 months[14]), slow onset (immunomodulatory agents, precluding them for use in disease flare-ups), and deleterious side-effects (including increased risk of infection from corticosteroid and TNF-α antagonist use, and increased risk of lymphoma from TNF-α antagonist[15] and immunomodulatory agent use[16]). Patients with refractory UC may undergo a colectomy, though this surgery may have complications (high stool frequency[17], female infertility[18], cumulative incidence of pouchitis[19]). These factors indicate an urgent need for a more effective, safe, targeted therapy for IBDs like UC.

Cyclic nucleotide phosphodiesterases (PDEs) are a family of enzymes that are involved in numerous inflammatory diseases[20,21,22]. PDEs play a role in regulation of signal transduction, by catalysing degradation of cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP). Cyclic nucleotide signalling is involved in the pathology of IBDs; the cGMP synthetic enzyme guanylate cyclase-C and its activators are downregulated in UC[23] and decreases in expression of these molecules correlate with disease severity[24]. Additionally, cGMP in the gastrointestinal (GI) tract is involved in fluid and electrolyte secretion, barrier function, inflammation, and proliferation[25]. One PDE, phosphodiesterase 10A (PDE10A), hydrolyses both cAMP and cGMP[26]. In healthy individuals, PDE10A expression is limited, with high levels only seen in the striatum (caudate nucleus and

putamen) of the brain and in the testes[27], and PDE10A inhibitors have primarily been investigated to treat neurological conditions[28]. However, upregulation of PDE10A was observed in the colon in UC patients in non-clinical studies done by BenevolentAI Cambridge Ltd, compared to low expression levels in healthy colon samples. Upregulation of cGMP hydrolysing PDE10A alongside reduction in cGMP synthesis in UC suggest that inhibiting PDE10A could restore cGMP signalling to normal levels and reverse pathological changes in UC.

6.2 Review of investigational medicinal product

BenevolentAI Cambridge Ltd is developing BEN8744 as an oral treatment for UC. BEN8744 is a potent and selective small molecule PDE10 inhibitor that inhibits cAMP and cGMP targeted hydrolytic activity of PDE10A, which is upregulated in UC colonic mucosa when compared with healthy colonic mucosa. It is expected that BEN8744 will reduce colonic inflammation, as seen in UC and IBDs.

This trial is the first time that BEN8744 has been administered to humans. Several non-clinical studies of BEN8744 have been conducted to date. Non-clinical data are presented in the investigator's brochure (IB)[29] and summarised below.

6.2.1 Non-clinical pharmacology

In vitro, BEN8744 was found to be a potent inhibitor of human PDE10A cell-free hydrolysis of cAMP (IC_{50} 0.2 nM) and cGMP (IC_{50} 0.1 nM), with comparable inhibition of mouse PDE10A, and predicted comparable inhibition in rat and dog (as the binding pocket of PDE10A is fully conserved across species). Potency of inhibition was demonstrated in a human embryonic kidney cell line 293 (HEK293) expressing recombinant human PDE10A (IC_{50} 1.2 nM). BEN8744 (1 μM or 10 μM) had > 1,000-fold selectivity for PDE10A in an activity assay of PDEs 1–11.

PDE10A expression was found to be significantly upregulated in UC colon tissue samples compared with healthy controls, and when tested *ex vivo* on inflamed colonic mucosa biopsies from IBD patients, BEN8744 demonstrated a significant, dose-dependent reduction in release of inflammatory cytokines.

In vivo, in a model of colitis (induced by adoptive transfer of CD44-/CD62L+ T-cells enriched from C57Bl/6 donor mice into $RAG^{2-/-}$ recipient mice), BEN8744 showed improvement in body weight gain and colitis severity scores that was comparable to an anti-TNFα monoclonal antibody reference control.

6.2.2 Non-clinical pharmacokinetics

The non-clinical PK of BEN8744 have been investigated in the mouse, rat, dog, and cynomolgus monkey.

After oral dosing, BEN8744 plasma PK was characterised by rapid absorption, with t_{max} ranging 0.31– 1.3 h, and t½ ranging 2.1–4.0 h. Both mouse and rat were dosed

in the fed state, whereas dog and monkey were dosed in the fasted state. Bioavailability (F) or the oral dose relative to the intravenous doses ranged 18–31% in rat, mouse, and monkey, and was > 90% in dog. Appreciable levels of unchanged drug were found in the faeces of all species after both IV and oral administration.

Distribution and metabolism studies using mouse, rat, cynomolgus monkey, dog and human plasma, and rat colon tissue, showed high binding of BEN8744 (at 1 μM) to plasma proteins in all species. In plasma samples, binding was highest in mouse and rat (97%) and lowest in dog (95%); binding in the rat colon was 3-fold higher than in plasma.

BEN8744 was designed not to cross into the brain, to reduce side effects seen in other drugs with the same mechanism of action. In rats, BEN8744 concentration was significantly greater in the plasma than in the brain (mean brain:plasma ratio was 0.03), indicating limited blood brain barrier penetration.

BEN8744 is moderately stable in microsomes and hepatocytes across species and is metabolised predominantly by CYP3A4 with negligible contribution from other cytochrome P450 (CYP) enzymes. BEN8744 is an inhibitor of CYP2C8; however, human unbound exposure is expected to be approximately 30-fold lower than the IC_{50} for that isoform. BEN8744 demonstrated some induction of CYP3A4 at 10 uM, but no significant induction of CYPs was observed at 0.1 or 1 uM relative to the positive control. BEN8744 is therefore not expected to trigger direct drug-drug interactions by interfering with CYP enzymes at the concentrations used in this study.

BEN8744 is primarily eliminated in rat faeces as unchanged drug, with some elimination in urine (approximately 1%).

6.2.3 Non-clinical safety and toxicology

Safety pharmacology

Safety pharmacology endpoints were primarily investigated in 28-day repeat-dose toxicology studies in rats and dogs.

No BEN8744 related effects were detected at single doses of 40 mg (respiratory system and in an Irwin study) or ≤ 200 mg/kg twice-daily (BID) (other central nervous system [CNS]) in rats. BEN8744 produced a dose-dependent, statistically significant decrease in respiratory rate at single oral doses of 100 and 200 mg/kg in rats. No effects were observed on tidal volume or minute volume at any of the doses tested.

No BEN8744 related cardiovascular system effects were detected up to 5 mg/day in Beagle dogs. Additionally, there were no ECG or heart rate effects noted in the dog 4-week toxicity study at doses up to 10 mg/kg/day.

BEN8744 produced a concentration-dependent inhibition of the human Ether-à-go-go-Related Gene (hERG) tail current repolarisation in hERG channel

expressing Chinese hamster ovary cells *in vitro*, but only at high concentrations of BEN8744 (IC_{50} = 9.3 µM [4.8 µg/mL], which exceeds the expected C_{max} in humans by > 50-fold).

Toxicology

In a 28-day good laboratory practice (GLP) repeat-dose study, doses of 40–200 mg/kg (equivalent to 80–400 mg/kg/day) BID, administered by oral gavage, was well tolerated in both male and female rats. Reversibility of BEN8744 related effects was assessed after 14-day washout in rats dosed with 400 mg/kg/day. An overall decrease in body weight (13%) was seen in male rats at the highest tested dose, and a statistically significant decrease in terminal body weight. Minor haematology changes were seen in females at 200 and 400 mg/kg/day, and males at 400 mg/kg/day, but these were reversible after a 14-day washout period. Statistically significant increases in relative heart and kidney weights and decreases in thymus weights, were also seen after 400 mg/kg/day. None of these changes correlated with microscopic findings and all were at least partially reversible after 14-day washout; changes were therefore considered non-adverse. Based on these results, the no observed adverse effect level (NOAEL) was 400 mg/kg/day (equivalent at 28-days to mean AUC_{last} of 429 or 614 µg·hour/mL and mean C_{max} of 34 or 45.7 µg/mL, for males and females, respectively).

In a 7-day dose range finding study in Beagle dogs, a maximum tolerated dose of 60 mg/kg/day was determined. In a 28-day GLP repeat-dose study, doses of 5–30 mg/kg BID (equivalent to 10–60 mg/kg/day) was given by oral gavage in Beagle dogs. However, doses of 15 and 30 mg/kg were not tolerated after a single dose. Dosing was ceased in all animals, and adverse clinical signs included tremors, poor co-ordination, decreased activity, and dry gums. One animal receiving 15 mg/kg was euthanised on Day 1 due to severity of adverse effects.

BEN8744 was administered by oral gavage at doses of 1.5–5 or 7.5 mg/kg (equivalent to 3–10 or 15 mg/kg/day) when the study restarted after 33 days. Reversibility of BEN8744 related effects was assessed after 14-day washout in dogs dosed with 10/15 mg/kg/day. A single dose of 7.5 mg/kg (the first of BID dosing to give a total daily dose of 15 mg/kg/day) was not tolerated (with similar adverse clinical signs to those seen at 15 and 30 mg/kg), and the dose was subsequently lowered to 5 mg/kg in those animals, to give a total daily dose of 10 mg/kg/day. Doses of 10 mg/kg/day were associated with transient decreased activity and/or subdued behaviour, and slight head tremors in some animals at Day 4 – these were deemed to be non-adverse. Transient poor co-ordination was seen in 2 animals after 6 mg/kg/day after first administration, and decreased activity seen in 1 animal on Day 5. After 28-days of doses up to 10 mg/kg/day, there were no BEN8744 related effects on body weight, ophthalmology, electrocardiology, clinical pathology parameters or organ weights and there were no macroscopic or microscopic findings. Based on these results, the NOAEL was 10 mg/kg/day (equivalent at 28-days to

mean AUC_{last} of 23.8 or 25.3 µg·hour/mL, and mean C_{max} of 4.45 or 4.97 µg/mL, for males and females, respectively).

Other studies

No carcinogenicity or reproductive and development toxicity studies have been conducted with BEN8744.

The mutagenic and clastogenic potential of BEN8744 was assessed in bacterial and mammalian assays. There was no evidence of mutagenicity or genotoxicity *in vitro* or *in vivo*. Additionally, no impurities of known or potential mutagenic concern were considered likely to be present in final drug substance at a level exceeding the appropriate threshold of toxicological concern as per International Conference on Harmonisation M7 guidance[30] at the planned clinical dose range.

BEN8744 showed no phototoxic potential when tested up to the maximum recommended concentration of 100 µg/mL in the Neutral Red Uptake test in BALB/3T3 fibroblasts, clone A31.

6.2.4 Clinical experience

Experience with BEN8744 in humans is limited. To date, 32 healthy subjects have received single oral doses of 2, 6, 20, or 60 mg BEN8744, or placebo (Part A, Cohorts A1–A4).

Safety and tolerability

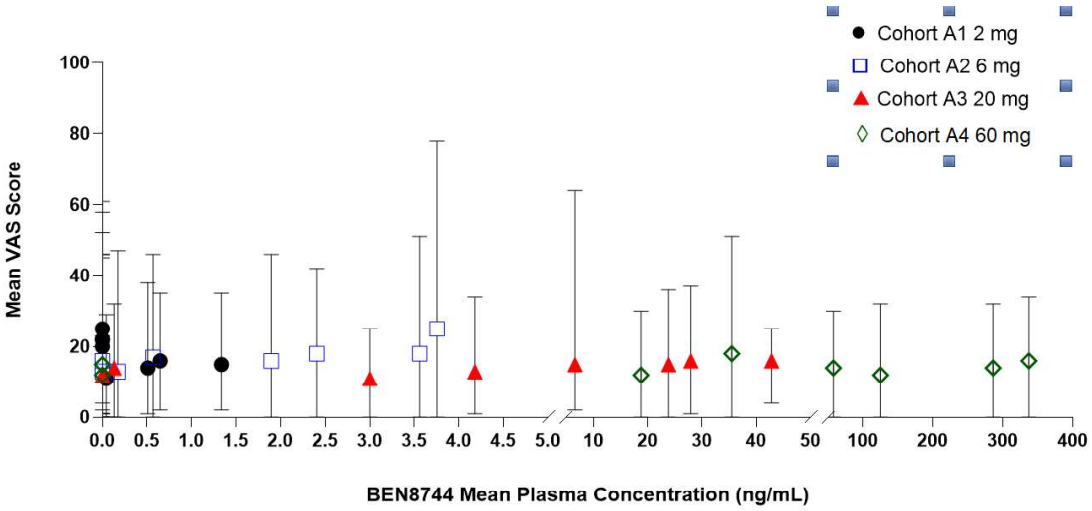
Single doses of 2–60 mg BEN8744 were safe and well tolerated: there were no serious AEs, and all AEs were mild or moderate in severity (see Table 1). There were no withdrawals due to an AE. The study is still blinded, it is not known which subjects received placebo or active treatment, meaning assigning causality to BEN8744 cannot yet be done.

Table 1: Adverse Events (Cohorts A1–A4)

Subject	Dose (mg)	Adverse Event	Severity	Related to administration of BEN8744
1005	2	Toothache	Moderate	Unlikely to be related
1009	6	Costochondritis	Mild	Unlikely to be related
1022	20	Acid reflux	Mild	Unlikely to be related
1023	20	Fatigue	Mild	Possibly related
1024	20	Sleepiness	Mild	Possibly related
1028	60	Gastroenteritis (shigella)	Moderate	Not related
1032	60	Headache	Mild	Possibly related

There were no clinically significant changes in laboratory assessments (routine haematology, clinical chemistry, and urinalysis), physical examination, 12-lead ECG, vital signs (blood pressure, pulse rate, respiratory rate, and tympanic temperature) OAAS/S and VAS (for sedation). In humans, sedation is the most common AE seen with PDE10 inhibitors, that cross the blood brain barrier and penetrate the brain, and BEN8744 has been designed to be a non-brain penetrant inhibitor. Results from Cohort A1-A4 support this, there were no dose-related CNS AEs. Of note, analysis of mean VAS scores (for sedation) vs BEN8744 plasma concentrations (Figure 1) showed no trend for an increase in sedation with increasing plasma concentrations.

Figure 1: Mean (min, max) VAS scores* vs mean BEN8744 plasma concentration following single doses of 2–60 mg in healthy subjects



VAS = visual analogue scale; min = minimum; max = maximum. *VAS to monitor sedation.

Pharmacokinetics

PK data has been reviewed from Cohorts A1–A4, and mean (range) PK parameters and plasma concentration–time profiles for single oral doses of 2–60 mg (observed) and 100 mg (predicted) BEN8744 are presented in Table 2 and Figure 2, respectively.

A linear non-parametric superposition approach was used to predict drug concentrations after single or multiple dosing using Phoenix WinNonlin® Version 8.4. Predicted drug concentrations at 100 and 140 mg QD, and 50 mg BID, were based on both mean plasma concentration profiles and the individual plasma profile of the subject with the highest exposure to date (Cohort A4 [60 mg]).

Table 2: Summary of (mean [range]) actual and predicted (100 and 140 mg) BEN8744 plasma PK parameters after single oral doses of 2–60 mg in healthy subjects

Dose (mg)	N	Mean (range)			
		C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{24} (ng*h/mL)	AUC_{inf} (ng*h/mL)
2[b]	6	1.34 (0.59–2.68)	2.00 (2.00–2.00)	–	–
6	6	5.03 (1.33–11.30)	1.50 (0.50–3.00)	15.23 (5.68–26.6)	15.16 (5.67–26.4)
20	6	46.1 (20.7–57.7)	2.00 (1.00-3.00)	163.25 (77.40–210)	164.12 (77.30–210)
60	6	352.83 (130–688)	1.00 (1.00-2.00)	1,057.27 (494–2,380)	1,059.2 (494–2,390)
100 pred[c]	–	1,100	1.35	3,950	3,986
140 pred[c]	–	1,541	1.35	5,530	5,581

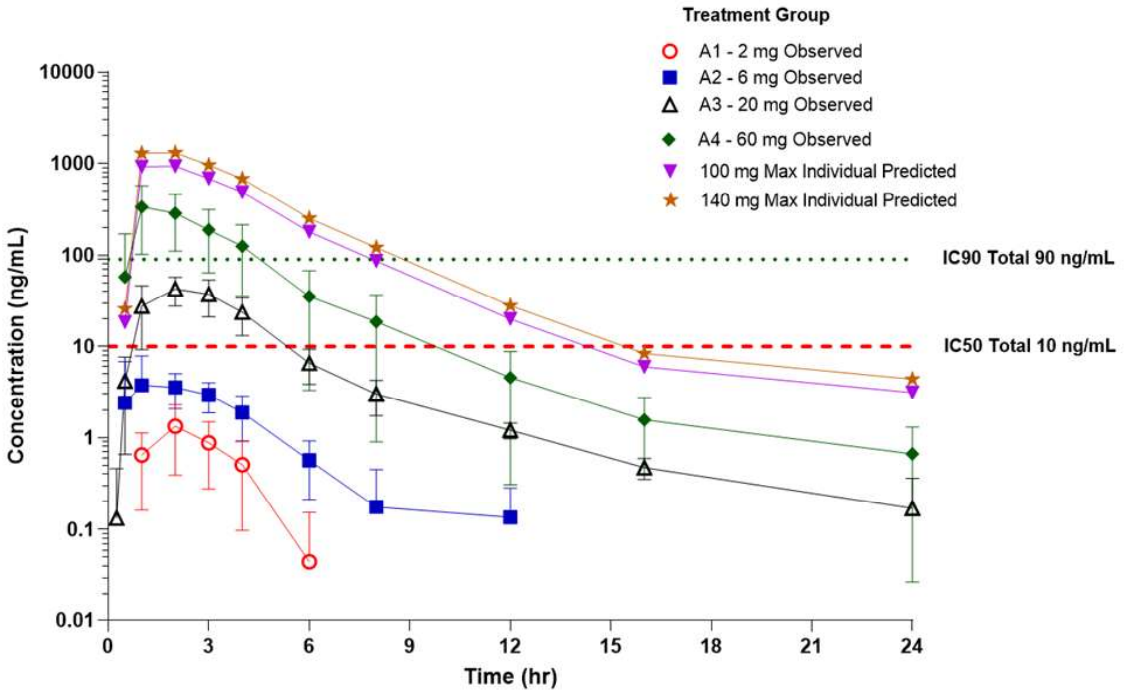
SD = standard deviation; C_{max} = maximum plasma concentration; t_{max} = time of C_{max}; AUC_{24} = area under the concentration–time curve from time zero to time 24 h; AUC_{inf} = area under the concentration– time curve extrapolated to infinite time; pred: predicted: max: maximum.

[a] Median (min – max).

[b] Insufficient plasma concentration data at terminal phase to estimate terminal phase related pk parameters.

[C] 100 mg and 140 mg profiles predicted based on the individual plasma profile of the subject with the highest exposure to date (Cohort A4 [60 mg]), using a nonparametric superposition function.

Figure 2: Mean (SD) BEN8744 plasma concentration–time profiles after single oral doses of 2–60 mg (observed) and 100 mg (individual predicted) in healthy subjects (linear and semilogarithmic scale)



SD = standard deviation; IC50/90 = concentration required for 50%/90% inhibition.

After single doses of 2–60 mg, BEN8744 demonstrated a shorter than expected elimination half-life, ranging approximately 2–4 h. At the highest dose tested (60 mg), mean C_{avg} was below IC_{90}. However, a single subject had a higher AUC_{inf}, approximately 2-fold above the mean and above IC_{90}. In all subjects after 60 mg BEN8744, plasma concentrations decreased below the IC_{50} by 11 h postdose. Considering the observed short half-life, and predicted required time above IC_{50} for efficacy in patients, a twice daily dosage regimen will be required in Part C (MAD Phase) to achieve exposures above IC_{50} for up to 18–24 h.

The impact of gut P-glycoprotein (P-gp) efflux and gut cytochrome p450 3A4 (CYP3A4) mediated metabolism was not expected to be significant in humans; however, emerging clinical data suggests there is an impact which is significant at lower doses. Between 2 and 6 mg QD the increase in PK parameters appeared dose-proportional, but escalation between 6, 20 and 60 mg QD resulted in a greater than proportional increase in AUC_{inf}, suggestive of non-linear PK. Additionally, between-subject variation was high. While the linear approach overpredicted exposures at low doses, the mean C_{max} and AUC_{inf} at 60 mg aligns with predicted exposures. Mean apparent clearance (CL/F) decreased with an increase in dose from 6 to 60 mg QD, which may indicate approaching saturation of gut P-gp and CYP3A4. Hence, at higher doses exposure is expected to be closer to dose-proportional.

6.3 Rationale for the trial

This first time in human (FTIH) study will investigate the safety, tolerability, PK of BEN8744 after single and multiple ascending oral doses in healthy subjects, in both the fed and fasted state. The results of this study will be used to select doses for subsequent studies in patients. Part B of this study was designed in line with the US Food and Drug Administration (FDA) guidelines on food-effect bioavailability studies.

6.4 Participant input into trial design

This is a phase 1, exploratory study in healthy volunteers, with no anticipated therapeutic benefit to the participants; involvement of patients, service users or members of the public in the design of the trial is not appropriate.

6.5 Rationale for choice of dose(s)

At the time of writing, Cohorts A1–A4 (Part A) have completed the study (see section 6.2.4 for details). After a single 60 mg dose (Cohort A4), 1 subject met 89% of the protocol-defined AUC_{inf} threshold (based on IC_{90} predicted *ex vivo* data). The protocol (section 8.5.4) states that doses in Part C (MAD) cannot be predicted to exceed the maximum observed C_{max} and AUC_{inf} achieved in Part A (SAD). Due to the PK profile and indication-specific tissue exposure requirements, further dose

escalation in Part A up to a maximum of 140 mg QD may be required to support the MAD phase of the study, and future studies of BEN8744. So, the protocol has been subject to a substantial amendment, incorporating data from completed Cohorts A1–A4, to provide rationale to allow dosing up to 140 mg QD in Part A (which is expected to exceed the previous threshold but remain within the updated PK threshold: the NOAEL in the most sensitive species [dog]).

6.5.1 Doses up to Cohort A4

Before the present study (BB-8744-1001), BEN8744 had not yet been administered to humans, so no human exposure data existed. However, PDE10 inhibition as a mechanism of action has been described in humans, with numerous molecules under development as therapeutic agents. Two such examples are Mardepodect and Balipodect, both of which have completed clinical trials. The most frequently reported adverse effects from acute dosing of both agents is somnolence, which is often reported in a dose-dependent manner and is attributed to on-target activity of PDE10A inhibition in the brain when receptor occupancy exceeds 20%. This effect has also been seen in other preclinical species.

Based on *in vitro* potency and prediction of human PK from animal studies, it was calculated that a starting dose of 2 mg for BEN8744 was predicted to have < 1% PDE10A enzyme occupancy in the brain and about 20% average enzyme occupancy in the periphery. At this low dose on BEN8744, any potential side effects (ie sedation) are minimised (in contrast to other PDE10A inhibitors where uptake into the brain is about 10-fold higher than that predicted for BEN8744). The exposure level at this dose was predicted to be > 690-fold below levels where sedation occurs in pre-clinical animals.

The proposed doses in Part A of this study were selected based on physiologically based PK modelling, analysis of safety, tolerability and PK data from non-clinical studies, and previous published information on compounds with a similar mechanism of action. The rationale for dose selection is discussed in detail in the IB[29], and summarised below.

Toxicology-based safe starting dose

The maximum recommended starting dose in man (MRSD) was estimated using the method outlined by the FDA[31], calculating a human equivalent dose (HED) using the body surface area conversion factor (BSA-CF) and a safety factor. Pharmacological activity was also taken into account in selecting the human starting dose.

For the purposes of the calculation, a normal human volunteer was assumed to weigh 70 kg. The most appropriate species for estimating the MRSD was selected according to the FDA guidance, as the lowest estimate between the 2 safety species (rat and dog).

The HED at the lowest NOAEL was in dog, obtained in repeat-dose toxicity studies (BenevolentAI Cambridge Ltd, report CRL-522041). The dog was selected as the species most sensitive to the effects of BEN8744, as adverse clinical signs related to the test item were observed (see section 6.2.3). In the 4-week dog study, the NOAEL was 10 mg/kg, producing a C_{max} of 4,710 ng/mL and AUC_{last} of 24,500 ng.h/mL. Using a conversion factor of 0.54, that corresponds to a HED of 5.4 mg/kg/day (or approximately 378 mg/day for a human weighing 70 kg). Once a safety factor of 10 is applied, the MRSD would be 37.8 mg/day in humans with a body weight of 70 kg.

In the SAD part (Part A), the proposed starting dose was 2 mg. Details of the PK/PD modelling used are included in the IB[29]. The predicted data are shown in Table 3. Subsequent doses were decided by the SRG as described in section 8.5.

Relative to the NOAEL in the most sensitive species (dog), large safety margins exist. Additionally, the $C_{average,u}$ for a single starting dose of 2 mg would result in about 20% PDE10A occupancy in the periphery. Taking into account brain to plasma ratios, $C_{average,u}$ in the brain is predicted to result in PDE10A occupancy of < 1%. This is > 690-fold below the exposure (AUC_{24}) where adverse effects were observed in the dog. The proposed starting dose of 2 mg was therefore supported from a non-clinical safety perspective.

Table 3: Safety Margins to Predicted Human Exposure for a starting dose, PAD, MRSD, top dose and HED.

	Human dose	Predicted % receptor occupancy C_{avg} (plasma)	C_{max} (ng/ml)	AUC_{24} (ng.h/ml)	Safety margin C_{max}	Safety margin AUC_{24}
Starting dose	2 mg QD	19	6.6	48	714	510
PAD	10 mg QD	56	75	261	63	94
MRSD	38 mg QD	82	346	936	14	26
Top dose	140 mg QD	90	1,190	2,674	4	9
HED	380 mg QD	98	3,704	9,794	1	3

Abbreviations: HED = human equivalent dose; MRSD = maximum recommended starting dose; PAD = pharmacodynamically active dose; QD = once-daily; C_{max} = maximum plasma concentration; C_{avg} = average plasma concentration during multiple-dose administration; AUC_{24} = area under the concentration–time curve from time zero to time 24 h.
Safety margins are calculated based on the NOAEL in the dog (5 mg/kg BID) from a 28-day toxicity data (Report CRL-522041); Dog NOAEL 10mg/kg/day. HED calculated by multiplying mg/kg/day by appropriate conversion factor (0.54 for dogs) to obtain the HED in mg/kg, and multiply by body weight, based on 70 kg human. MRSD calculated using a 10-fold safety margin from the HED.
PK dose simulations and receptor occupancy calculations for doses reported in 22-8744-005PK.

Anticipated human pharmacologically active dose range

Before the start of this study, PAD doses were predicted based on the target unbound average plasma concentrations ($C_{average}$) of 0.7 to 7.0 nM (the IC_{50}–IC_{90} of BEN8744) after BID dosing of BEN8744 for 14 days. Considering the variability in the model predictions, a dose range was predicted to be 5–12 mg BID and 46–69 mg BID based on $C_{average,u}$ for free IC_{50} and IC_{90} levels, respectively, in humans. These dose

estimations are theoretical, based on *in vitro* IC_{50}, plasma protein binding, and predicted PK in humans. A single dose of 10 mg BEN8744 was predicted to provide about 50% enzyme occupancy in the periphery. The highest planned dose in this study is 140 mg, which is predicted to achieve the theoretical IC_{90} $C_{average,u}$. Dose levels may change (upwards or downwards) depending on observed human exposure, but no dose will exceed 140 mg/day.

6.5.2 Subsequent dose levels

Based on the observed PK profile so far, and the relationship between PDE10 theoretical target engagement and BEN8744 concentrations seen in this study to date, it is predicted that due to the short half-life of BEN8744 (~2–4 h) an estimated daily dose of approximately 100 mg (50 mg BID) will be required to maintain sufficient target engagement in all target tissues over a 24 h period in future studies.

The maximum planned dose for Part A (140 mg QD), is predicted to achieve an absolute maximum blood concentration of C_{max} = 1,541 ng/mL, AUC_{24} = 5,530 ng*h/mL, and AUCinf = 5,581 ng*h/mL (see Table 2). That is 3- and 4-fold below the NOAEL in the 28-day dog study for C_{max} and AUC, respectively, and will not be exceeded in any 24 h period. The planned dose for Cohort A5 is 100 mg QD. Planned doses for Parts B and C may be adjusted to account for differences between predicted and actual/observed PK, in line with the dose escalation criteria in section 8.5.

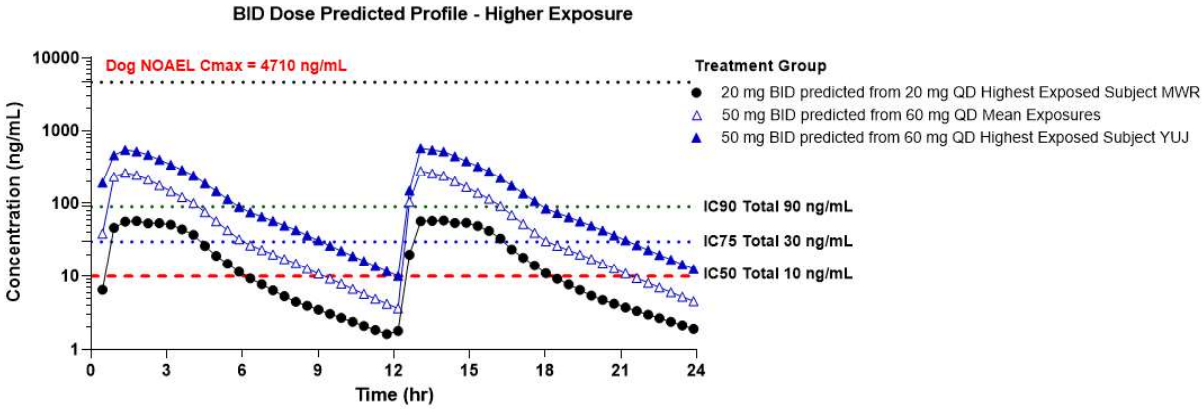
Based on non-parametric superposition modelling (see Table 4), using data from the subject with the highest exposure to date (Cohort A4 [60 mg]), it is anticipated that the BEN8744 pharmacologically active dose will be ~ 50 mg BID. As shown in Figure 3, the 50 mg BID dose is expected to a achieve a time (T) > IC_{50} of 18 (mean) to 24 h (maximum) with a C_{trough}/IC_{50} ratio of approximately 1. In order to proceed with Part C (MAD) dosing at > 30 mg BID, the limit in section 8.5.2 has been updated to the NOAEL in the most sensitive species (dog), to allow dosing up to 140 mg to achieve the T > IC_{50} and C_{trough}/IC_{50} ratio predicted to achieve the required efficacy for BEN8744.

Table 4: Predicted BEN8744 plasma pharmacokinetic parameters (maximum and mean) following BID administration at 20 and 50 mg

Cohort/Dose (BID)*	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	$T > IC_{50}$ (h)	C_{trough}/IC_{50} Ratio	Margin to dog NOAEL (C_{max}/AUC)
20 mg Observed	57.36 (mean 42)	488.12 (mean 320)	11.57 (mean 10)	0.17	82/50
50 mg Predicted	550.21 (mean 264)	4,063.33 (mean 1,744)	24.53 (mean 18)	1.06	9/6

BID: twice-daily; C_{max}: maximum plasma concentration; AUC: area under the concertation–time curve; AUC24: AUC from time 0 to 24 h; IC_{50}: concentration required for 50% inhibition; C_{trough}: trough plasma concentration. NOAEL: no observed adverse effect level; T = time.
* The 20 mg BID profile predicted based on observed A3-20 mg QD mean PK profile and 50 mg BID profile predicted based on Subject ID YUJ (highest exposed subject) 60 mg QD profile, using nonparametric superposition.

Figure 3: Predicted BEN8744 plasma concentration–time profiles following 20 and 50 mg twice-daily oral administration in healthy subjects



BID: twice-daily; QD: once-daily; NOAEL: no observed adverse effect level; $IC_{50/75/90}$: concentration required for 50%/75%/90% inhibition.

6.6 Assessment and management of risk

Any safety risk to study participants is mitigated by the considerations in Table 5. Any risks are adequately mitigated by safety assessments, and by the medical cover provided by the investigator site, and by appropriate IMP manufacture, according to Good Manufacturing Practice (GMP).

There will be no direct health benefit for study participants from receipt of study medication. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical examination received at screening and during the study.

Overall, the investigators consider the overall risk benefit balance to be acceptable.

Table 5: Summary of study risk mitigation strategy

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
CNS effects	In clinical trials of brain penetrating PDE10A inhibitors, the most frequently reported AE was somnolence, which was attributed to on- target activity of PDE10A inhibition in the brain when receptor occupancy exceeded 20%. In pre-clinical toxicology studies, CNS related AEs were identified, including tremor, decreased activity and/or subdued behaviour, impaired coordination, and dry gums (further details can be found in the IB[29]).	An OAAS/S and VAS will be used to monitor alertness and sedation at the timepoints listed in section 12. Volunteers with a history of suicidal behaviour or ideation will be excluded from the study, as per exclusion criterion 5. The Columbia-Suicide Severity Rating Scale (C-SSRS) for Suicidal Ideation will also be given to study participants in Part C on the day of discharge from the ward and at follow-up to assess any potential suicidal ideation or behaviour.
Changes in haematology parameters	In pre-clinical studies, changes in haematology parameters (including a reduction in red cell mass, increases in reticulocyte and neutrophil counts), body and organ weights have been observed. However, those changes were considered non-adverse due to the lack of correlating microscopic findings and evidence of reversibility.	Subjects will be excluded if their screening tests show clinically relevant abnormal haematology parameters (see exclusion criterion 2). Haematology parameters will be assessed as part of the postdose laboratory safety assessments.
Effect on human embryo/fetus	No reproductive toxicology studies have been done. Therefore, demonstrated or possible teratogenicity/fetotoxicity should be assumed.	WOCBP must use a highly effective method of contraception with low user dependency during the trial. Men must not have sex during the trial without using a condom. Participants should not plan to become pregnant or father a child during exposure to BEN8744. Further details of the contraceptive requirements are in section 11.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study considerations		
This is the first clinical study of BEN8744 in humans.	To date, BEN8744 has only been investigated in non-clinical studies[29].	Because BEN8744 has never been given to humans before, this study has been designed according to the EMA guidance on risk mitigation of FIH and early phase trials[32]. Details about starting dose and maximum intended dose selection are in section 6.5. A sentinel dosing approach will be used for the first dose, and at each new ascending single dose level, as detailed in section 10.5. As this is a FIH, the investigator must obtain a reply from the General Practitioner (GP), or have a valid GP reply on file, before dosing a subject in Part A. HMR is accredited by the Medicines and Healthcare products Regulatory Agency (MHRA) to do first in human studies and will follow its standard operating procedures (SOPs).
	In any clinical trial there is a risk of an unexpected adverse reaction.	HMR maintains its own resuscitation team (HMR SOP: SS329) to deal with medical emergencies, including anaphylaxis and cardiac arrest. The team will be on duty continuously, until at least 24 h after each dose. Subjects will be monitored frequently throughout the study for safety and tolerability. The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs.

6.7 Conducting the trial during the COVID-19 pandemic

The investigator and sponsor have reviewed the risks of conducting the trial during the current COVID-19 pandemic. Our priority is the safety of trial subjects and staff, but we also have an ethical duty to preserve the scientific integrity of the trial as far as possible.

BEN8744 is unlikely to increase the risk of contracting COVID-19 infection, or to worsen the severity of an infection. BEN8744 has no immunosuppressive effect, and is not associated with cough, pyrexia, or anosmia, which would require isolation of subjects.

BEN8744 is unlikely to affect the efficacy of a vaccine against SARS-CoV-2. However, to delineate adverse events (AEs) caused by BEN8744 or a vaccine, vaccines will be prohibited from 28 days before (first) dosing until the follow-up visit. That's ethically acceptable owing to the short duration of participation for each subject.

This clinical trial will be done in accordance with HMR's COVID-19 risk mitigation policy (RMP), which documents HMR's COVID-19 virus testing strategy for volunteers and staff, social distancing measures, and management of COVID-19-like symptoms. HMR's RMP was first notified to the Medicines and Healthcare Products Regulatory Agency (MHRA) and Health Research Authority (HRA) on 22 May 2020 and applies across all HMR's trials. The mitigation measures specified in the HMR COVID-19 RMP are deemed adequate for this trial. Any deviations from the RMP will be documented in a separate COVID-19 trial-specific risk assessment, prepared by the investigator. Any deviations from the protocol that result from the COVID-19 pandemic, and COVID-19 related AEs or serious adverse events (SAEs), will be documented.

Taking the above factors into account, and the proposed mitigation, we believe that it is medically and ethically acceptable to proceed with the trial during the current COVID-19 pandemic.

7 Objectives and endpoints

7.1 Objectives

7.1.1 Primary objectives

Part A: To assess the safety and tolerability of single ascending oral doses of BEN8744 in healthy subjects

Part B: To characterise the effect of food on the pharmacokinetic (PK) profile of at least 1 dose of BEN8744

Part C: To assess the safety and tolerability of multiple ascending oral doses of BEN8744 in healthy subjects

7.1.2 Secondary objectives

Part A: To assess the PK profile of BEN8744 after single oral doses in healthy subjects

Part B: To assess the safety and tolerability of a single dose of BEN8744 following high-fat food intake relative to fasting conditions in healthy subjects

Part C: To assess the PK profile of BEN8744 after repeated oral doses in healthy subjects

7.1.3 *Exploratory objective*

Part B (and optional in Part C):

To measure BEN8744 in urine and determine renal clearance in healthy subjects*

Exploratory characterisation of BEN8744 and its metabolites in plasma, urine, and faeces†

*If significant amounts of the parent compound are detected in Part B, the parent compound may be measured in Part C (in urine at 2 dose levels [low and high]).

†Faeces will be analysed in Part B only. If significant amounts of metabolites are detected in Part B, exploratory metabolite analyses may be conducted in Part C (in plasma and urine at 2 dose levels [low and high] on Day 1 and Day 14).

7.2 Endpoints

7.2.1 Primary endpoints

Safety and tolerability (Parts A and C): vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead electrocardiogram (ECG), cardiac telemetry (Part A only), physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), adverse events (AEs), and Observer's Assessment of Alertness/Sedation scale (OAAS/S), visual analogue scale (VAS) to monitor sedation, and C-SSRS (Part C only).

PK (Part B): C_{max}, t_{max}, AUC_{24}, AUC_{72}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL/F, V_Z/F

7.2.2 Secondary endpoints

PK (Part A): C_{max}, t_{max}, AUC_{24}, AUC_{72}, AUC_{last}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL/F, V_Z/F

Safety and tolerability (Part B): vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead ECG, physical examination, laboratory safety tests (haematology, clinical chemistry, and urinalysis), AEs, and OAAS/S and VAS to monitor sedation.

PK (Part C): C_{max}, t_{max}, C_{trough}, AUC_{tau}, AUC_{last}, AUC_{72}, AUC_{inf}, $\%AUC_{extrap}$, $t_{½}$, λ_Z, CL_{SS}/F, V_Z/F, $R_{ac(AUC)}$, $R_{ac(Cmax)}$, $SR_{(AUC)}$

7.2.3 Exploratory endpoints

PK (Part B and optional in Part C): Ae_{72}, $f_e \cdot F$, CL_R

8 Overall trial design

8.1 Trial design

This is a Phase 1, FTIH, single-centre, randomised, double-blind, placebo-controlled, dose escalation trial to assess the safety and tolerability, PK, and food effect of BEN8744 in healthy subjects.

The trial will be in 3 parts: Part A will investigate single ascending oral doses of BEN8744; Part B is a 2-way crossover assessment of the effect of food on the PK of BEN8744; and Part C will investigate multiple ascending oral doses of BEN8744.

A schematic diagram of the study design is in section 8.2.

8.1.1 Part A

Enrolment of up to 64 healthy subjects is planned, in up to 5 groups (Groups A1–A5) and 3 optional groups (Groups A6–A8). Each group will consist of 8 subjects.

Subjects will receive a single dose of BEN8744 or placebo, as capsules, after an overnight fast of at least 10 h. At each dose level, 6 subjects will receive BEN8744 and 2 will receive matching placebo in an overall ratio of 3:1.

The starting dose for Group 1 is 2 mg BEN8744 or placebo. It is intended that subsequent cohorts will receive higher doses. The planned doses are in Table 6.

Table 6: Planned doses in Part A

Group	Dose of BEN8744
A1	2 mg
A2	6 mg
A3	20 mg
A4	60 mg
A5	100 mg
A6 (optional)	TBC
A7 (optional)	TBC
A8 (optional)	TBC

Additional intermediate or higher dose levels may be explored in 3 optional groups (Groups A6–A8). The dose levels will be selected by the safety review group (SRG) as described in section 8.5.

The dose will not be escalated unless the safety and tolerability of the previous dose are acceptable, and the conditions in section 8.5 are met. There will be an appropriate interval between sequential groups, to allow for review of those data.

Because BEN8744 has never been given to humans before, each new ascending dose will be staggered: 2 sentinel subjects will be dosed first, and the remaining subjects will be dosed at least 23 h later. To maintain the blind nature of the study, the 2 sentinel subjects will be randomised to ensure that 1 subject receives active treatment and the other receives placebo. Since one subject will receive placebo treatment, the sentinel subjects may be dosed at least 5 min apart. Provided the investigator considers the safety and tolerability in the sentinel subjects to have been acceptable, the remaining subjects will be dosed, at intervals of at least 10 min.

If the dose level selected is no higher than one that has already been shown to cause no safety concerns, sentinel subjects will not be required, and subjects will be dosed at intervals of at least 10 min.

Subjects will be screened within 28 days before their (first) dose of trial medication. Subjects will be resident on the ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4). They will return for a follow-up visit 7 (±2) days after their inpatient stay (Day 11 ±2 days).

8.1.2 Part B

Enrolment of up to 12 healthy subjects is planned, in up to 2 groups (Groups B1 and B2).

Each subject in Part B will have 2 study sessions (Sessions 1 and 2), in which they will receive a single dose of BEN8744, by mouth. Each subject will receive BEN8744 after an overnight fast of at least 10 h in one session, and after an FDA high-fat breakfast (1,013 kcal, 59.2 g fat [of which 28.1 g saturated fat]) in the other session; the order will be randomised 1:1, as shown in Table 7. A subject's doses

will be separated by a washout of at least 7 days (or 5 half-lives as determined in Part A, whichever is longer). Subjects dosed on the same day may be dosed at intervals of at least 10 min.

Table 7 Treatment sequence for each group (n=6 each) in Part B

	Session 1	Session 2
n=3 subjects	Fed	Fasted
n=3 subjects	Fasted	Fed

The dose to be tested in Group B1 will be decided following review of the interim safety, tolerability, and PK data from at least 3 dose levels in Part A, as described in section 8.5.3.

To reduce the risk of unexpectedly high plasma concentrations, the dose selected for Group B1 will be no higher than 50% of the highest dose tested in Part A that caused no safety concerns.

Group B2 is optional and may be required if the Sponsor decides to test the effect of food at an additional dose level (for example, if absorption and hence exposure is not proportional to dose in Part A) or under different conditions (eg with different fasting requirements or after a different meal such as a standard breakfast). The dose and food requirements for Group B2 will be decided following review of the interim safety, tolerability, and PK data from Group B1 and all available data from Part A.

Subjects will be screened within 28 days before their first dose of trial medication. Subjects will be resident on ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4). They will return for a follow-up visit 7 (±2) days after their inpatient stay in Session 2 (Day 11 ±2 days).

8.1.3 Part C

Enrolment of up to 32 healthy subjects is planned, in up to 3 groups (Groups C1–C3) and 1 optional group (Group C4). Each group will consist of 8 subjects.

Each subject will receive daily doses of BEN8744 or placebo, by mouth, for 14 days. At each dose level, 6 subjects will receive BEN8744 and 2 will receive matching placebo. Doses will be taken once or twice daily in the fasted state, unless emerging data indicate they should be taken in the fed state.

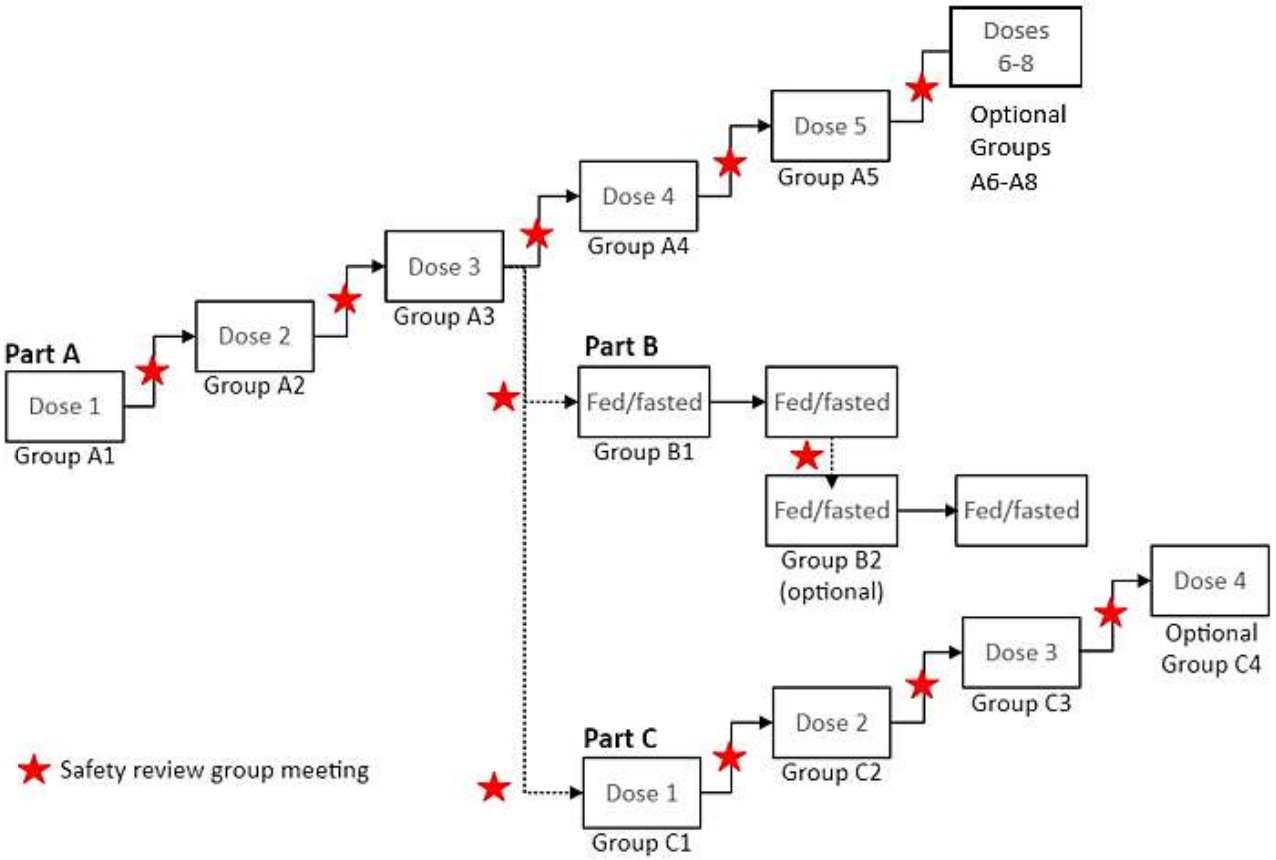
Part C will not start until at least 3 dose levels have been completed in Part A, as described in section 8.5.4. Part C may also be conducted in parallel with Part B. The dose, dosing regimen (once or twice daily), and whether the dose is taken fed or fasted, will be determined based on review of the available safety, tolerability and PK results from Parts A and B, and previous groups in Part C, as described in section 8.5.

The first total daily dose (ie, morning plus evening dose, if a twice-daily dosing regimen is chosen) tested in Part C (Group C1) will be the same as, or lower than, a single dose that has been given in Part A without any safety concerns. See also section 8.5.

Subjects will be screened within 28 days before their first dose of trial medication. Subjects will be resident on ward from the day before their dose (Day −1) until up to 72 h after their final dose (Day 17). They will return for a follow-up visit 7 (±2) days after their inpatient stay (Day 24 ±2 days).

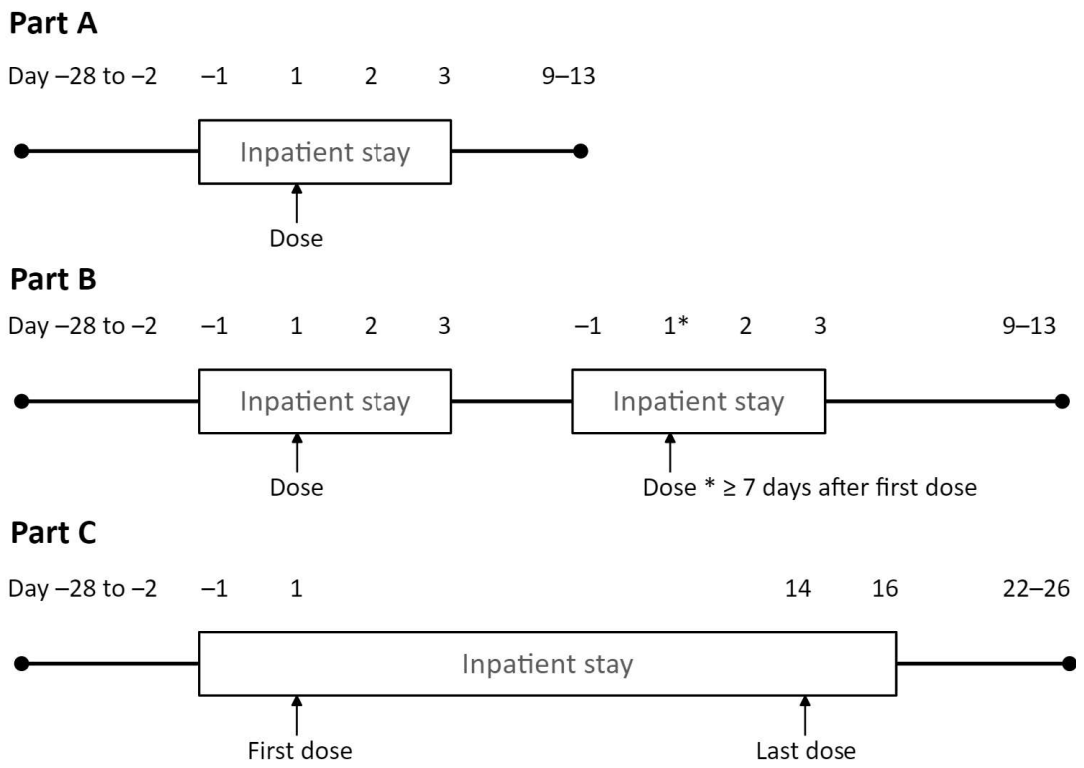
8.2 Study flow chart

Figure 4: Schematic of the overall study design



Note: Dose 1 in Part A will be 2 mg. Subsequent doses will be decided by the safety review group. Doses in Parts B and C will be decided by the safety review group after at least 3 dose levels have been investigated in Part A.

Figure 5: Schematic of the study design of Parts A, B, and C



8.3 Definition of the end of the trial

The end of the trial is defined as the final follow-up visit by the last subject. If the trial is terminated prematurely, the trial ends when the sponsor notifies the investigator in writing that the trial has finished, or when the last subject attends the final follow-up visit, whichever is later.

8.4 Stopping criteria

8.4.1 Trial stopping criteria

The trial will be stopped if either of the following occurs:

- 1 or more SAEs considered to be at least possibly related to study treatment; or
- 2 or more severe or clinically significant adverse events (AEs) that are considered to be at least possibly related to study treatment at any dose level.

In Parts A and C, treatment allocations may be unblinded to aid safety review, provided that the unblinding is appropriately documented. In Part B, all subjects will receive BEN8744.

If, after an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the MHRA and research ethics committee (REC). The trial will not restart until the amendment has been approved by the MHRA and REC.

8.4.2 Dose escalation stopping criteria

A dose level will not be repeated, or exceeded, if:

- the results of safety tests for that dose level give the sponsor or investigator cause for concern,
- the investigator or sponsor considers that dose level to be poorly tolerated.

In addition, a dose level will not be exceeded if:

- plasma concentrations at higher doses in any individual subject are predicted to exceed the exposure threshold (see section 8.5).
- 1 or more Hy's Law cases; Hy's Law is defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations $\geq 3 \times$ upper limit of normal (ULN) in the presence of a total bilirubin increase $\geq 2 \times$ ULN in the absence of other findings of cholestasis such as a significant increase in alkaline phosphatase (ALP) and without an alternative diagnosis that could explain the increase in ALT/AST and bilirubin.

- 2 or more subjects have a mean QTcF of > 500 msec or increase from baseline of > 60 msec

The trial will be stopped if any criterion in section 8.4.1 is met.

Dosing will be discontinued in an individual subject if any criterion in section 9.4.2 is met.

8.5 Criteria for dose selection

8.5.1 Review of data by the Safety Review Group

During the study, the dose will be increased only if the safety, tolerability, and PK of the previous dose are acceptable.

All doses will be selected by the Safety Review Group (SRG), which will include (as a minimum) the principal investigator (or delegate) and the sponsor's medically qualified representative (or delegate). Each dose decision will be made and documented in line with HMR standard operating procedures (SOPs).

Before selecting a new dose level (for any group), the SRG will review, as a minimum, the safety, tolerability, and PK data from the previous dose level and (if different) the highest dose level tested to date, as described below. Safety, tolerability, and PK data obtained from the previous group(s) will also be reviewed, if applicable. All data used to support dose selection will be quality checked.

Review of safety and tolerability data

The SRG will review (as a minimum) safety and tolerability data, up to 48 h after final dosing, from at least 4 evaluable subjects who have received active treatment at the highest dose level tested to date. An evaluable subject is one who completes dosing and has undergone procedures until 24 h after final dosing, and had no major protocol deviations. To maintain blinding, data from at least 6 of the 8 subjects in each group must be reviewed to ensure that the dataset includes at least 4 evaluable subjects on active treatment. If fewer subjects than planned are dosed, any subjects required to complete the group may be dosed in parallel with subsequent groups.

The safety data reviewed will include, as a minimum:

- AEs and SAEs, including description, frequency, intensity, onset, duration, and relationship to treatment
- physical examinations
- vital signs
- 12-lead safety ECG
- telemetry (Part A)
- laboratory safety tests

- C-SSRS (Part C)

Review of pharmacokinetic data

The SRG will review (as a minimum) PK data up to at least 24 h after final dosing from at least 4 evaluable subjects on active treatment at the highest dose level tested to date before the dose is escalated.

When PK data are reviewed, dummy-subject identifiers will be applied to the data by the bioanalytical laboratory, or an unblinded programmer at HMR, so that individual data may be reviewed without unblinding the sponsor and investigator. If fewer subjects are dosed than planned, to avoid potential unblinding, individual data will not be reviewed – mean, minimum and maximum data will be reviewed, and number of subjects will not be presented. If there are missing PK data at a particular timepoint, the missing data may be replaced by an interpolated value to maintain blinding.

8.5.2 Dose escalation Part A (SAD)

The dose will be increased such that the predicted plasma concentrations in any subject (C_{max} and AUC) after the top dose do not exceed the following limits, which are based on the NOAEL in the most sensitive species (dog).

C_{max}: 4,710 ng/mL	**AUC_{last}: 24,500 ng.h/mL**

Dose escalation in Cohorts A1–A4 is complete. The planned dose for A5 is 100 mg.

Three further intermediate or higher dose levels may be explored in the optional groups of subjects (Groups A6–A8).

The maximum dose in Part A will not exceed 140 mg. The predicted plasma concentrations in any subject at the maximum dose (140 mg) are predicted to be 3-fold and 4-fold below the C_{max} and AUC limits above, respectively. The predicted plasma concentrations and rationale for the maximum dose (140 mg) are provided in section 6.5.2.

The trial will be stopped if the criteria in section 8.4.1 are met.

8.5.3 Dose selection Part B (food effect)

Part B will not proceed until the SRG has reviewed safety, tolerability (up to 48 h after dosing), and PK data (up to 24 h after dosing) from at least 3 groups in Part A, as described in section 8.5.1.

The dose selected for Group B1 will be no higher than 50% of the highest dose tested in Part A that caused no safety concerns.

If Group B2 is required, it will proceed once the SRG has reviewed safety and tolerability (up to 48 h), and PK data from at least 4 subjects in Group B1, up to 24 h

after dosing in each treatment session, and available data from Part A. The dose selected for Group B2 will be the same or lower than one that has been given in Part A without any safety concerns.

8.5.4 Dose escalation Part C (MAD)

Part C may start before the completion of Part A. At a minimum, Part C will not proceed until the SRG has reviewed safety and tolerability (up to 48 h), and PK data (up to 24 h after dosing) from at least 3 groups in Part A, as described in section 8.5.1.

The dose, dosing regimen (once or twice daily), and whether the dose is taken fed or fasted, will be determined by the SRG based on review of available safety, tolerability, and PK data from Parts A and B and previous cohorts in Part C.

Dose selected for Group C1: The first total daily dose (ie, morning plus evening dose, if a twice-daily dosing regimen is chosen) selected for Part C (Group C1) will be the same as, or lower than, a single dose that has been given in Part A without any safety concerns. Additionally, to account for possible accumulation, at the proposed first dose level the predicted C_{max} and AUC_{tau} (at steady state) in any individual subject must not exceed the maximum observed C_{max} and AUC_{inf} achieved so far in Part A.

Doses selected for Groups C2–C3 and optional group C4: It is expected that the dose level tested will increase in each new group. However, the dose will be increased only if, at the new proposed dose level, C_{max} and AUC_{tau} (at steady state) in any individual subject are not predicted to exceed the maximum observed C_{max} and AUC_{inf} achieved following a single dose in Part A that caused no safety concerns.

The daily dose will be increased such that it does not exceed 3.5 times the highest daily dose previously tested in Part C that was safe and well tolerated. Dosing will be discontinued if the criteria in section 8.4.1 are met.

8.5.5 Repeating a dose level or selection of a lower dose level (Parts A and C)

In Parts A and C, the SRG may decide to test a lower dose level of BEN8744, or to repeat a dose level, provided it does not meet the criteria in section 8.4. Such decisions will be made and documented in line with HMR SOPs.

A dose level may be repeated under the following circumstances.

- If it was safe and well tolerated, and resulted in BEN8744 plasma concentrations within the limit (section 8.5.2).
- If AEs occurred that caused mild or moderate discomfort, but did not in any way threaten the health of the subject, that dose level may be repeated with the aim of exploring further the relationship between dose and AE. If, in the SRG's judgement, it would be unreasonable to expose further subjects to the level of

discomfort experienced by the subjects who have already received the dose, a lower dose may be tested. The selected dose will be either a lower dose level that has already been given, or an intermediate level that has not previously been given; in either case, the aim is to learn more about the relationship between AEs and dose (or plasma concentration) of BEN8744.

9 Trial population

9.1 Planned number of subjects

Up to 108 healthy volunteers, excluding replacements: up to 64 in Part A (including 3 optional groups); up to 12 in Part B; and up to 32 in Part C (including 1 optional group).

9.2 Inclusion criteria

The inclusion criteria detailed below should be used to determine eligibility at screening only (unless otherwise specified).

1. Male or female healthy volunteer in good health, as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory assessments at the time of screening, as judged by the Investigator.
2. Aged 18–65 years at the time of consent.
3. A body mass index (BMI; Quetelet index) in the range 18.0–30.9 and weight ≥ 50 kg

$$\text{Body Mass Index} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

4. Ability to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial.
5. Willingness to give written consent to participate after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or their delegate.
6. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Agree to follow the contraception requirements of the trial as described in section 11.
8. Agree not to donate blood or blood products during the study and for up to 3 months after the administration of the trial medication.
9. Registered with a General Practitioner (GP) in the UK (Part A only).

10. Willingness to give written consent to have data entered into The Overvolunteering Prevention System.

9.3 Exclusion criteria

The exclusion criteria detailed below should be used to determine eligibility at screening only (unless otherwise specified).

1. Woman who is pregnant or lactating, or pre-menopausal woman who is sexually active and not using a reliable method of contraception (see section 11).
2. Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the volunteer.
3. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the volunteer's participation in the trial or make it unnecessarily hazardous.
4. History of seizures or at risk of seizure (eg history of significant head trauma).
5. Significant suicidality history or suicidality risk (as assessed by the C-SSRS assessment). Subjects recording "yes" on item four or five of the Suicidal Ideation Section of the C-SSRS with the ideation occurring in the past six months, or "yes" on any item of the Suicidal Behaviour Section.
6. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any psychotic mental illness.
7. Surgery (eg stomach bypass) or medical condition that might affect absorption of medicines.
8. History of severe adverse reactions or allergies, or history of an anaphylactic reaction to prescription or non-prescription medication or food (non-active hay-fever is acceptable).
9. Use of a prescription medicine during the 28 days before the first dose of trial medication or use of a non-prescription or over-the-counter medicine (including herbal and nutritional supplements), with the exception of up to 2 g acetaminophen (paracetamol) during the 7 days before and up to 24 h before the first dose of trial medication.
10. COVID-19 symptoms at screening or admission, or positive for COVID-19 testing on admission, as per HMR standard procedures.
11. Subjects with a COVID-19 vaccination within 28 days of their first dose of trial medication, or who are due to receive a dose of a COVID-19 vaccine while participating in the study.

12. Receipt of an investigational product (including prescription medicines) as part of another clinical trial within the 3 months before admission to this study; in the follow-up period of another clinical trial at the time of admission for this study.
13. Presence or history of drug or alcohol abuse, or intake of more than 14 units of alcohol weekly.
14. Habitual, regular use of tobacco and/or nicotine containing products (including e-cigarettes) within 3 months of screening, until the end of the study. Social smokers or vapers may be included in the study (at the discretion of the investigator) provided they can abstain from use of those products from 1month before the study until the end of the study.
15. Habitual and heavy consumption of caffeinated drinks (> 8 cups of coffee or equivalent per day).
16. Mean blood pressure and pulse rate in supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 40–90 mm Hg diastolic; pulse rate 40–100 beats/min.

    One set of repeats in triplicate is permitted if the mean values are borderline (ie values that are within 5 mm Hg for blood pressure or 5 beats/min for pulse rate) or if requested by the investigator. Subjects can be included if the repeat mean value is within range.
17. Possibility that the volunteer will not cooperate with the requirements of the protocol.
18. Evidence of drug abuse on urine testing.
19. Positive test for hepatitis B, hepatitis C or HIV.
20. Loss of more than 400 mL blood during the 3 months before the trial, eg as a blood donor.
21. Objection by GP to volunteer entering trial.
22. AST, ALT, gamma-glutamyl transferase (GGT), or total bilirubin ≥ 1.5 × ULN. A repeat is allowed on one occasion for determination of eligibility.
23. QT, PR, or QRS value, measured at screening visit on 12-lead ECG, outside of the following ranges: QT value > 450 msec (men) or > 470 msec (women), using Fridericia's formula (QTcF) for correction; PR value outside the range 110–220 msec; QRS value > 120 msec.

    Triplicate measurements will be made, and a mean value used to determine eligibility. A repeat (in triplicate) is allowed on one occasion for determination of eligibility.
24. Clinically significant findings on 24-hour Holter testing at screening as determined by the Investigator (Part A only).

25. Vegetarian or vegan, or unwilling to eat a high-fat breakfast including bacon (eg for personal or religious reasons) (Part B only).

9.4 Withdrawal of subjects from the trial

9.4.1 Subject withdrawal

Subjects are free to withdraw from the trial at any time without giving reasons. Furthermore, the investigator may withdraw a subject for reasons such as intolerance to trial medication, intercurrent illness, need for medication which is contraindicated, significant non-compliance with the requirements of the trial, or withdrawal of consent. The investigator will assess the reasons for withdrawal as far as possible and will fully record the circumstances and medical details.

Subjects will be informed before they agree to take part in the trial that, if they withdraw or are withdrawn:

- the investigator will stop collecting information about them; and
- they can ask the investigator to destroy any identifiable samples taken from them.

The investigator will ask withdrawn subjects to consent to a follow-up examination, to check that they have come to no harm as a result of taking part in the trial. Provided that the subject agrees, they will undergo, at withdrawal from the trial (or as soon as possible afterwards), the standard medical examination and laboratory tests which they would have undergone had they completed it. The investigator will record in the case report form (CRF) the results of the follow-up examination of withdrawn subjects, if they give their consent for that.

9.4.2 Individual subject stopping criteria

A subject who meets any of the following criteria will receive no further doses.

- SAE considered related to study treatment.
- mean QTcF of > 500 msec or increase from baseline of > 60 msec
- ALT ≥ 5 × ULN.
- ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN or international normalised ratio (INR) of ≥ 1.5, as per the guidelines for acute liver failure. (If a subject meets that withdrawal criterion, serum bilirubin fractionation should be performed.)
- ALT ≥ 3 × ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia). Subjects who have ALT ≥ 3 × ULN and < 5 × ULN, and total bilirubin < 2 × ULN, who do not exhibit hepatitis symptoms or rash, can continue in the study (and continue receiving trial

medication) as long as they can be monitored weekly until liver chemistries return to within baseline values.

Subjects who meet the above criteria will be considered discontinued from dosing. However, the investigator may ask the subject to continue their participation in the study, so they can be monitored for safety and PK, or the investigator may withdraw the subject from the trial.

9.4.3 Replacement of withdrawn subjects

Withdrawn subjects will be replaced at the discretion of the sponsor and investigator. Subjects withdrawn because of AEs considered possibly related to study treatment (see section 14.2) will not be replaced. Replacements for other withdrawn subjects will receive the treatments intended for the withdrawn subject, from the start of the trial. For subjects in Part B, the sponsor and investigator will decide which sessions the replacement subject will complete.

10 Treatments

10.1 Treatments administered

In Part A, subjects will receive a single oral dose of BEN8744 or placebo.

In Part B, subjects will receive a single oral dose of BEN8744 on 2 different occasions, separated by a washout of at least 7 days.

In Part C, subjects will receive once or twice-daily oral doses of BEN8744 or placebo for 14 days.

Fasting requirements are described in section 11.

All treatments will be administered orally with approximately 240 mL of water. All treatments will be given in the fasted state in Parts A, and in the fasted or fed state in Part C.

10.2 Overdose

Symptoms of overdose of BEN8744 are not yet known. In the case of accidental overdose, subjects should be treated symptomatically as no specific antidote is available.

10.3 Blinding (Parts A and C only)

The trial medication will be repackaged and relabelled by the HMR Pharmacy, according to the randomisation schedule. Active and placebo treatments will be labelled such that it is not possible to distinguish between them. If the expiry dates of placebo and active treatment differ, both treatments will be labelled with an expiry

date no later than the earlier of the 2 expiry dates. Each subject's treatment will be given a unique code number, traceable to the batch number of the medication.

The placebo and active treatments for each group will be identical in appearance, and similar in taste and smell. To maintain the blind nature of the trial, the same number of capsules will be given to each subject in a group.

A sealed copy of the randomisation code will be kept in a locked file in the HMR Pharmacy. A copy will also be kept by the bioanalytical laboratory. The investigator will be supplied with sealed envelopes, each one containing the treatment allocation for the subject whose number appears on the outside of the envelope. Those envelopes will be kept in the trial master file, readily accessible to clinical staff. Emergency procedures for revealing medication codes are specified in section 10.4.

The investigators, medical monitor and clinical monitor will remain blinded throughout the trial, unless safety concerns necessitate unblinding (see section 10.4 below).

10.4 Unblinding procedure

If unblinding is required in the interest of the safety of a subject (for example, in a medical emergency), the principal investigator or delegate will open the individual code-break envelope for that subject without prior consultation with the sponsor. In that event, the principal investigator or delegate will notify the sponsor as soon as possible (within 24 h) that the randomisation code has been broken for the subject. If unblinding may be helpful, but is not required immediately (for example, the information may be useful to make decisions for other subjects in the group), wherever possible, an investigator will discuss the matter with the sponsor before opening any individual code-break envelopes.

When the trial database for the relevant part has been locked, the HMR statistician will inform the sponsor of his or her intention to break the randomisation code. The statistician will break the code, and do the statistical analysis of the relevant data.

10.5 Method of assigning subjects to treatment groups

After passing all of the screening assessments, subjects will be allocated to study part and group, according to their availability and the scheduled trial dates.

Subjects will be numbered consecutively, in the order in which they arrive on the ward and are entered into the trial. Subject numbers are presented in Table 8. Subject numbers will be allocated to treatments (active or placebo) according to a randomisation schedule prepared by an independent HMR statistician, using a SAS program.

Sentinel subject numbers in Part A are provided in Table 8; at each new dose level, 1 sentinel subject will receive active treatment and 1 sentinel subject will receive placebo.

Randomisation is described further in section Table 8.

Table 8: Subject and sentinel numbers

	Group	Subject numbers	Sentinel subjects
Part A	A1	1001–1008	1001 and 1002
	A2	1009–1016	1009 and 1010
	A3	1017–1024	1017 and 1018
	A4	1025–1032	1025 and 1026
	A5	1033–1040	1033 and 1034
	A6 (optional)	1041–1048	1041 and 1042
	A7 (optional)	1049–1056	1049 and 1050
	A8 (optional)	1057–1064	1057 and 1058
Part B	B1	2001–2006	Not applicable
	B2 (optional)	2007–2012	Not applicable
Part C	C1	3001–3008	Not applicable
	C2	3009–3016	Not applicable
	C3	3017–3024	Not applicable
	C4 (optional)	3025–3032	Not applicable

Replacements for withdrawn subjects will be given a number equal to that of the subject that they replaced plus 100. So, Subject 1001 would be replaced by Subject 1101, and Subject 3017 would be replaced by Subject 3117, and so on.

10.6 Selection and timing of dose for each subject

The treatments to be administered and intervals between subjects are described in sections 8.1 and 10.1. Subjects will be randomly assigned to treatment, as described in section 10.5 above.

Because BEN8744 has never been given to humans before, in Part A each new ascending dose will be staggered as described in section 10.5.

In Part C, doses will be given at the same time each day (if once daily dosing) or every 12 h at the same time each day (if twice daily dosing). Doses will be given ±15 mins from times on Day 1.

10.7 Previous and concomitant treatment

Previous treatment restrictions are described in section 9.3.

During the trial, concomitant medication may be given if the Investigator believes it to be necessary. In addition, up to 2 g paracetamol (acetaminophen) will be allowed per day for mild analgesia (up to 1 g per dose). Any other concomitant treatment

will be given only if deemed strictly necessary by the investigator or co-investigator. In any case, all concomitant treatments will be reported in the CRF along with their daily dosage, duration, and reasons for administration. Subjects who have received any concomitant treatment may be withdrawn from the trial at the discretion of an investigator.

10.8 Assessment of compliance

Subjects will be dosed on the research ward under the supervision of 2 suitably trained members of HMR staff. Mouth checks will be done immediately after dosing.

11 Dietary and lifestyle restrictions

Subjects will abide by HMR house rules while on the ward.

Part A

In Part A, subjects will fast (no food or drink other than water) overnight for at least 10 h before dosing, until 4 h after dosing. Standard meals and drinks will be provided at about 4, 10 and 24 h after dosing. Water will not be allowed for 1 h before and after dosing.

Part B

In Part B, subjects will receive a dose of trial medication in the fed and fasted states. The dose level, fasting requirements and whether the dose will be taken after a high-fat or standard breakfast will be decided by the SRG based on emerging data.

Group B1

- In one treatment session, subjects will fast (no food or drink other than water) overnight for at least 10 h before dosing, until 4 h afterwards, and water will not be allowed for 1 h before and after dosing.
- In the other treatment session, subjects will take their dose of BEN8744 after a standard high-fat breakfast consisting of: 2 fried eggs, 2 strips of bacon, 2 slices of toast and butter, 4 ounces of hash brown potatoes, and a glass of whole milk. Subjects will fast (no food or drink other than water) overnight and will start the breakfast approximately 30 min before dosing, and they must eat all of the breakfast at least 10 min before dosing.
- In both treatment sessions, standard meals and drinks will be provided at 4, 10 and 24 h after dosing. The content of those meals will be the same in both sessions.

Group B2

- In one treatment session, subjects will fast (no food or drink other than water) overnight for at least 10 h before dosing, until 4 h afterwards, and water will not be allowed for 1 h before and after dosing.
- In the other treatment session, subjects will take at least 1 dose of BEN8744 after a high-fat breakfast or a standard breakfast (consisting of 2 slices of toast, 1 bowl of cereal with semi-skimmed milk, 2 portions of butter/margarine, and 1 portion of jam) having fasted overnight. The dose level, dosing regimen, and the predose meal will be decided following review of the data from Group B1 and available data from Part A.
- In both treatment sessions, standard meals and drinks will be provided at 4, 10, and 24 h after dosing. The content of those meals will be the same in both sessions.

Part C

In Part C, we anticipate that doses will be given once or twice daily in the fasted state unless emerging data indicate they should be taken in the fed state. Fasting requirements in Part C will be decided by the SRG after review of results from Parts A and B. Therefore, for the morning dose, subjects will either:

- fast from midnight on the evening before each dose, until 4 h after their morning dose, on the first and last dosing days, and until 2 h after dosing on all other dosing days. Water will not be allowed for 1 h before and after dosing; or
- fast from midnight before each dose, until about 30 min before the morning dose on all dosing days. Subject will be given a standard breakfast to finish before dosing, consisting of 2 slices of toast, 1 bowl of cereal with semi-skimmed milk, 2 portions of butter/margarine, and 1 portion of jam. Water will not be allowed for 1 h before and after dosing.

In once-daily dosing sessions, standard meals and drinks will be provided at about 4 and 10 h after dosing on all dosing days, and at 24 h after the last dose on the final dosing day.

If subjects are dosed twice daily, they will take their evening doses approximately 1 h after dinner. Water will not be allowed for 1 h before and after dosing.

All parts

No food or drink containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits) will be allowed from 14 days before (first) dosing until the end of the trial. No alcoholic or caffeinated drinks, or xanthine-containing products (eg chocolate) will be allowed during the period from 24 h before admission until the end of the period of residence, and for 24 h before each outpatient visit (including screening). Subjects should be advised to avoid eating food containing poppy seeds

from screening until the end of the study, because that can cause a positive drugs of abuse test result.

No strenuous exercise will be allowed from 24 h before admission, and for 48 h before each outpatient visit (including screening).

Regular smokers or users of tobacco and/or nicotine containing products (including e-cigarettes) are excluded from the study (see section 9.3). 'Social' smokers or vapers must abstain from smoking/vaping from 1 month before their first dose of study medicine until the end of the study.

Subjects must not sunbathe or use a sunbed during the study.

Subjects must use a reliable method of contraception, as follows.

Men

Male subjects must not plan to father a child, or donate sperm, during the trial (from [first] dose until their follow-up visit).

During the trial (from [first] dose until their follow-up visit), male subjects must not have sex without using a condom, if their partner is a woman of childbearing potential.

Women

Women of childbearing potential must use a low user dependent method of contraception during the trial. They must have been using that method for at least 28 days before the start of the trial. Low user dependent methods of contraception include:

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (with surgical success confirmed by medical assessment)

A woman is considered to be of non-childbearing potential if she meets one of the following criteria:

- is post-menopausal (the last menstrual period was at least 12 months ago, and follicle-stimulating hormone (FSH) at screening confirms post-menopausal status)
- has no uterus, ovaries or fallopian tubes

Women who are taking hormone replacement therapy (HRT) must use contraception (as described above) during the trial.

Subjects who practise true abstinence or who only have same-sex relationships need not use contraception, provided it is in line with their preferred and usual lifestyle (note: periodic abstinence (eg calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of

contraception). Should any such subject stop practising true abstinence, they must use contraception as described above.

12 Procedures and observations

Only subjects who meet all the inclusion and no exclusion criteria will be eligible for enrolment into the trial (see section 9). Each subject will be allocated a unique trial number (see section 10.5).

The schedule of procedures is in section 12.1.

Additional timepoints may be introduced, and changes to timepoints may be made, in accordance with section 12.2.

The following assessments will be made.

Safety and tolerability:

Laboratory assessments (routine haematology, clinical chemistry, and urinalysis), physical examinations, 12-lead ECGs, and vital signs (blood pressure, pulse rate, respiratory rate, and tympanic temperature) and C-SSRS (Part C only) will be done frequently until the subject's last visit. Cardiac telemetry (Part A only) will be done from 1 h before until 24 h after dosing. AEs will be recorded from screening until the subject's last visit.

Laboratory safety variables to be assessed during the study are in Table 11.

From screening until the follow-up visit, AEs and concomitant medication will be documented as they are reported by the subjects. Subjects will be questioned (using a non-leading question, such as 'How are you feeling?) about AEs on admission to the ward, when procedures are done, and when they return to the ward at follow-up.

As previous safety studies in animals (28-day toxicity study in dogs) indicated that BEN8744 may cause sedation, an OAAS/S and VAS will be used to monitor alertness and sedation. The OAAS/S and VAS will be done immediately before PK blood samples frequently up to 72 h after dosing in Parts A and B, and up to 72 h after dosing on Day 1 in Part C.

Pharmacokinetics

Blood samples for assay of BEN8744 will be taken before, and frequently up to 72 h after dosing in Parts A and B, and up to 72 h after dosing on Day 1 and Day 14 in Part C.

Urine will be collected continuously for up to 72 h after dosing in Part B, and may be taken for up to 72 h after dosing on Days 1 and 14 in Part C, for assay of BEN8744 and its metabolites.

A predose faecal sample will be collected from Day –2 to predose on Day 1 in Part B Session 1. Faecal samples will be collected continuously for up to 72 h after dosing in Part B for the exploratory characterisation of BEN8744 and its metabolites.

12.1 Schedules of procedures

12.1.1 Schedule of procedures (Part A)

Assessment / Day / Time (h)	Screening [1]	Treatment session																	FU[2]
		–1	1													2		3	4	11 ±2
			Pre	0	0.25	0.5	1	2	3	4	5	6	8	12	16	24	36	48	72	
Informed consent	X																			
Demography	X																			
Medical history	X	X																		
Inclusion/exclusion criteria	X	X																		
Height and weight[3]	X	X																		X
Dose of BEN8744 or placebo[4]				X																
Inpatient visit[5]		◄	►																	
Outpatient visit	X																			X
Safety assessments																				
Physical examination[6]	X	X																	X	X
Laboratory safety tests[7]	X	X														X		X	X	X
Serology	X																			
Pregnancy/FSH test[138]	X	X																		X
Urine drug screen, and alcohol and cotinine tests	X	X																		
Vital signs[9]	X	X	X			X	X	X		X			X	X		X		X	X	X
12-lead safety ECG[10]	X		X			X	X	X		X			X	X		X		X	X	X
24 h Holter[11]	X																			
Cardiac telemetry[12]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
C-SSRS	X																			
OAAS/S and VAS[13]			X		X	X	X	X	X	X		X	X			X		X	X	
Pharmacokinetic assessments																				
Blood sampling[14]			X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Ongoing subject review																				
Adverse events	◄	►																		
Concomitant medication	◄	►																		

Abbreviations: C-SSRS Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle stimulating hormone; FU = follow-up; OAAS/S = Observer's Assessment of Alertness/Sedation scale; PK = pharmacokinetics; VAS = visual analogue scale.

Notes:

1. Screening will be within 28 days before dosing.
2. Follow up will be 7 (±2) days after discharge.
3. Height at screening only.
4. Subjects will receive a single dose of BEN8744 or placebo in the fasted state, by mouth.
5. Subjects will be resident on the ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4).
6. Full physical examinations will be done at screening. Brief (symptom-directed) physical examinations will be done at all other timepoints.
7. Laboratory safety tests consist of clinical chemistry, haematology, and urinalysis.
8. Pregnancy tests in women of child-bearing potential only. FSH tests in post-menopausal women at screening only.
9. Vital signs consist of: supine systolic and diastolic blood pressure, pulse rate, tympanic temperature and respiratory rate. Triplicate measurements (obtained ≥ 2 min apart) will be made at screening. Single measurements will be made at all other timepoints. Measurements should be made with subjects in a supine position, after resting for 5 min.
10. Triplicate ECG recordings (made ≥ 2 min apart) will be made at screening; single recordings will be done at all other timepoints. Recordings should be made with subjects in a supine position, after resting for 5 min.
11. Subjects will have a 24 h Holter monitor applied during screening and will return the monitor to HMR the following day.
12. Heart rhythm will be monitored continuously (telemetry, 3-lead ECG) from 1 h before until 24 h after dosing.
13. The OAAS/S and VAS will be done immediately before PK blood samples frequently up to 72 h after dosing at the following timepoints: predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h; on Day 2 (24 h); on Day 3 (48 h); and on Day 4 (72 h).
14. Blood samples for assay of BEN8744 will be taken on Day 1 at predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 h; on Day 2 (24 and 36 h); on Day 3 (48 h); and on Day 4 (72 h).

When more than one procedure is scheduled at a specific timepoint, procedures should be done in the following order: ECG, vital signs, blood samples (at the scheduled time). Blood sampling should be done on time. Other procedures should be done as close as possible to the scheduled timepoint.

12.1.2 Schedule of procedures (Part B)

Assessment / Day	Screening[1]	Treatment session 1 and 2[2]																FU[3]
		–1	1												2		3	4	11 ±2
Time (h)			Pre	0	0.25	0.5	1	2	3	4	6	8	12	16	24	36	48	72	
Informed consent	X																		
Demography	X																		
Medical history	X	X																	
Inclusion/exclusion criteria	X	X																	
Height and weight[4]	X	X																	X
Dose of BEN8744[5]				X															
Inpatient visit[6]																			
Outpatient visit	X																		X
Safety assessments																			
Physical examination[7]	X	X																X	X
Laboratory safety tests[8]	X	X													X		X	X	X
Serology	X																		
Urine drug screen, and alcohol and cotinine tests	X	X																	
Vital signs[9]	X	X	X			X	X	X		X		X	X		X	X	X	X	X
12-lead safety ECG[10]	X		X			X	X	X		X		X	X		X		X	X	X
Pregnancy/FSH test[11]	X	X																	X
C-SSRS	X																		
OAAS/S and VAS[12]			X		X	X	X	X	X	X	X	X			X		X	X	
Pharmacokinetic assessments																			
Blood sampling[13]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine and faecal sample collection[14]																			
Ongoing subject review																			
Adverse events	◄———																		———►
Concomitant medication	◄———																		———►

Abbreviations: C-SSRS Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle stimulating hormone; FU = follow-up; PK = pharmacokinetics; VAS = visual analogue scale.

Notes:

1. Screening will be within 28 days before first dose.
2. Each subject will have 2 study sessions, with a washout period of at least 7 days between doses.

3. Follow up will be 7 (±2) days after discharge in Session 2.
4. Height at screening only.
5. Subjects will receive a single dose of BEN8744, by mouth, in each session: 1 in the fasted state, and 1 in the fed state.
6. Subjects will be resident on the ward from 1 day before their dose (Day –1) until up to 72 h after dosing (Day 4).
7. Full physical examinations will be done at screening. Brief (symptom-directed) physical examinations will be done at all other timepoints.
8. Laboratory safety tests consist of clinical chemistry, haematology and urinalysis.
9. Vital signs consist of: supine systolic and diastolic blood pressure, pulse rate, tympanic temperature and respiratory rate.
   Triplicate measurements (obtained ≥ 2 min apart) will be made at screening. Single measurements will be made at all other timepoints.
   Measurements should be made with subjects in a supine position, after resting for 5 min.
10. Triplicate ECG recordings (made ≥ 2 min apart) will be made at screening; single recordings will be done at all other timepoints. Recordings should be made with subjects in a supine position, after resting for 5 min.
11. Pregnancy tests in women of child-bearing potential only. FSH tests in post-menopausal women at screening only.
12. The OAAS/S and VAS will be done immediately before PK blood samples frequently up to 72 h after dosing at the following timepoints: predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h; on Day 2 (24 h); on Day 3 (48 h); and on Day 4 (72 h).
13. Blood samples for assay of BEN8744 will be taken on Day 1 at predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 16 h; on Day 2 (24 and 36 h); on Day 3 (48 h); and on Day 4 (72 h) in each treatment session.
14. Continuous urine and faecal sample collection for exploratory characterisation of BEN8744 and its metabolites will be taken after dosing on Day 1 at 0–12 h, 12–24 h, 24–48 h, and 48–72 h.
    A urine spot sample will be taken before dosing on Day 1.
    A predose faecal sample will be collected from Day –2 to predose on Day 1 in Part B Session 1.

When more than one procedure is scheduled at a specific timepoint, procedures should be done in the following order: ECG, vital signs, blood samples (at the scheduled time). Blood sampling should be done on time. Other procedures should be done as close as possible to the scheduled timepoint.

12.1.3 Schedule of procedures (Part C)

	Screening[1]	Treatment session									Follow-up[2]
		Day –1	Day 1	Days 2–6	Day 7	Days 8–13	Day 14	Day 15	Day 16	Day 17	Day 24 ±2
Informed consent	X										
Demography	X	X									
Medical history	X										
Inclusion/exclusion criteria	X	X									X
Height and weight[3]	X	X									X
Dose of BEN8744 or placebo[4]			X	X	X	X	X				
Inpatient visit[5]		◄	———	———	———	———	———	———	———	►	
Outpatient visit	X										X
Safety assessments											
Physical examination[6]	X	X	X		X		X			X	X
Laboratory safety tests[7]	X	X	X		X		X			X	X
Serology	X										
Urine drug screen, and alcohol and cotinine tests	X	X									
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X
12-lead safety ECG[9]	X	X	X	X	X	X	X	X		X	X
Pregnancy/FSH test[10]	X	X									X
OAAS/S and VAS[11]			X	X[11]							
C-SSRS	X									X	X
PK assessments											
Blood sampling[12]			X	X			X	X	X	X	
Urine collection[13]			X	X[13]			X	X	X		
Ongoing subject review											
Concomitant medicines	◄	———	———	———	———	———	———	———	———	———	►
Adverse events	◄	———	———	———	———	———	———	———	———	———	►

Abbreviations: C-SSRS Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle stimulating hormone; FU = follow-up; OAAS = Observer's Assessment of Alertness/Sedation scale; PK = pharmacokinetics; VAS = visual analogue scale.

Notes:

1. Screening will be within 28 days before first dose.

2. Follow up will be 7 (±2) days after discharge.
3. Height at screening only.
4. Subjects will receive a daily dose of BEN8744 or placebo, by mouth, on Day 1–14. Doses will be given at approximately the same time/s each day (±15 min from time/s on Day 1). Doses will be taken once or twice daily in the fasted state, unless emerging data indicate they should be taken in the fed state. If BEN8744 will be given twice daily, the last dose will be given in the morning of Day 14.
5. Subjects will be resident on the ward from 1 day before their dose (Day –1) until up to 72 h after final dosing (Day 17).
6. Full physical examinations will be done at screening. Brief (symptom-directed) physical examinations will be done at all other timepoints. On Days 1, 7 and 14, the brief physical examinations should be done before dosing.
7. Laboratory safety tests consist of clinical chemistry, haematology and urinalysis.
8. Vital signs consist of: supine systolic and diastolic blood pressure, pulse rate, tympanic temperature and respiratory rate.

   During the period of residence, they will be assessed at the following timepoints on Days 1 and 14: predose, 2, 4, 8 and 12 h postdose. Predose vital signs (including on Days 2–13) should be measured up to 90 min before dosing. If twice-daily dosing, vital signs should be measured before the morning dose only.

   Triplicate measurements (obtained ≥ 2 min apart) will be made at screening. Single measurements will be made at all other timepoints. Measurements should be made with subjects in a supine position, after resting for 5 min.
9. During the period of residence, ECGs will be recorded at the following timepoints on Days 1 and 14: predose, 2, 4, 8 and 12 h postdose. Predose ECGs (including on Days 2–13) should be done up to 2 h before dosing. If twice-daily dosing, ECGs should be done before the morning dose only.

   Triplicate ECG recordings (made ≥ 2 min apart) will be made at screening; single recordings will be done at all other timepoints. Recordings should be made with subjects in a supine position, after resting for 5 min.
10. Pregnancy tests in women of child-bearing potential only. FSH tests in post-menopausal women at screening only.
11. The OAAS/S and VAS will be done frequently at specific timepoints immediately before PK blood samples up to 72 h after dosing on Day 1 at the following timepoints: predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h; on Day 2 (24 h); and on Day 3 (48 h).
12. Blood samples for assay of BEN8744 will be taken on:
    - Once-daily dosing: Days 1 and 14 at predose and postdose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 h; on Days 2 (24 h) and Day 15 (24 and 36 h); on Day 16 (48 h); and on Day 17 (72 h).
      Trough samples will be taken predose on Days 3, 5, 7, 9, 11, and 13.
    - Twice-daily dosing: Day 1 and 14 at predose, and postdose at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 h (pre-evening dose on Day 1); on Day 1 at 12.5, 13, 14, 15, and 16 h; Days 2 (20 and 24 h) and Day 15 (24 and 36 h); on Day 16 (48 h); and on Day 17 (72 h).
      Trough samples will be taken pre-morning dose on Days 3, 5, 7, 9, 11, and 13.
13. Depending on the results of Part B, continuous urine collection for assay of BEN8744 may be taken after dosing on Day 1 and Day 14 at 0–12 h, 12–24 h, and on Day 2 and 15 (24–48 h), and Day 3 and 16 (48–72 h). A spot sample will be taken before dosing on Day 1 and 14.

When more than one procedure is scheduled at a specific timepoint, procedures should be done in the following order: ECG, vital signs, blood samples (at the scheduled time). Blood sampling should be done on time. Other procedures should be done as close as possible to the scheduled timepoint.

12.2 Sampling timepoints and additional tests

With the sponsor's approval, additional timepoints may be introduced, and changes to timepoints may be made, if we have reason to believe that the change might improve the quality of the data (for example, if we believe that an important effect of the IMP is occurring at a time when no measurements are scheduled), or if extra procedures are needed in the interest of subject safety. However, the total volume of blood taken in the trial will not exceed the value given in section 12.5. Any additional urine collections may include continuous, total collections, if necessary. Any additional faecal collections may include continuous, total collections, if necessary. An additional 48 hours' residence in the ward (including in each treatment period in Part B), and additional outpatient visits, will be permitted, in the event of a technical failure, and/or if extra observations or samples of blood or urine are needed.

Extra procedures and changes to timepoints which have a significant impact on the scientific value and/or safety of the trial participants will be implemented only after approval of a substantial amendment from the Regulatory Authority (MHRA), unless the changes constitute an urgent safety measure.

With the sponsor's approval, the washout period between treatments in Part B may be changed, if data collected during the trial support the change. However, the washout period will not be reduced to less than 5 half-lives of the trial medicine.

The following will **not** be regarded as protocol deviations.

Table 9: Acceptable deviation times for Parts A and B

Procedure	Timepoint	Acceptable deviation
PK blood sampling	Predose	Up to 30 min before dosing
	Up to and including 1 h postdose	± 5 min of the scheduled time
	After 1 h to 4 h postdose	± 10 min of the scheduled time
	After 4 h to 24 h postdose	± 15 min of the scheduled time
	More than 24 h postdose	± 1 h of the scheduled time
PK urine and faecal sample collection (Part B only)	Any timepoint (except predose urine spot sample and faecal sample)	± 90 min of the scheduled time
All other procedures*	Predose	Up to 90 min before dosing
	Up to and including 4 h postdose	± 10 min of the scheduled time
	After 4 h to 24 h postdose	± 15 min of the scheduled time
	More than 24 h postdose	± 1 h of the scheduled time

* samples for urinalysis may be collected anytime from when the subject awakes until the scheduled time.

Table 10: Acceptable deviation times for Part C

Procedure	Study day	Timepoint	Acceptable deviation
PK blood sampling	Days 1 and 14	Predose (morning dose)	Up to 30 min before dosing
		Up to and including 1 h after the morning dose	± 5 min of the scheduled time
		After 1 h to 4 h after the morning dose	± 10 min of the scheduled time
		After 4 h to 24 h after the morning dose	± 15 min of the scheduled time
	Days 2–13	Predose (morning dose)	Up to 30 min before dosing
	Day 15–17	> 24 h after the morning dose	± 1 h of the scheduled time
	Day 18 onward	Outpatient visits	± 2 days
PK urine and faecal sample collection (optional)	Days 1–3 and 14–16	Any timepoint (except predose urine spot sample)	± 90 min of the scheduled time
All other procedures*	Days 1 and 14	Predose (morning dose)	Up to 90 min before dosing*
		Up to and including 4 h after the morning dose	± 10 min of the scheduled time
		After 4 h to 24 h after the morning dose	± 15 min of the scheduled time
	Days 2–13	Predose (morning dose)	Before dosing
	Day 15–17	> 24 h after the morning dose	± 1 h of the scheduled time
	Day 18 onward	Outpatient visits	± 2 days

* Samples for urinalysis may be collected anytime from when the subject awakes until the scheduled time.

12.3 Follow-up

Subjects will return to the ward 7 ±2 days after dosing (Part A) or after their final dose of trial medication (Parts B and C) for a follow-up visit. Withdrawn subjects who consent to a follow-up visit will undergo the same procedures (see section 9.4).

The follow-up period may be extended if:

1. a subject has an unresolved AE at the follow-up visit, which, in the opinion of the investigator, merits further follow-up;

2. plasma concentrations of IMP were higher than predicted, and/or the half-life of the IMP was very long, and the investigator considers that additional follow-up is necessary; or
3. new information becomes available that supports an extended follow-up period.

The investigator will decide on the nature of the follow-up. For example, subjects may have a telephone follow-up at which they are asked about AEs, or subjects may be asked to attend extra outpatient visits for additional monitoring of blood levels or effects of IMP, and for extra safety tests. The extra safety tests might include tests that are not described in this protocol. The investigator reserves the right, during or after the study, to repeat safety tests or to do any extra safety tests that are in the best interest of the subjects.

12.4 Methods

Blood collection

Blood will be taken by venepuncture or via a cannula. Cannulae may be inserted under local anaesthesia with lidocaine 0.5%, for withdrawal of venous blood.

After each blood sample, the cannula will be flushed with 3–5 mL normal saline, to keep it patent. In order to minimise dilution of each subsequent blood sample with normal saline, the following procedure will be used: about 1 mL will be drawn via the cannula into the sampling syringe, and discarded. The definitive blood sample will then be taken.

Blood volumes of specific types of samples may vary from those described below, but any change to the sample volumes will not cause the total volume of blood taken during the study to exceed that given in section 12.5.

Samples for laboratory safety tests

Blood will be taken for:

- haematology (2.7 mL in EDTA)
- clinical chemistry, serology, serum pregnancy and/or FSH (4.0 mL in tubes with a gelatin plug)

Blood samples will be collected into 13 × 75 mm tubes. Urine and faeces will be collected in Universal containers. Samples will then be transferred to the laboratory. For logistical reasons, blood, urine, and/or faecal samples may be collected in tubes other than those stated above.

Processing and analysis of samples for laboratory safety tests

Processing of samples will be done by the HMR Analytical Laboratory in accordance with the laboratory's SOPs.

The HMR Analytical Laboratory will do safety tests on blood and urine samples using instruments interfaced to a validated laboratory information management

system (LIMS). Data from analysers that are not interfaced will be entered manually into the LIMS.

Table 11: Laboratory safety tests

Haematology:

- haemoglobin (Hb)
- red blood cells (RBC)
- mean corpuscular volume (MCV)
- mean corpuscular haemoglobin (MCH)
- mean corpuscular haemoglobin concentration (MCHC)
- haematocrit
- white blood cells (WBC) and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- platelets

Urinalysis:

- dipstick: protein, blood, ketones, glucose, bilirubin, urobilinogen, leukocyte esterase, specific gravity, nitrites, pH
- microscopy: only if dipstick test for protein, blood, leukocyte esterase or nitrites is abnormal

Serology:

- hepatitis B (hepatitis B surface antigen)
- hepatitis C antibody
- HIV screen (HIV 1 and 2)

Clinical chemistry:

- urea
- creatinine
- uric acid
- total bilirubin
- total protein
- albumin
- globulin
- alkaline phosphatase (ALP)
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- gamma-glutamyl transpeptidase (GGT)
- glucose
- phosphate
- cholesterol
- triglycerides
- potassium
- sodium
- calcium
- chloride

Pregnancy and FSH tests

Serum pregnancy and serum FSH tests will be done using an immunochemiluminometric method.

Drugs of abuse, alcohol, and cotinine tests

Urine will be tested for drugs of abuse, alcohol, and cotinine according to the laboratory's SOP. Tests will include: amphetamines, cocaine, opiates, cannabis, barbiturates, benzodiazepines, alcohol, and cotinine.

Collection and processing of samples for pharmacokinetic analysis

Details on blood, urine, and faecal sample collection and processing, including labelling and shipment instructions, will be documented in a separate study procedures manual.

Physical examination

Physical examination will be done by a physician. The following will be examined: general appearance; head, ears, eyes, nose and throat; thyroid; lymph nodes; back and neck; heart; chest; lungs; abdomen; skin; and extremities. The following systems will be assessed: musculoskeletal and neurological.

Height and weight

Height and weight will be measured by trained staff at HMR.

Vital signs

Blood pressure and pulse rate will be measured using SpaceLabs oscillometric equipment. Measurements will be made with subjects in a supine position; subjects will remain supine for at least 5 min before vital signs are measured.

Tympanic temperature will be measured using digital thermometers.

Respiratory rate will be measured by observation of the chest.

Repeat vital signs measurements

During the trial, if vital signs fall outside the ranges in Table 12, a physician will review and decide on an appropriate course of action. The procedure will be repeated only if instructed by a physician.

Table 12: Vital signs ranges

Vital sign	Range
Supine systolic blood pressure	90–140 mm Hg
Supine diastolic blood pressure	40–90 mm Hg
Supine pulse rate	40–100 beats/min
Temperature	35.5–37.8°C
Respiration rate	10–16 breaths/min

If the result of the repeat measurement is still out of range, the investigator will decide on an appropriate course of action.

Standard 12-lead ECGs

12-lead ECGs will be recorded using Mortara ELI250c and ELI280 cardiographs. Each recording will be printed on a single A4 page at paper speed 25 mm/sec and

calibrated to 10 mm/mV. Recordings will be made with subjects in a supine position; subjects will remain supine for at least 5 min before the ECG is recorded. PR, RR, QRS and QT intervals will be captured on source documents. QT interval will be corrected using Fridericia's formula (QTcF).

During the trial, if ECG values fall outside the ranges in Table 13, a physician will review and decide on an appropriate course of action. The procedure will be repeated only if instructed by a physician.

Table 13: ECG ranges

ECG parameter	Range
Ventricular rate	35–100 beats/min
QRS	≤ 120 msec
PR interval	110–220 msec
QTcF (men)	≤ 450 msec
QTcF (women)	≤ 470 msec

If the result of the repeat measurement is still out of range, the investigator will decide on an appropriate course of action.

Holter monitoring (Part A only)

24-h Holter monitoring will be done at screening using recorders made either by Ela Medical or Burdick. The results will not be recorded in detail in the CRF unless they constitute an AE.

Telemetry (Part A only)

Heart rhythm will be monitored continuously (telemetry, 3-lead ECG) from 1 h before until 24 h after dosing, using a SpaceLabs system. Results from that safety monitoring will be recorded in detail in the CRF only if they constitute an AE.

Observer's Assessment of Alertness and visual analogue scales

Symptoms of sedation will be assessed using OAAS/S and VAS.

In the OAAS/S, the investigator or their delegate will score the subject's level of alertness on a scale of 0 to 5, where 0 is absence of response to stimulus, and 5 is readily responsive to the subject's name in a normal tone.

In the VAS, subjects will complete a self-reported post-dosing questionnaire. Subjects will be asked to score/rate their alertness. To reduce variability, subjects will be able to see their previous responses. A copy of the questionnaire can be found in Appendix A.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a suicidal ideation rating scale used to evaluate suicidality[35]. The questionnaire will be administered by the investigator or their delegate. The 'baseline' questionnaire will be used at screening, and the 'since last visit' questionnaire will be used at all other timepoints.

12.5 Total volume of blood removed

The maximum total volume of blood taken from any volunteer in the trial will be about 175 mL, as stated in Table 14 (Part A), Table 15 (Part B), Table 16 (Part C). Additional blood samples for assay of BEN8744 or for laboratory safety tests may be taken as described in section 12.2. No more than an extra 50 mL of blood will be taken from any subject.

Table 14: Planned blood volume (Part A)

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	6	2.7	16.2
Clinical chemistry/ serology/pregnancy/FSH	6	4.0	24
Pharmacokinetics	15	2.7	40.5
Discard (when using a cannula)	12	1	12
		Total	**92.7 mL**

Table 15: Planned blood volume (Part B)

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	10	2.7	27
Clinical chemistry/ serology/pregnancy/FSH	10	4.0	40
Pharmacokinetics	30	2.7	81
Discard (when using a cannula)	24	1	24
		Total	**172 mL**

Table 16: Planned blood volume (Part C)

Once-daily dosing

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	7	2.7	18.9
Clinical chemistry/ serology/pregnancy/FSH	7	4.0	28
Pharmacokinetics	31	2.7	83.7
Discard (when using a cannula)	22	1	22
		Total	**152.6 mL**

Twice-daily dosing

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	7	2.7	18.9
Clinical chemistry/ serology/pregnancy/FSH	7	4.0	28
Pharmacokinetics	37	2.7	99.9
Discard (when using a cannula)	28	1	28
		Total	**174.8 mL**

13 Trial materials

13.1 Identity of test product(s)

Size 0 Swedish orange capsules containing 2 mg, 10 mg, and 40 mg BEN8744 and matching placebo capsules contain excipients only, will be provided to the HMR Pharmacy by Quotient Sciences Ltd (Reading, UK). The capsules are packaged in high density polyethylene (HDPE) bottles with child-resist polypropylene (PP) twist-off cap.

Full details of BEN8744 and placebo formulations are included in the IB[29] and Investigational Medicinal Product Dossier (IMPD)[36].

The sponsor will provide to HMR a certificate of analysis (CoA), and a Certificate of GMP Compliance (CoC) for the test product for HMR's Qualified Person to release batches of IMP.

13.2 Packaging and labelling

The trial medication will be packaged and labelled by the HMR Pharmacy, in accordance with The Rules Governing Medicinal Products in the European Union, Volume 4: Good Manufacturing Practice (GMP), and with HMR's Manufacturing Authorisation for IMPs (MIA(IMP)). The IMP labels will include all the information required by Annex 13 to GMP[37].

13.3 Storage and accountability of IMP

The IMP will be stored and accounted for according to GMP and HMR SOPs.

At the end of the trial, all unused IMP supplies will be returned to the sponsor or destroyed in accordance with the sponsor's instructions.

14 Adverse events

14.1 Definitions of adverse events

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with that treatment.

Adverse drug reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. Note that, according to the ICH Guideline for Good Clinical Practice (ICH GCP), the phrase 'response to an IMP' means that a causal relationship between the medicinal product and an AE is at least a reasonable possibility, ie a relationship cannot be ruled out.

Unexpected AR

An AR, the nature or severity of which is not consistent with the applicable product information (eg IB for an unauthorised investigational product, or summary of product characteristics for an authorised product).

Serious adverse event (SAE) or serious adverse drug reaction (SAR)

An AE or AR that:

- is fatal;
- is life-threatening;

- requires inpatient hospitalisation, or prolongs existing hospitalisation;
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly or birth defect.

Note that:

- the term 'life-threatening' in the definition of 'serious' refers to an event or reaction in which the patient was at risk of death at the time of the event; it does not refer to an event or reaction which hypothetically might have caused death had it been more severe; and
- in accordance with the ICH Guideline on Clinical Safety Data Management: Definitions and Standards of Expedited Reporting, events or reactions that are not immediately life-threatening or may not result in death or hospitalisation, but might jeopardise the subject or require intervention to prevent one of the other outcomes listed above, should usually be considered serious.

Significant AE or AR

Any SAE or SAR, or an AE or AR which is not serious but is otherwise significant. The following should normally be considered significant:

- a marked haematological or other laboratory abnormality;
- an AE or AR that leads to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy; or
- any AE or AR that the investigator considers to be significant.

14.2 Procedures for recording adverse events

Subjects will be carefully monitored for AEs. The investigator or delegate will question the subjects about AEs using a non-leading question, such as 'How are you feeling?'. The investigator will also record AEs reported spontaneously by the subjects. Clinically significant changes in the findings of physical examination, and clinically significant abnormalities in the results of objective tests (eg laboratory variables, x-ray, ECG) may also be recorded as AEs. The investigator will use the following criteria when deciding whether to report an abnormal result as an AE.

1. The test result is associated with accompanying symptoms.
2. Results of additional diagnostic tests cause concern or necessitate medical intervention.
3. As a consequence of the test result, the dose administered to the subject is changed, the subject is withdrawn, or the subject is given concomitant treatment.
4. The investigator considers the result to constitute an AE.

If any of the above criteria are met, the investigator will report the result as an AE.

A record will be kept in the source documents of all AEs as reported, whether believed to be related or unrelated to the treatment. The record will include the following.

- **Clinical symptoms**: a simple, brief description.
- **Date and time of onset and end** of clinical symptoms.
- **Frequency**: constant or intermittent.
- **Severity**. The following categories will be used:

  Mild: the AE does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort.

  Moderate: the AE interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.

  Severe: the AE results in alteration, discomfort or disability which is clearly damaging to health.

- **Relationship to treatment**: The assessment of relationship of AEs to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used.

  Possibly related

- An event for which, after careful medical evaluation, a connection with trial medication cannot be ruled out with certainty. The event occurs after exposure to trial medication. The event may occur at a reasonable time in relation to the time of administration of the trial medication, but might also be attributable to a commonly occurring alternative cause. Alternatively, the event may not occur at a reasonable time in relation to the time of administration of trial medication, but may not be attributable to an alternative cause.

  Unlikely to be related

- An event which occurs before exposure to the trial medication, or which does not occur at a reasonable time in relation to the time of administration of trial medication, and can be attributed to a commonly occurring alternative cause. Alternatively, the event is unrelated to the trial (eg road traffic accident), unless it can be demonstrated that the treatment could have caused the event.

- **Action taken**: none, drug treatment, subject withdrawn, other (specified).
- **Outcome**: recovered/resolved, recovering/resolving, not recovered/not resolved, or unknown.

14.3 Procedures for dealing with serious adverse events

In the event of any SAE which, in the investigator's opinion, justifies termination or modification of the trial (see section 8.4), dosing will be stopped and the sponsor's medical monitor will be informed immediately (within 24 h of the investigator becoming aware of the event) by telephone or email, as follows.

Medical monitor:	Arpeat Kaviya
Tel:	07753 828 096
Email:	arpeat.kaviya@benevolent.ai

All SAEs occurring after the signing of the ICF until the follow up visit, regardless of study drug relationship, must be reported to the sponsor's pharmacovigilance provider, with as much information as possible, within 24 h of the investigator becoming aware of the event. The investigator will complete an SAE form and provide it to the sponsor's pharmacovigilance provider, via the following contact details.

QbD Group Ltd	
Email (primary):	pv@qbdgroup.com
Tel (back-up):	+44 (0) 1865 893 290

The sponsor will also be notified by email (adepeju.oshisanya@benevolent.ai).

The investigator will notify the REC of SAEs that occur during this trial, if applicable, in accordance with the SOPs issued by the Research Ethics Service (RES)[38].

The sponsor is responsible for determining the expectedness of the event, using the reference safety information in the IB[29]. The sponsor will notify the MHRA of all suspected unexpected serious adverse reactions (SUSARs), and will be responsible for ensuring that the REC is notified of SUSARs, if applicable. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

14.4 Procedures for handling withdrawals due to adverse events

The investigator will assess the reason for withdrawal as far as possible and will fully record the circumstances and medical details. Provided that subjects give written informed consent, they will undergo the standard medical examination and laboratory tests at withdrawal from the trial which they would have undergone had they completed it (see also section 9.4).

14.5 Procedures for reporting pregnancies

Subjects will be asked to follow the contraception guidance in section 11.

If, during the study, the investigator becomes aware of a pregnancy in a subject or their partner, they will inform the sponsor's pharmacovigilance provider immediately (within 24 h of the investigator becoming aware of the event), as follows.

QbD Group Ltd

Email (primary): pv@qbdgroup.com

Tel (back-up): +44 (0) 1865 893 290

The investigator will follow-up the pregnancy according to HMR SOPs, provided the subject (or their partner) consents to that. A pregnancy will not constitute an SAE unless it meets one of the criteria in section 14.1.

15 Data management and quality assurance

Paper source documents will be securely stored within HMR. Data collected in source documents (see section 18.2) will be transcribed into an electronic CRF (eCRF).

The investigator is responsible for ensuring the accuracy and completeness of the data entered into the eCRF, and the timeliness of data entry. Clinical data (including AEs, concomitant medication, etc) will be entered into a 21 CFR Part 11-compliant Medrio M-1 database. The Medrio M-1 system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data reported in the eCRF, derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Where the data violate data validation checks, queries will be generated for resolution by clinical staff. All edits made to the database upon resolution of queries will be recorded in an electronic audit trail.

The database will be locked after the following have been completed: all expected eCRF data have been entered and accounted for; all discrepancies have been resolved; data have been coded as appropriate; SAEs have been reconciled; all site audit findings impacting the database have been closed; and QC inspection has been completed.

Data in source documents will be checked by the HMR Quality Assurance (QA) Department. In addition, the HMR QA Department will audit the trial report; that audit will include checks to ensure that statistical output is correctly reproduced in the report. If requested, the investigator will provide the sponsor, MHRA, and REC with direct access to the original source documents.

16 Statistical methods

16.1 Pharmacokinetic methods

The pharmacokinetic analysis will be done by the Statistics and Data Management Department at HMR, using WinNonlin 8.3 or higher.

Actual times will be used to derive pharmacokinetic parameters. Missing data will not be imputed.

For calculation of all PK parameters, and for individual concentration–time plots, plasma concentrations below the limit of quantification of the assay (BLQ) will be treated as follows: values that occur before t_{max} will be taken as zero; all other values will be taken as missing.

For calculation of plasma concentration summary statistics, BLQ values will be taken as zero, unless they fall between two quantifiable concentrations, in which case they will be treated as missing.

For urine concentrations reported as BLQ, it is not possible to impute a value. The amount excreted will be set to zero when the concentration is BLQ.

The pharmacokinetic parameters listed in sections 16.1.1 and 16.1.2 will be derived.

16.1.1 Plasma parameters

Part A and B (single dose)

Text symbol	Definition	Calculation
	Concentrations and times	
C_{max}	Maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
t_{max}	Time to reach maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
	Half-life	
λ_z	Terminal rate constant	Estimated by linear regression of logarithmically transformed concentration versus time data.
$t_{½}$	Terminal half-life	Calculated from the terminal slope of the log concentration–time curve, as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$
	Areas under the curve	
AUC_{last}	Area under the plasma concentration–time curve from time zero to time of last measurable concentration	Calculated using the trapezoidal method.
AUC_{inf}	Area under the plasma concentration–time curve from time zero to infinity	Calculated using the trapezoidal method for the interval 0 to t_{last} (time t_{last} is the time at which the last non-zero level was recorded), plus the area under the

Text symbol	Definition	Calculation
		exponential curve from t_{last} to infinity, calculated as follows: $AUC_{t-\inf} = \frac{\hat{C}_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.
AUC_{24}	Area under the plasma concentration–time curve from time zero to time 24 h	Calculated using the trapezoidal method. If λ_z is not estimable, a partial AUC is not calculated (when $t_{last}<t$).
AUC_{72}	Area under the plasma concentration–time curve from time zero to time 72 h	Calculated using the trapezoidal method. If λ_z is not estimable, a partial AUC is not calculated (when $t_{last}<t$).
$\%AUC_{extrap}$	Percentage of AUC_∞ extrapolated from t_{last} to infinity	$\%AUC_{extrap} = \frac{100 \times AUC_{t-\inf}}{AUC_{\inf}}$
	Clearance, volume of distribution and mean residence time	
CL/F	Apparent total clearance from plasma after oral administration	Calculated using the following formula: $CL/F = \frac{Dose}{AUC_{\inf}}$
V_z/F	Apparent volume of distribution during terminal phase after non-intravenous administration	Calculated using the following formula: $V_z/F = \frac{Dose}{\lambda_z \bullet AUC_{\inf}}$

Part C (multiple dose)

Day 1

Text symbol	Definition	Calculation
	Concentrations and times	
C_{max}	Maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
t_{max}	Time to reach maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
	Areas under the curve	
λ_z	Terminal rate constant	Estimated by linear regression of logarithmically transformed concentration versus time data.
$t_{½}$	Terminal half-life	Calculated from the terminal slope of the log concentration–time curve, as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$

Text symbol	Definition	Calculation
	Areas under the curve (after final dose)	
AUC_{tau}	Area under the plasma concentration–time curve during a dosing interval (tau)	Calculated using the trapezoidal method.
AUC_{last}	Area under the plasma concentration–time curve from time zero to time of last measurable concentration	Calculated using the trapezoidal method.
AUC_{72}	Area under the plasma concentration–time curve from time zero to time 72 h	Calculated using the trapezoidal method.
AUC_{inf}	Area under the plasma concentration–time curve from time zero to infinity	Calculated using the trapezoidal method for the interval 0 to t_{last} (time t_{last} is the time at which the last non-zero level was recorded), plus the area under the exponential curve from t_{last} to infinity, calculated as follows: $AUC_{t-\inf} = \frac{\hat{C}_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.
$\%AUC_{extrap}$	Percentage of AUC_{∞} extrapolated from t_{last} to infinity	$\%AUC_{extrap} = \frac{100 \times AUC_{t-\inf}}{AUC_{\inf}}$

Days 2–14

Text symbol	Definition	Calculation
	Concentrations during and after multiple dosing	
C_{trough}	Trough plasma concentration	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]) obtained directly from the concentration–time data.

Final dosing day

Text symbol	Definition	Calculation
	Concentrations and times (after final dose)	
C_{max}	Maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
t_{max}	Time to reach maximum (peak) plasma concentration	Obtained directly from the concentration–time data.
	Half-life (after final dose)	
λ_z	Terminal rate constant	Estimated by linear regression of logarithmically transformed concentration versus time data.
$t_{½}$	Terminal half-life	Calculated from the terminal slope of the log concentration–time curve, as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$

Text symbol	Definition	Calculation
	Areas under the curve (after final dose)	
AUC_{tau}	Area under the plasma concentration–time curve during a dosing interval (tau)	Calculated using the trapezoidal method.
AUC_{last}	Area under the plasma concentration–time curve from time zero to time of last measurable concentration	Calculated using the trapezoidal method.
AUC_{72}	Area under the plasma concentration–time curve from time zero to time 72 h	Calculated using the trapezoidal method.
AUC_{inf}	Area under the plasma concentration–time curve from time zero to infinity	Calculated using the trapezoidal method for the interval 0 to t_{last} (time t_{last} is the time at which the last non-zero level was recorded), plus the area under the exponential curve from t_{last} to infinity, calculated as follows: $AUC_{t-\inf} = \frac{\hat{C}_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.
$\%AUC_{extrap}$	Percentage of AUC_{∞} extrapolated from t_{last} to infinity	$\%AUC_{extrap} = \frac{100 \times AUC_{t-\inf}}{AUC_{\inf}}$
	Clearance, volume of distribution and mean residence time (after final dose)	
CL_{SS}/F	Apparent total clearance from plasma at steady state after non-intravenous administration	Calculated using the following formula: $CL_{SS}/F = \frac{Dose}{AUC_{tau}}$
V_z/F	apparent volume of distribution after non-intravenous administration calculated at steady state	Calculated using the following formula: $V_z/F = \frac{Dose}{\lambda_z \bullet AUC_{tau}}$
Accumulation and time invariance ratios		
$R_{ac(AUC)}$	Accumulation ratio for AUC	Calculated from AUC_{tau} at steady state and AUC_{tau} after a single dose
$R_{ac(Cmax)}$	Accumulation ratio for C_{max}	Calculated from C_{max} at steady state and C_{max} after a single dose
$SR_{(AUC)}$	Stationarity ratio for AUC	Stationarity ratio will be calculated from AUC_t at steady state and AUC_{∞} after single dose $SR_{AUC} = \frac{AUC_{\tau}}{AUC_{\infty}}$

16.1.2 Urine sample parameters (Parts B and C)

Text Symbol	Definition	Calculation
	Urinary recovery	
Ae_{72}	Cumulative amount of unchanged drug excreted into the urine at 72 h	Calculated as the sum of the products of concentration and urine volume over the appropriate collection intervals
$f_e \cdot F$	Fraction of non-intravenously administered drug excreted into the urine	Calculated as Ae_{24}/Dose administered
	Renal clearance	
CL_R	Renal clearance of drug from plasma	Calculated from the ratio of the appropriate values for urinary recovery and area under the plasma concentration–time curve, using the following formula: $$\mathrm{CL}_R = \frac{\mathrm{Ae}_{24}}{\mathrm{AUC}_{24}}$$

16.2 Statistical methods

16.2.1 Planned analyses

Final statistical analysis, including analysis of PK parameters, will be done by HMR. A statistical analysis plan will be prepared by the HMR Statistics and Data Management Department after completion of the final protocol and before database lock.

All statistical analysis and reporting will be done using SAS 9.4 or higher.

16.2.2 Statistical hypotheses

The trial is an exploratory one, and there are no null hypotheses to be tested.

16.2.3 Analysis populations

The following populations will be identified:

Safety population: All subjects who received at least one dose of study drug.

PK concentration population: All subjects who received at least one dose of study drug and for whom a pharmacokinetic sample has been analysed.

PK parameter population: All subjects in the PK concentration population for whom pharmacokinetic parameters can be derived.

In all populations, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomised.

The primary endpoint will be analysed using the safety and PK populations.

16.2.4 General considerations for data analyses

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), median, minimum, and maximum. 95% confidence intervals (CI) will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented to the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters). The mean, median and percentiles (eg Q1, and Q3) will be presented to one additional decimal place. The standard deviation and standard error will be presented to 2 additional decimal places.

'Baseline' will be the latest value obtained before IMP administration (predose on Day 1, or Day −1 if not recorded at predose, or screening if not recorded at predose or on Day −1. Out-of-range laboratory tests may be repeated. If a test is out of-range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

16.2.5 Study population analyses

16.2.5.1 Disposition of subjects

The disposition of all subjects in the enrolled population will be summarised including: number of subjects randomised; number completing the study, by treatment; and number discontinued from the study.

All subjects who withdraw or are withdrawn from the study will be listed, by treatment, with the reason for withdrawal.

16.2.5.2 Demographic and baseline characteristics

Demographic and baseline characteristics (eg physical examination, vital signs and ECGs) will be summarised.

Subjects who take concomitant medication will be listed. All non-trial medication will be coded using the latest version of the World Health Organisation Drug Dictionary Enhanced (WHO DDE) current at the time of database lock.

16.2.5.3 Treatment compliance

Dates and times of dosing will be listed.

16.2.6 Safety data analyses

Summaries and listings of safety data will use the safety population.

16.2.6.1 Adverse events

AEs will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) current at the time of database lock.

All AEs will be listed.

A treatment-emergent adverse event (TEAE) is an AE that emerges during treatment (having been absent before treatment) or that worsens after treatment[39].

The number of subjects with at least one TEAE will be tabulated by actual treatment and MedDRA system organ class and preferred term.

For each of the following, the number of TEAEs and subjects with TEAEs will be summarised by actual treatment as follows:

- TEAEs, by system organ class and preferred term
- drug-related TEAEs, by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the maximum causality, for each system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and possibly related, respectively.

AEs leading to withdrawal, deaths and other SAEs will be listed separately (fatal events will be listed separately from non-fatal events).

16.2.6.2 Clinical laboratory evaluations

Data from haematology and clinical chemistry will be summarised by treatment.

Any laboratory value outside the reference interval for that variable will be flagged with an ‘H’ if it is higher than the reference interval, and with an ‘L’ if it is lower. Additionally, if, during the course of the trial, a variable changes from baseline by more than a predetermined amount (as defined by the principal investigator), that value will receive a flag ‘I’ if increased, or ‘D’ if decreased. Therefore, if a value both falls outside the reference interval and alters from the baseline value by more than the predetermined amount, it will attract a double flag and will be considered to be potentially clinically important.

All laboratory values of potential clinical importance will be listed. In a separate listing, laboratory values of potential clinical importance will be listed with all related laboratory results (ie haematology or clinical chemistry). Frequencies of laboratory values of potential clinical importance will be summarised.

16.2.6.3 Other safety measures

Vital signs at each planned assessment, and change in vital signs from baseline at each planned post-baseline assessment, will be summarised by actual treatment.

Vital signs of potential clinical importance will be listed separately.

QT interval will be corrected using Fridericia's (QTcF) formulae.

ECG variables will be summarised by treatment and timepoint. Differences from baseline will be summarised by treatment and timepoint.

QTcF > 450 msec and increases in QTcF from baseline (Day 1 predose) of > 30 msec will be considered to be potentially clinically important. The number of subjects with a potentially clinically important QTcF will be summarised by actual treatment and timepoint, giving the numbers of subjects with QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of subjects with increases in QTcF from baseline of > 30 msec and > 60 msec[40]. A supporting listing of all subjects with a QTcF value of potential clinical importance, and a separate listing of ECG findings classified as abnormal by the investigator, will also be provided.

Abnormal physical examination findings will be listed.

Positive C-SSRS data will be listed (Part C only).

16.2.7 Pharmacokinetic data analyses

PK concentration data will be summarised using the PK concentration population. PK parameters will be summarised using the PK parameter population.

For log-transformed parameters, the primary measure of central tendency will be the geometric mean[41]; for untransformed parameters, it will be the arithmetic mean or median.

For all variables, N (number of subjects in receiving the treatment/formulation in the population), n (number of observations), arithmetic mean, median, minimum, maximum, SD, %CV (coefficient of variation), and the 95% CI of the arithmetic mean will be derived. For log-transformed variables, all of the above plus the geometric mean, its 95% CI, and the SD of the log-transformed variables, will be provided.

Plasma concentrations and PK parameters will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically. All available data will be used to derive PK parameters in individual subjects.

In Parts B and C, urine concentrations, and urine PK parameters will be listed and summarised, by treatment, using descriptive statistics.

Food effect analysis

To assess the effect of food in Part B, analysis of variance (ANOVA) models will be fitted with the logarithm of the PK parameters (AUC_{inf}, AUC_{last} and C_{max}) as the dependent variables, and formulation as a fixed effect. The estimated least square means and residual variance from the model will be used to construct 90% CIs for the difference in means on the log scale for the comparison of fed versus fasted solutions. Food effect will be concluded if the 90% CI of the ratio (fed:fasted) is not included within the range 80–125%.

For t_{max}, the Hodges Lehmann estimator of the difference between fed and fasted solutions in median values and the 90% CI generated with the Moses method will be presented.

16.3 Determination of sample size

Since this is a Phase 1 study, no formal sample size determination is appropriate.

17 Ethical and regulatory requirements

The trial proposal will be reviewed by a recognised REC, and by the MHRA. The trial will not proceed unless the sponsor obtains from the MHRA a clinical trial authorisation (CTA), and the REC approves the trial.

The trial will be done at HMR, in compliance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and current amendments[42], The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019[43], The Human Medicines (Amendment etc) (EU Exit) Regulations of 2019 and 2020[44,45], GMP[37], the SOPs issued by RES for RECs in the UK[38], and Good Clinical Practice, which has its origins in the Declaration of Helsinki.

All subjects must give written consent to participate in this trial. Consent for screening evaluations may be obtained using the information and consent form for the HMR healthy volunteer panel, which has been approved by the Health Research Authority's Generic Review Committee. The trial-specific information and consent form will be signed by the subject either before any screening evaluation or after the investigator confirms the eligibility of the subject for the trial and before the subject is randomised to receive the first administration of IMP. Before giving consent, subjects must read the information sheet about the trial. They must also read the consent form. They will then discuss the trial with the investigator or his deputy and be given the opportunity to ask questions. The trial-specific information sheet and the consent form must be approved by the REC.

Each subject is free to withdraw from the trial at any time, without giving a reason. If a subject withdraws, the investigator will ask the subject to consent to a follow-up examination. For withdrawn subjects, the investigator will use a special information and consent form which has been ethically approved. If the subject consents to the

follow-up examination but asks the investigator to destroy all identifiable samples taken from the subject and/or not enter into the eCRF results of the follow-up examination, the investigator will comply with the subject's requests.

The sponsor will ensure that the MHRA and the REC, are informed promptly of SUSARs (see section 14.3), and that any new reports of SUSARs from other ongoing trials of the IMPs under investigation in this trial are notified to the MHRA, and to the REC, if applicable. The sponsor will provide the investigator, the REC and the MHRA with annual safety reports of each IMP under investigation, and listings of all suspected serious adverse reaction (SSAR) reports. The sponsor will also inform the investigator promptly of any new safety or toxicology data that might affect the safety of the subjects in this study.

The investigator will promptly inform the sponsor and, if applicable, the REC of any SAE that occurs during this trial (see section 14.3). The investigator will provide the REC with annual progress reports of the trial, if the trial lasts longer than a year.

The investigator will report to the REC any protocol deviation that is, in his opinion, of clinical significance. The investigator will also inform the REC in the event of several deviations which, although of no clinical significance, cause inconvenience and/or discomfort to the volunteers. The sponsor will notify the MHRA and REC of any serious breach of good clinical practice (for example, the investigator puts subjects' safety at risk, falsifies data, or persistently fails to comply with this protocol or good clinical practice).

Within 90 days after the end of the trial, the sponsor will ensure that the REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The sponsor will supply a summary of the clinical trial report to the MHRA and REC within 1 year after the end of the trial.

Trial procedures at HMR will be subject to audits by the HMR QA Department, to ensure compliance with the protocol and applicable regulatory requirements.

18 Trial documentation

18.1 Protocol amendments

After the protocol has been approved by the REC and the MHRA, no changes may be made without the agreement of both the investigator and the sponsor.

The MHRA and REC do not need to approve any substantial change to the protocol that needs to be implemented urgently to avoid an immediate hazard to trial subjects. The sponsor will ensure that the MHRA and REC are informed of urgent amendments or a temporary halt to the trial in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 (and current amendments)[42] and the SOPs issued by RES for NHS RECs[38].

All agreed protocol amendments will be recorded on a written agreement which will be signed and dated by the investigator and sponsor, and attached to the original protocol. The REC and/or MHRA must approve substantial amendments before they are implemented.

The standard text in our information and consent form template explains that the planned doses for Part A may change during the trial, and that we may give the subjects any dose that has been approved by the MHRA and REC in Part A. However, if we want to reduce the planned dose, we consider it essential to fully inform the subject of our reasons, because a reduction in dose might be due to poor tolerability, and that might affect the subject's decision to remain in the trial. Wherever possible, we will obtain prior approval from the REC for the information and consent form that we give to subjects before we reduce the dose. But, owing to the nature of trials on healthy volunteers, it is likely that we will sometimes have to implement an urgent amendment to lower the planned dose, to avoid immediate hazard to the subjects. We will fully inform the subjects of the reason for reducing the dose, and will notify the REC and MHRA promptly of the urgent amendment, in accordance with statutory requirements.

18.2 Case report forms

The eCRF will be designed and produced by HMR.

To preserve confidentiality, the CRF will not bear the subject's name. The subject number and/or HMR volunteer number will be used for identification.

The investigator is responsible for ensuring the accuracy and completeness of the data entered into the eCRF, and the timeliness of data entry. Clinical data (including AEs, concomitant medication, etc) will be entered into a 21 CFR Part 11-compliant Medrio database. The Medrio system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Data reported in the eCRF, derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Where the data violate validation checks, queries will be generated for resolution by clinical staff. All edits made to the database upon resolution of queries will be recorded in an electronic audit trail.

Source documents

Before the start of the study, the sponsor and investigator will sign an agreement listing the source documents to be used in this trial.

18.3 Reporting of results

HMR will prepare a draft report for discussion with the sponsor. The report will contain results and discussion of the trial, to which will be attached tables, figures and listings in compliance with ICH E3[46].

Completed eCRFs will be supplied separately to the sponsor by HMR.

19 Obligations of the sponsor and investigator

19.1 Monitoring, auditing and inspection

The trial will be monitored by the sponsor.

A sample of documents generated by HMR which form part of this trial, and the ensuing data, will be audited by the HMR Quality Assurance Department to assess compliance with the quality management system of HMR. That system incorporates the requirements of The Medicines for Human Use (Clinical Trials) Regulations 2004 (and current amendments)[42], ICH GCP, GMP[37], and the SOPs issued by RES for RECs in the UK[38], and is based on ISO 9001.

The sponsor may do a quality assurance audit, and regulatory authorities may inspect this study, at any time during or after the study. The sponsor and investigator agree to allow auditors and inspectors direct access to all relevant documents, and to allocate time to discuss findings with the auditors or inspectors.

19.2 Compensation of volunteers

The sponsor agrees to abide by the Association of the British Pharmaceutical Industry (ABPI) Guidelines for medical experiments in non-patient human volunteers (2018 edition)[47], and undertakes to compensate the subjects for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

19.3 Confidentiality

All personal details of the participating subjects and the results of the trial will be kept strictly confidential. Each subject's GP (or equivalent physician) will be informed of the nature and timing of the trial.

All unpublished documents including the protocol, the CRF, and the IB are confidential. Those documents cannot be disclosed to a third party without the written consent of the sponsor. However, submission of those documents to a REC is expressly permitted.

The investigator agrees that the sponsor maintains the right to use the results of this trial, in their original form and/or in a global report, for submission to governmental and regulatory authorities of any country.

19.4 Publication

If the data merit, the investigator and the sponsor will discuss the preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for

presentation, oral or written, to a learned society or symposium. Either party may undertake the task but both must agree to the strategy before the work is started. Each party will allow the other 30 days to comment before any results are submitted for publication or presentation. Authorship should reflect work done by the investigators and personnel of the sponsor, in accordance with generally recognised principles of scientific collaboration.

19.5 Archiving

The sponsor and HMR will keep in a trial master file all the essential documents required by GCP. HMR will ensure that the investigator's master file, and all data generated during the trial, will be archived in a secure place for at least 25 years. Documents will be stored such that they are readily available for inspection at the request of the sponsor or a regulatory authority. Any transfer of ownership of the investigator's data or documents will be documented, and the sponsor will be informed.

20 Premature termination of the trial

The sponsor and investigator reserve the right to terminate this trial should severe AEs, SAEs or any other safety issue occur during the trial. If the trial is terminated prematurely, and the sponsor or investigator, as appropriate, will provide a written statement of the reasons for termination. The sponsor will ensure that the MHRA and REC are notified, as described in section 17.

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