AstraZeneca

Revised Clinical Study Protocol 2	
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A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

Sponsor:

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Quintiles representative

[redacted]

The following Amendments and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of Local Amendment
1	[redacted]		
2			
3			
Administrative Change No.		**Local Administrative Change No.**	**Date of Local Administrative Change**
1			

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PROTOCOL SYNOPSIS

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

Principal Investigator/National Co-ordinating Investigator

[redacted]

Study centers and number of subjects planned

This will be a multicenter study conducted in the United States (US). A sufficient number of male and female subjects with - major depressive disorder (MDD) and a history of poor response to antidepressants between the ages of 18-65 years old inclusive will be screened to ensure that approximately 150 subjects are randomized into the study to obtain 135-140 evaluable subjects. Approximately 30 centers will participate.

Study period		**Phase of development**
Estimated date of first subject enrolled	[redacted]	IIb
Estimated date of last subject completed	[redacted]	

Objectives

Primary objective: The primary objective of the study is to determine whether a superior antidepressant effect can be achieved at Week 3 with multiple infusions of AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with one Food and Drug Administration (FDA)-approved antidepressant, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion or mirtazapine, in subjects with MDD and a history of poor response to antidepressants, as assessed by a change from baseline to Week 3 in the Montgomery-Åsberg Depression Rating

Scale (MADRS) total score. A second drug for depression is allowed if prescribed for a duration of at least 6 weeks.

Secondary objectives:

1. To determine whether a superior antidepressant effect can be achieved at 3 days with AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with SSRIs, SNRIs, bupropion or mirtazapine in subjects with MDD and a history of poor response, as assessed by a change from baseline to 3 days in the MADRS total score.

2. To evaluate the rapid antidepressant efficacy of AZD6765 at 1 day after a first infusion, as assessed by a change from baseline to 1 day in the Quick Inventory of Depressive Symptomology Self-Report 16-item scale (QIDS-SR-16) total score.

3. To determine whether AZD6765 will demonstrate a superior antidepressant efficacy compared to adjunctive placebo, as assessed by subjects in remission (defined as MADRS total score ≤10) at each scheduled assessment and in particular at Week 3.

4. To determine whether AZD6765 will demonstrate a superior response compared to placebo, as assessed by subjects who are responders (defined as a ≥50% reduction from baseline in the MADRS total score) at each scheduled assessment and in particular at Week 3.

5. To evaluate the efficacy of AZD6765 in reducing suicidal ideation, as assessed by a change from baseline to Week 3 in the Beck Scale for Suicide Ideation (BSS) total score.

6. To investigate the effects of multiple infusions of AZD6765 (100 or 150 mg/infusion) at each scheduled assessment on subject mood, anxiety, and perception using a battery of scales: QIDS-SR-16, MADRS, Clinical Global Impressions-Severity of Illness and Improvement (CGI-S and CGI-I), Hamilton Depression Rating for Anxiety and Depression (HAM-A and HAM-D), and Visual Analog Scale (VAS).

7. To determine whether AZD6765 will demonstrate a superior sustained response compared to placebo, as assessed by responders at Week 3 who maintain response at all times between Week 3 and Week 8.

8. To assess the safety and tolerability of multiple infusions of AZD6765 (100 or 150 mg/infusion) via intravenous (IV) administration when administered concomitantly with other compounds used to treat depression as assessed by incidence of adverse events (AEs), vital signs, changes in weight and body mass index (BMI), physical examination, changes in clinical laboratory evaluations, electrocardiograms (ECGs), changes in the Clinician Administered Dissociative States Scale (CADSS), and suicidality (change in BSS total score and incidences of

suicidal behavior and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale [C-SSRS]).

9. To evaluate the effect of adjunctive AZD6765 versus adjunctive placebo on the health-related quality of life (QoL) in subjects with MDD and a history of poor response to antidepressants, as assessed by change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) total score (sum of items 1-14) at Week 3.

10. To characterize the pharmacokinetics (PK) of AZD6765 in subjects with MDD utilizing a population PK approach.

11. To conduct exploratory analysis of the genes involved in the PK/pharmacodynamics (PD), safety, and tolerability related to AZD6765 treatment.

Study design

This will be a multicenter, randomized, double-blind, placebo-controlled, outpatient, parallel group, efficacy and safety study conducted in male and female subjects between the ages of 18 and 65 years old inclusive with MDD and a history of poor response to antidepressants. History of poor response is defined as treatment failure on 1 or more antidepressants (in addition to the antidepressant the subject is taking at enrollment) after exposure at adequate doses or maximum tolerated doses for ≥4 weeks. This study will consist of a screening period of up to 30 days, a single-blind intravenous (IV) placebo (saline 0.9%) run-in infusion, a 3-week outpatient treatment period, and a 5-week outpatient follow-up period. Subjects will receive the investigational product, AZD6765, as an adjunct treatment to their current FDA-approved antidepressants. The dose of the adjunctive antidepressants will not be changed after randomization.

Target subject population

The study will enroll male and female subjects (aged 18 to 65 years inclusive) diagnosed with MDD, single episode or MDD, recurrent as confirmed by the Mini-International Neuropsychiatric Interview (MINI). A HAM-D score of ≥20, CGI-S score of ≥4, and QIDS-SR-16 score of ≥16 are required at: (i) screening (Visit 1); (ii) at the single-blind placebo run-in infusion (Visit 2); (iii) and at the baseline assessment before randomization (Visit 3). If the subject qualifies, the subject will be randomized and given the first infusion of AZD6765 or placebo the same day (randomization). Also, subjects with ≥50% reduction in MADRS total score after the single-blind IV placebo (saline) run-in infusion (Visit 2) will be classified as placebo responders and will not be eligible for randomization.

Investigational product, dosage and mode of administration

AZD6765 100 or 150 mg will be administered intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 1.67 mg/min for AZD6765 100 mg and 2.50 mg/min for AZD6765 150 mg over 60 minutes. Subjects will receive multiple infusions of AZD6765 during the treatment period. There will only be one

infusion administered per each study treatment visit day during Weeks 1 through 3. During non-treatment Weeks 4 through 8, there will be no administration of double-blind treatment (consisting of either AZD6765 100 mg, 150 mg, or placebo by infusion).

Comparator, dosage and mode of administration

The comparator in this study is placebo (0.9% saline) and will be administered intravenously. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min over 60 minutes. Subjects will receive multiple infusions of placebo during the treatment period.

Duration of treatment

Eligible subjects will have a screening period of up to 30 days. Following the screening period, subjects will enter a single-blind IV placebo (saline) run-in infusion period, which will occur 2 to 4 days before the randomization visit. While the Visit 2 IV saline run-in infusion will be conducted on a single day, the duration of the placebo run-in (2-4 days) will be longer (including time for measuring response to run-in placebo). Afterwards, subjects will enter a 3-week double-blind treatment period. After 3-weeks of treatment, subjects will enter a 5-week post-treatment follow-up (maintenance) period.

Outcome variables:

- **Efficacy**
  - **Primary outcome variable**: Change from baseline to Week 3 in the MADRS total score.
  - **Secondary outcome variables**:
  - Change from baseline in 3 days in the MADRS total score.
  - Change from baseline in 1 day in the QIDS-SR-16 total score.
  - Remission (defined as MADRS total score ≤10) at each scheduled assessment and in particular at Week 3.
  - Response (defined as ≥50% reduction from baseline in MADRS total score) at each scheduled assessment and in particular at Week 3.
  - Change from baseline to Week 3 in the BSS total score.
  - CGI-I score at each scheduled assessment (categorized as ≤2 and >2), and change from baseline at each scheduled assessment in QIDS-SR-16 total score, MADRS total score, CGI-S score, HAM-A and HAM-D total scores, and VAS total score.
  - Sustained response (defined as maintenance of response at all times between Week 3 and Week 8).

- **Safety**

  - Incidence and nature of adverse events (AEs); vital signs; weight and BMI changes; physical examination changes; clinical laboratory evaluations; ECG; change in CADSS score; suicidality (change from baseline at each scheduled assessment in BSS total score and incidences of suicidal behavior and suicidal ideation after baseline as measured by the C-SSRS).

- **Patient Reported Outcomes (PROs)**

  - Change from baseline in Q-LES-Q-SF total score (sum of items 1-14) at Week 3.

- **Pharmacokinetics**

  - AZD6765 plasma concentration levels (for population PK analysis).

- **Pharmacogenetics**

  - Exploratory analysis of the genes involved in the PK, PD, safety and tolerability related to AZD6765 treatment may be performed. The polymorphism of genes that may be correlated with the disposition and response to AZD6765 may be analyzed.

- **Biomarker analysis**

  - Serum samples for optional exploratory inflammatory cytokine biomarker analysis.

  - Urine samples for optional exploratory renal biomarker analysis.

Statistical methods

Efficacy analyses will be based on the modified intent-to-treat (mITT) analysis set that will include all randomized subjects, classified according to randomized treatment, who took investigational product and who have a randomization (baseline) MADRS total score assessment and at least 1 MADRS total score post randomization. Safety and tolerability assessments will be based on the safety analysis set which will include all randomized subjects who are given study treatment (analyzed according to the treatment received).

The primary efficacy variable is change from baseline to Week 3 in the MADRS total score, using the last observation carried forward (LOCF) principle to impute missing values. It will be analyzed by an analysis of covariance (ANCOVA) model with treatment, randomization stratification (co-morbid generalized anxiety disorder [GAD]), and baseline score as fixed effects, and center as a random effect. Each AZD6765 dose will be compared to placebo, with Dunnett's procedure used to adjust for multiplicity. As a supportive analysis, a similar analysis will be performed with OC in the mITT analysis set.

Secondary efficacy variables include change from baseline in the MADRS total score in 3 days (72 hours) and at the other scheduled assessments, change from baseline in the QIDS-SR-16 total score in 1 day (24 hours) and at the other scheduled assessments, change from baseline in the BSS total score to Week 3, remission (yes or no), response (yes or no), CGI-I score (≤2 vs. >2) at each scheduled assessment, sustained response (yes or no), and change from baseline at each scheduled assessment in VAS total score, CGI-S score, and HAM-A and HAM-D total scores. For the continuous efficacy endpoints, ANCOVA models similar to that used for the primary analysis may be used with LOCF in the mITT analysis set. For the binary efficacy endpoints, a logistic model in which treatment, randomization stratification (co-morbid GAD) and baseline score are included as fixed effects may be used with LOCF in mITT analysis set. No multiplicity adjustment will be made for the secondary efficacy variables.

For safety, AE incidence rates will be tabulated by preferred term and system organ class; also SAEs, AEs leading to death, and AEs leading to withdrawal of subjects will be tabulated for each treatment group. All laboratory test results, vital signs, ECG results, weight, and BMI will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline. The proportions of subjects who have a weight gain ≥7% compared to baseline will be tabulated. Suicidality measures based on the BSS and C-SSRS will be summarized for each treatment.

For the Q-LES-Q-SF total score, change from baseline to Week 3 will be analyzed using ANCOVA models similar to that used for the primary analyses with LOCF in the mITT analysis set for Week 3.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	adverse event (see definition in Section 7.3.1)
ALT	alanine transaminase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATHF	Antidepressant Treatment History Form
BP	blood pressure
BSS	Beck Scale for Suicide Ideation
C_{max}	Maximum plasma drug concentration
CADSS	Clinician Administered Dissociative States Scale
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity of Illness
CI	confidence interval
eCRF	electronic case report form
CRO	contract research organization
CSA	clinical study agreement
CSP	clinical study protocol
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DAE	discontinuation due to adverse event
DM	data management
DNA	deoxyribonucleic acid
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram

Abbreviation or special term	Explanation
ECT	electroconvulsive therapy
eDC	electronic data capture
EU	European Union
FDA	United States Food and Drug Administration
GAD	generalized anxiety disorder
GCP	Good Clinical Practice
HAM-A	Hamilton Depression Rating Scale for Anxiety
HAM-D	Hamilton Depression Rating Scale for Depression
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries, the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
IV	intravenous
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LIMS	Laboratory Information Management System
LOCF	last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
mITT	Modified intent-to-treat
NMDA	N-methyl-D-aspartate
OAE	Other Significant Adverse Event (ie, AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 12.1.2
OC	observed case

Abbreviation or special term	Explanation
PCP	phencyclidine
PD	pharmacodynamics
PI	principal investigator
PP	per protocol
PK	pharmacokinetics
QIDS-SR-16	Quick Inventory of Depressive Symptomatology Self-Report 16-item scale
QoL	quality of life
Q-LES-Q–SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
RBC	red blood cell
SAE	serious adverse event (see definition in Section 7.3.2)
SAP	statistical analysis plan
S-β-hCG	serum beta human chorionic gonadotrophin pregnancy test
SDV	source data verification
SNRIs	serotonin and norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
eRT	eResearch Technology
T_0	time before start of infusion
T_1	at least 1 hour after start of infusion
T_2	at least 2 hours after start of infusion
T_4	at least 4 hours after start of infusion
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse event
THC	tetrahydrocannibinol
TSH	thyroid-stimulating hormone
UDS	urine drug screen
UTS	urine toxicology screen
US	United States
VAS	(Bond-Lader) Visual Analog Scale
WBC	white blood cell

1. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

1.1 Medical emergencies and contacts

The principal investigator (PI) is responsible for ensuring that procedures and expertise are available to handle medical emergencies which may arise during the course of the study. **A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such, see Section 7.3.4**

In the case of a medical emergency, the Investigator should contact the following personnel below.

Name	**Role in the study**	**Address & telephone number**
[redacted]	Medical Monitor - Responsible for protocol implementation in US	[redacted]
Other contact information		
Name	**Role in the study**	**Address & telephone number**
[redacted]	Central laboratory	[redacted]
[redacted]	Central ECG laboratory	[redacted]
[redacted]	Interactive Voice Response System (IVRS)	[redacted]

1.2 Overdose

In the event of an overdose, the extent of the overdose, causative factors and medical complications should be determined. No specific treatment is available to reverse the effects of AZD6765.

Based on human studies to date, dizziness, lightheadedness, nausea, vomiting, headache, and blurred vision can occur when AZD6765 is administered in excess. In the event of these or other adverse events (AEs), the subject should be monitored carefully and treated symptomatically. In the event of excessive anxiety or dissociative reactions, a benzodiazepine such as lorazepam can be administered.

An overdose is a dose in excess of the doses specified for the dose group. For recording purposes:

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the electronic data capture (eDC) system as an AE of "Overdose" unless there are associated symptoms or signs. The associated symptoms or signs will be the AE terms documented in the source documentation and eDC system.
- An Overdose with associated SAE(s) must be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the source documentation and eDC system only.
- An Overdose with associated non-serious AEs must be recorded as the AE diagnosis/symptoms on the relevant AE forms in the source documentation and in eDC, and on the separate AstraZeneca "Clinical Study Overdose Report Form". Only overdoses of study medication will be reported.
- An Overdose without associated symptoms must be only reported on the separate AstraZeneca "Clinical Study Overdose Report Form".

Information on overdoses in study subjects is collected by AstraZeneca or representative and forwarded to AstraZeneca's clinical patient safety data entry sites. Should a subject experience an overdose during the course of the study (whether accidental or deliberate), the investigator or qualified designee must contact AstraZeneca or representative within **five business days** of the investigator or qualified designee first becoming aware of the overdose. Follow-up information on the outcome of the overdose will be forwarded to AstraZeneca.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such (see Section 7.3.3). If an SAE occurs in conjunction with the overdose, then the reporting time frame for an SAE (**one business day**) must be met. AstraZeneca or representative will provide instructions on how to collect this information (see Section 7.3.4).

1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca or representative on the pregnancy form.

1.3.1 Maternal exposure

Requirements for contraception in females of child-bearing potential are specified in inclusion criteria #2 (see Section 5.1).

In the event of pregnancy, pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If a subject or the female partner(s) of a male study subject becomes pregnant during the course of the study, the investigator or qualified designee must inform AstraZeneca or representative no later than the end of the next business day of the investigator or qualified designee first becoming aware of the pregnancy. The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to AstraZeneca's clinical patient safety data entry site within 30 calendar days.

If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (**one business day**) must be met. AstraZeneca or representative will provide instructions on how to collect pregnancy information.

AstraZeneca's Pregnancy Outcome Report, part 1, is used to report the pregnancy and the Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy.

1.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose until 1 week after the last dose must be followed up and documented.

Male subjects must refrain from fathering a child during the study and **three** months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, have not been thoroughly investigated.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

2. INTRODUCTION

2.1 Background

AZD6765 dihydrochloride is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist undergoing evaluation as therapy for major depressive disorder (MDD). Unlike standard antidepressants that appear to work by increasing levels of synaptic neurotransmitters (eg, serotonin, norepinephrine, and dopamine), NMDA-receptor antagonists appear to achieve an antidepressant effect by reducing synaptic transmission at the NMDA-receptor, hypothetically leading to a dampening of receptor function (Skolnick 1999).

NMDA-receptor antagonists with current medical indications include memantine and ketamine. Memantine is approved for treatment of moderate- to- severe dementia of Alzheimer's type, while ketamine is approved for induction of anesthesia prior to administration of general anesthesia. Historically, ketamine use has been limited to anesthesia because of emergence reactions, ie, psychological manifestations - typically of short-term duration - that vary from pleasant dream-like states to emergence delirium.

However, more recently as part of ongoing experimental work with NMDA antagonists, 2 studies with ketamine (Berman et al 2000, Zarate et al 2006) showed antidepressant effects in patients with MDD. However, the low-affinity NMDA antagonist memantine did not demonstrate any antidepressant effect (Zarate et al 2006).

AZD6765 was originally developed as an intravenous (IV) treatment for stroke because of neuroprotective and antiepileptic properties demonstrated in early nonclinical studies. Although this development did not expand beyond Phase IIa studies (efficacy in patients with stroke was not established as anticipated), the results of Phase I and II studies provided an acceptable safety and tolerability profile, as well as a pharmacokinetics (PK) profile that supported exploratory examination of AZD6765 in humans for other pharmacodynamically driven indications, including MDD. Importantly, AZD6765 has not been withdrawn from clinical investigation in any country because of safety concerns.

Major depressive disorder can often remain a chronic, severely debilitating illness associated with significant morbidity and mortality. Despite the availability of a wide range of antidepressant drugs, clinical trials indicate that 30-40% of patients with MDD fail to respond to first-line antidepressant treatment, despite adequate dosage, duration, and compliance. Most antidepressants have not been studied in patients with a history of poor response to antidepressants. Electroconvulsive therapy (ECT) is a treatment that is available for MDD of at least moderate severity, but it has significant limitations including stigma, poor acceptability, cost, high resource utilization, and cognitive adverse effects. Clearly, there is a need to develop novel and improved therapeutic agents for MDD.

The pharmaceutical form of AZD6765 dihydrochloride is a concentrate solution containing 15 mg/mL of AZD6765 base (which corresponds to 20.5 mg of AZD6765 dihydrochloride). Before use, the concentrate solution is diluted in commercially available normal saline solution (9 mg/mL) for infusion and administered over time (as specified per protocol).

There was a signal for reduction in depressive symptoms seen at 72 hours after infusion of 100 mg AZD6765 in the Phase IIa study in patients with MDD who had treatment resistance by history. In this study, 34 subjects were randomized to one infusion of AZD6765 IV 100 mg (n=16) or placebo (n=18).

Additional Phase I studies to examine food effects, safety in special populations, and drug-drug interactions will be conducted, as necessary, to support the efficacy trials.

Effect of concomitant medicines on systemic exposure of AZD6765

The systemic exposure to AZD6765 may be altered by concomitant medicines that are cytochrome P450 (CYP) and other relevant enzyme inhibitors, inducers or substrates. Since the metabolism of AZD6765 is mediated by multiple enzymes, and the metabolites only account for ~30% of the total plasma circulation, the metabolism relevant effect caused by these concomitant medicines would only increase AZD6765 exposure by ~30% at the assumed worst case scenario (inhibition), which is still within the exposure safely tested in the clinical program (well-tolerated dose=250 mg IV). However, since active tubular secretion may be involved in the kidney elimination of AZD6765, there is a possibility that the systemic exposure to AZD6765 would be altered by concomitant medicines due to modulating/competing relevant transporters involved in the same elimination pathway.

Effect of AZD6765 on systemic exposure of concomitant medicines

The observations in AZD6765 disposition suggest that contributing to drug-drug interaction potential is CYP3A4/5 inhibition at concentration >2.7 μM, under which the systemic exposure to these concomitant medicines could be higher due to enzyme inhibition, especially for those metabolism that involve CYP3A4 only. Since the inhibition by AZD6765 is competitive, the effect, if any, should be subject to the difference in affinity to CYP3A between individual concomitant medicines and AZD6765, and subject to the enzyme levels expressed in individuals. In addition, if the concomitant medicines require transporters for kidney elimination/active tubular secretion, there is a possibility that the systemic exposure to these medicines would be increased in the presence of AZD6765 due to competition for the same potential transporters.

Conclusions

Pharmacokinetics drug-drug interaction potential based on CYPs caused by adjunct administration of concomitant medicines and AZD6765 is low.

2.2 Preliminary human experience

AZD6765 had been in clinical development in Europe as an IV treatment for stroke and other indications between 1994 and 2001. To date, six Phase I studies to investigate the safety and tolerability and PK of AZD6765 in healthy volunteers were completed. In addition, two Phase IIa studies were completed in stroke patients and another in sleep apnea. A total of 316 volunteers and patients (including 225 patients) have been exposed to various doses of AZD6765.

Human volunteer studies in exploratory development have shown that the compound is well tolerated in both single and multiple doses. The most common AEs were transient dizziness, impaired concentration, somnolence and nausea based on the clinical experience with the drug in normal volunteers. No serious adverse events (SAEs) were observed in the normal volunteer studies. SAEs related to disease progression or associated conditions (myocardial infarction) did occur in the stroke trials but were not considered to be due to drug administration.

AZD6765 loading doses of 160 mg in normal volunteers and 250-460 mg in stroke patients were shown in previous studies to be generally well tolerated up to a C_{max} of 3000 ng/mL (15.1 μM). In the proposed study, as well as in future studies in depression, a C_{max} well below 3000 ng/mL (15.1 μM) or less will be targeted.

Preclinical studies found small, transient increases in systolic blood pressure in rats and dogs at higher doses of AZD6765. In the clinical studies, an increase in systolic blood pressure was generally observed towards the end of the 1-hour loading-dose infusion. Increases in systolic blood pressure were on the order of 10 mmHg, transient, and not associated with any adverse sequelae. While these effects are not considered clinically significant, the protocol for the proposed study will specify frequent vital sign measurements to monitor such changes.

No other clinically significant changes in diastolic blood pressure, heart rate, or ECG findings were observed. Likewise, no dose-related effects on QTc were seen. In the proposed study, ECGs will be obtained to monitor cardioelectrical activity.

There have been no consistent or dose-related changes in clinical chemistry, hematology, thyroid function tests, urinary cortisol excretion or urinalysis.

In human experience to date, with exposure in 316 volunteers and patients (including 225 patients), mild and transient AEs of the central nervous system (CNS), especially at IV doses above 250 mg, have occurred. The most common AEs were transient dizziness, impaired concentration, somnolence and nausea based on the clinical experience with the drug in normal volunteers. Transient dizziness was seen more often in AZD6765 compared to placebo in the MDD study. The frequency and intensity of behavioral and cognitive effects were much less than that seen with other NMDA antagonists such as ketamine or phencyclidine (PCP). Notably, the behavioral profile of AZD6765 has more in common with that of other weak NR1/NR2A antagonists, such as memantine. No hallucinations or dissociative episodes were reported in any of the 91 healthy, young and elderly volunteers who received AZD6765 at doses up to 160 mg. In the two stroke studies, about 6% of patients had hallucinations after doses of 250 to 460 mg of AZD6765. No hallucinations or dissociative episodes were observed during or after 100 mg infusion in 16 patients with MDD.

In addition, in the stroke studies, an increase in systolic blood pressure (BP) was generally observed towards the end of the 1-hour loading-dose infusion. Increases in systolic BP were on the order of 10 mmHg, transient, and not associated with any adverse sequelae. In the MDD study, change from baseline in diastolic and systolic BP at 0.5, 2.5 and 3.5 hours was higher for AZD6765-treated subjects compared to placebo. The clinical meaning of this

finding is unclear at this time, particularly because the change was transient and the subjects in the AZD6765 arm had higher baseline BP than placebo subjects.

For further information, please refer to the Investigator's Brochure (IB).

2.3 Research hypothesis

The primary goal of this study is to test the hypothesis that AZD6765 will demonstrate superiority over adjunctive placebo in decreasing depression symptoms as measured by change from baseline to Week 3 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Secondary goals of the study include evaluation of safety and tolerability of AZD6765 in subjects with MDD with a history of poor response to antidepressants and further assessment of AZD6765's efficacy using clinician and patient-rated instruments.

The exploratory hypothesis tested is that PK/PD is related to genetically determined differences in drug uptake and metabolism.

2.4 Rationale for conducting this study

The overall rationale for this study is to assess the antidepressant effect of AZD6765 in subjects with MDD who have a history of poor response. History of poor response is defined as treatment failure on 1 or more antidepressants (in addition to the antidepressant the subject is taking at enrollment) after exposure at adequate doses or maximum tolerated doses for ≥4 weeks.

AZD6765 is being developed as an alternative to ECT for patients with a history of poor response to antidepressants with at least moderate symptomatology. In an attempt to expand the treatment options currently available for the treatment of MDD and to build upon existing clinical data observed with the use of NMDA antagonists to exert an antidepressant effect, the current study will explore the use of AZD6765 at a dose of 100 and 150 mg in the treatment of MDD.

2.5 Benefit/risk and ethical assessment

The current assessment of risk with AZD6765 is based on previous clinical experience and preclinical safety and toxicology studies. Potential risks include mild, transient elevations in systolic blood pressure, behavioral effects at excessive doses and in the extreme, neuronal vacuolation (only seen at high doses in rats) genotoxicity secondary to the formation of stilbazole. In addition, potential risks based on preclinical safety studies include renal tubular toxicity with accompanying adaptive hypertrophy and degenerative myocardial changes resulting in replacement fibrosis (only seen in daily oral doses in rats). The histological changes observed in the heart and skeletal muscles are consistent with chronic hypokalemia.

The current study will monitor weekly Troponin I and T and ECGs, which are sensitive markers of cardiac damage. Dosing would be stopped in any subject with elevated Troponin I

or T levels and subjects will be monitored and followed as clinically appropriate. Weekly urinalyses including urine electrolytes will be monitored as well. In addition, dosing will be stopped and subjects followed clinically as appropriate if in any subject with clinically significant changes in serum or urinary metabolites reflective of kidney dysfunction.

The major risks of participating in this trial are AEs related to the use of AZD6765. Commonly reported AEs include transient dizziness, headache, nausea, vomiting, fever, blurred vision, and impaired concentration/confusion. Injection site reactions were not common and occurred both in subjects treated with AZD6765 and subjects treated with placebo. An additional risk is worsening of symptoms of MDD due to lack of response.

The potential for AZD6765 to be effective in MDD is based on its pharmacological properties as a noncompetitive NMDA receptor antagonist, on its PK properties (including rapid tissue distribution and a 9- to 15-hour half-life) and on findings of antidepressant effects with other NMDA antagonists. However, the full benefit-to-risk assessment will depend on the clinical efficacy and safety data collected from patients with MDD. The benefit of AZD6765 is that it may provide relief from depression in patients diagnosed with MDD. It should be noted that adjunctive treatment with antidepressants is not being provided in this study by AstraZeneca.

The discontinuation of clinically prescribed antidepressants can be challenging in depression and includes the risk of exacerbation of depression. The risk of any drug-drug interaction with AZD6765 is low with commonly prescribed antidepressants. This permits study of AZD6765 with adjunctive antidepressants without any discontinuation and eliminates the risk from antidepressant discontinuation.

Few treatment options are available to patients with a history of poor response to antidepressants and at least moderate symptomatology. Electroconvulsive therapy is sometimes used in this population; however, its use is limited by social stigma, adverse effects and cumbersome procedures including anesthesia. This study explores the efficacy and safety of AZD6765 in this population.

The potential to relieve depression in patients with a history of poor response to antidepressants supports a positive benefit-to-risk ratio.

Please refer to the IB for additional information regarding risks.

3. STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study and its associated variable is described in Table 1.

Table 1 Primary objective

Primary Objective: To determine whether a superior antidepressant effect can be achieved at Week 3 with multiple infusions of AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with one FDA-approved antidepressant, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion or mirtazapine in subjects with MDD and a history of poor response to antidepressants, as assessed by a change from baseline to Week 3 in the MADRS total score. A second drug for depression is allowed if prescribed for a duration of at least 6 weeks.	
Dependent variable	**Description**
Change from baseline to Week 3 in the MADRS total score	The MADRS is a 10-item scale for the evaluation of depressive symptoms (Montgomery and Åsberg 1979). Each MADRS item is rated on a 0-6 scale. Higher MADRS scores indicate higher levels of depressive symptoms.

3.2 Secondary objectives

The secondary objectives and associated variables are described in Table 2.

Table 2 Secondary objectives

Secondary Objective 1: To determine whether a superior antidepressant effect can be achieved at 3 days with AZD6765 (100 or 150 mg/infusion) versus placebo when given adjunctively with SSRIs, SNRIs, bupropion or mirtazapine in subjects with MDD and a history of poor response, as assessed by a change from baseline to 3 days in the MADRS total score.	
Dependent variable	**Description**
Change from baseline to 3 days in the MADRS total score	Please refer to MADRS description in Table 1.
Secondary Objective 2: To evaluate the rapid antidepressant efficacy of AZD6765 at 1 day after first infusion, as assessed by a change from baseline at 1 day in the QIDS-SR-16 total score.	
Dependent variable	**Description**
Change from baseline to 1 day in the QIDS-SR-16 total score	The QIDS-SR is 16-question self-test done by the subject to assess the severity of depressive symptoms (Rush et al 2003). The test measures 9 different criterion domains of major depression.
Secondary Objective 3: To determine whether AZD6765 will demonstrate a superior antidepressant efficacy compared to placebo, as assessed by subjects in remission (defined as MADRS total score ≤10) at each scheduled assessment and in particular at Week 3.	
Dependent variable	**Description**
Remission at each scheduled assessment and in particular at Week 3	Remission (yes) is defined as a MADRS total score ≤10.

Table 2 Secondary objectives

Secondary Objective 4: To determine whether AZD6765 will demonstrate a superior response compared to placebo, as assessed by subjects who are responders (defined as a ≥50% reduction from baseline in the MADRS total score) at each scheduled assessment and in particular at Week 3.	
Dependent variable	**Description**
Response at each scheduled assessment and in particular at Week 3	Response (yes) is defined as a ≥50% reduction from baseline in the MADRS total score.
Secondary Objective 5: To evaluate the efficacy of AZD6765 in reducing suicidal ideation, as assessed by a change from baseline to Week 3 in the BSS total score.	
Dependent variable	**Description**
Change from baseline to Week 3 in BSS total score	The BSS is a 21-item report scale to assess the severity of suicidal ideation in adults and adolescents (Beck et al 1979).
Secondary Objective 6: To investigate the effects of multiple infusions of AZD6765 (100 or150 mg/infusion) on subject mood, anxiety, and perception using a battery of scales: QIDS-SR-16, MADRS, CGI-S and CGI-I, HAM-A and HAM-D, and VAS.	
Dependent variables	**Description**
Change from baseline at each scheduled assessment in QIDS-SR-16 total score	Please refer to QIDS-SR-16 description above.
Change from baseline at each scheduled assessment in MADRS total score	Please refer to MADRS description in Table 1.
Change from baseline at each scheduled assessment in CGI-S score	CGI-S rates the severity of the subject's illness at the time of assessment (Guy 1976). Each CGI-S item is scored on a scale from 1 to 7 (1=normal, not ill to 7=very severely ill). Higher CGI-S scores indicate greater illness severity.
CGI-I score (≤2 vs. >2)	CGI-I rates the subject's change post-treatment (Guy 1976). CGI-I scores of 1 and 2 indicate that a subject is "Very much improved" or "Much improved". Scores >2 range from 3 ("Minimally improved") to 7 ("Very much worse"). Higher CGI-S scores indicate greater illness severity. CGI-I scores greater than 4 indicate worsening, while scores less than 4 indicate improvement.

Table 2 Secondary objectives

Change from baseline at each scheduled assessment in HAM-A and HAM-D total scores	The HAM-A (Hamilton 1959) measures the severity of a subject's anxiety, based on 14 parameters. Each item is rated on a 5-point scale: 0 (not present) to 4 (severe). The HAM-D is a 21-item observer rated scale that assesses depressive symptoms (Hamilton 1960), each of which is rated from 0-2 or 0-4, where 0 is none/absent.
Change from baseline at each scheduled assessment in VAS total score	The modified Bond-Lader VAS is a questionnaire completed by the subject consisting of 16 scales that assess changes in subjective alertness, subjective calmness and subjective contentment (Bond and Lader 1974).
Secondary Objective 7: To determine whether AZD6765 will demonstrate a superior sustained response compared to placebo, as assessed by responders at Week 3 who maintain response at all times between Week 3 and Week 8.	
Dependent variables	**Description**
Sustained response	Sustained response (yes) is defined as maintenance of response at all times between Week 3 and Week 8.
Secondary Objective 8: To assess the safety and tolerability of multiple infusions of AZD6765 (100 or 150 mg/infusion) via IV administration when administered concomitantly with other compounds used to treat depression as assessed by incidence of AEs, vital signs, changes in weight and BMI, physical examination, changes in clinical laboratory evaluations, ECGs, change in CADSS, and suicidality (change in BSS total score and incidences of suicidal behavior and suicidal ideation as measured by C-SSRS).	
Dependent variables	**Description**
Incidence of AEs, discontinuations due to AEs, SAEs, death	AEs will be collected throughout the study (ie, from time of informed consent, throughout the treatment period, and including the follow-up period).
Change from baseline to each visit, when measured, in clinical laboratory test results (ie, clinical chemistry and hematology), ECG results, vital signs, weight, BMI, physical examination	Laboratory assessments, 12-lead ECG, height, weight, BMI, physical examination will be performed at screening (Visit 1), Visit 5 (Week 3), and Visit 10 (Week 8). Vital signs will be performed throughout the study at every scheduled visit through Week 8.
Change from baseline at each scheduled assessment in BSS total score	Please refer to BSS description above.

Table 2 Secondary objectives

Incidences of suicidal behavior and suicidal ideation after baseline as measured by the C-SSRS	The C-SSRS (Posner et al 2007) assesses the suicidal risk and suicidal ideation in subjects. Occurrence of suicidal behavior is defined as having answered "yes" to at least one of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation. Occurrence of suicidal ideation after baseline is defined as having answered "yes" to at least one of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.
Change from baseline at each scheduled assessment in CADSS total score	The CADSS is a 23 item self-report scale (Bremner et al 1998). Severity of each dissociative symptom range from 0 (not present) to 4 (extreme).
Secondary Objective 9: To evaluate the effect of adjunctive AZD6765 versus adjunctive placebo on the health-related quality of life (QoL) in subjects with MDD and a history of poor response to antidepressants, as assessed by change from baseline in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) total score (sum of items 1-14) at Week 3.	
Dependent variable	**Description**
Change from baseline in the Q-LES-Q-SF total score (sum of items 1-14) at Week 3	The Q-LES-Q-SF instrument has been developed to measure differences in degree of enjoyment and satisfaction (Endicott et al 1993). The short form used in this study has 16 items. The first 14 items will be used to derive a total score, and the remaining 2 are single items, measuring satisfaction with medication and overall QoL, respectively. Each item is rated into 5 categories. Higher scores indicate better health-related QoL. The instrument is sensitive to change over time following treatment. It has high internal consistency, test-retest reliability, and concurrent validity in patients with MDD and generalized anxiety disorder.

Table 2 Secondary objectives

Secondary Objective 10: To characterize the PK of AZD6765 in subjects with MDD utilizing a population PK approach.	
Dependent variable	**Description**
Population PK analysis	AZD6765 plasma concentration levels will be assessed.
Secondary Objective 11: To conduct exploratory analysis of the genes involved in the PK/PD, safety, and tolerability related to AZD6765 treatment.	
Dependent variable	**Description**
Pharmacogenetics	An optional blood sample will be taken from those subjects from whom an independent written consent for pharmacogenetic research is provided. Deoxyribonucleic acid (DNA) extracted from the optional blood samples may be used to explore relationships between genetic variability and AZD6765 PK/PD, safety, tolerability, response and depression.

4. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subjected to a peer review according to AstraZeneca's standard procedures.

4.1 Overall study design and flow chart

This will be a multicenter, randomized, double-blind, placebo-controlled, outpatient, parallel group efficacy and safety study conducted in male and female subjects between the ages of 18 and 65 years old inclusive with MDD and a history of poor response to antidepressants to determine whether a superior antidepressant effect can be achieved at Week 3 with multiple infusions of AZD6765 100 or 150 mg versus placebo. History of poor response is defined as treatment failure on 1 or more antidepressants (in addition to the antidepressant the subject is taking at enrollment) after exposure at adequate doses or maximum tolerated doses for ≥4 weeks.

A sufficient number of male and female subjects will be screened to ensure that approximately 150 subjects are randomized into the study to obtain 135-140 evaluable subjects. Approximately 30 centers in the US will participate in the study.

The study will consist of a screening period of up to 30 days, a single-blind IV placebo (saline 0.9%) run-in infusion period, a 3-week outpatient adjunctive investigational drug treatment period, and a 5-week outpatient follow-up period. During the treatment period, subjects will receive the investigational product as an adjunct to their existing FDA-approved antidepressant treatment (including SSRIs, SNRIs, bupropion or mirtazapine), as specified in

the protocol (Section 6.5). The dose of the adjunctive antidepressants will not be changed after randomization. A second adjunctive drug used for treatment of depression is allowed. During the 5-week outpatient follow-up period, subjects will continue with their antidepressant treatment they were taking during the adjunctive investigational drug treatment period. During this follow-up period, they will not receive investigational drug.

Each subject will receive one single-blind IV placebo (saline) run-in infusion (Visit 2) prior to randomization. The randomization visit will occur 2 to 4 days after the IV saline run-in infusion. Before randomization at Visit 3, assessments will be conducted to ensure that the HAM-D is ≥20, CGI-S is ≥4, and QIDS-SR-16 is ≥16. If the subject does not meet these criteria, the subject will be considered a screen failure and will not be randomized to the study. (Subjects who were considered screen failures under the entrance criteria outlined in the original protocol, but who would have qualified under these current criteria, may be considered for re-screening.) Subjects who qualify will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms:

- Treatment A: AZD6765 100 mg (total dose) by IV infusion.
- Treatment B: AZD6765 150 mg (total dose) by IV infusion.
- Treatment C: Placebo (0.9% saline) by IV infusion.

Subjects will receive multiple infusions of AZD6765 100 or 150 mg or placebo saline during the 3-week study treatment period and must be treated as outpatients during the entire course of the study. Subjects will undergo the study procedures and assessments at designated visits per the study assessments (Table 3).

The subject's depression and suicidality (suicide risk) will be assessed by the following rating scales: MINI, QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, VAS, CGI-S and CGI-I. The dissociative state will be assessed by CADSS. The subject's suicidality will be further assessed by the BSS and C-SSRS. The subject's QoL will be assessed by the self-reported Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) questionnaire.

Each treatment period will consist of 3 infusions per week for 3 weeks (Weeks 1, 2 and 3). For each week, there will be 3 visits and all subjects will receive a single infusion of AZD6765 or placebo per visit for a total of 3 infusions. During Week 1 (Visits 3, 4 and 5), the first infusion (Infusion 1, Visit 3) will be administered on Day 1 (randomization). The second infusion (Infusion 2, Visit 4) will be given on Day 4 after the first infusion. The third infusion (Infusion 3, Visit 5) will be given 2 to 3 days following the second infusion. During Weeks 2 and 3, subjects will receive a total of 3 infusions per week on any non-consecutive day at Visits 6, 7 and 8 (Week 2) and Visits 9, 10 and 11 (Week 3), respectively (Figure 1).

Dosing on consecutive days is prohibited at any time during the study. All dose weeks are defined by a 7-day period, relative to the first dose of randomized study drug (ie, if the first

dose is on a Wednesday, then all 3 dose weeks [Weeks 1, 2 and 3] are defined as Wednesday through Tuesday).

All females must have a negative serum pregnancy test and confirmed use (by the investigator) of a highly effective form of birth control. The highly effective form of birth control includes but is not limited to true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, intrauterine device (IUD)/intrauterine system (IUS) (copper coils), Depo-Provera injections, low dose combined oral contraceptive only if used in TriCycle regime, and Evra Patch or Nuvaring used in TriCycle regime. Women should be on a stable method of birth control for a minimum of 3 months prior to study entry.

4.1.1 Screening/enrollment period (Visit 1, Days -30 to -1)

The screening and enrollment period will be up to 30 days (Days -30 to -1) prior to Day 1 (randomization) of the treatment period.

Eligible subjects (aged 18 to 65 years inclusive), with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR; (American Psychiatric Association 2000) diagnosis of MDD, single episode (296.2x) or MDD, recurrent (296.3x) as confirmed by the Mini-International Neuropsychiatric Interview (MINI) will be evaluated.

At the screening visit, subjects will undergo all study procedures and assessments, including safety evaluations, listed in Table 3. Assessments will be conducted to ensure that the subject's HAM-D is ≥20, CGI-S is ≥4, and QIDS-SR-16 is ≥16. If the screening and randomization visits are <7 days apart, a repeat pregnancy test is not required before the placebo saline run-in infusion.

If the subject qualifies for enrollment based on the inclusion/exclusion criteria (including HAM-D ≥20, CGI-S ≥4, and QIDS-SR-16 ≥16), the subject will return to the study center for the single-blind IV placebo run-in infusion (Visit 2). If the subject does not meet these criteria, the subject will be considered a screen failure and will not be enrolled. (Subjects who were considered screen failures under the entrance criteria outlined in the original protocol dated 17 September 2008, but who would have qualified under these current criteria, may be considered for re-screening.)

Subjects will continue on their existing antidepressant treatment. The list of permitted antidepressants and dual-therapy combinations during the study is given in Table 8. The screening period (from Visit 1 to Visit 3) may take up to 30 days to allow the investigator to review the results of laboratory assessments which would confound the results of the study and also to ensure the safety of subjects.

4.1.2 Single-blind IV placebo saline run-in period (Visit 2, Day -3 to Day -1)

At Visit 2 (Day -3 to Day -1), qualified subjects will return to the study center and will receive one single-blind IV placebo saline run-in infusion prior to the randomization visit. The

subject will be blind to this information but the study staff (PI, coordinator) will be aware that the first infusion at Visit 2 will be a placebo saline run-in only to assess placebo response.

The purpose of the placebo saline infusion is to decrease placebo response during the study. The placebo saline infusion will be administered at a minimum of 2 days (and no more than 4 days) prior to randomization (Visit 3, Day 1). While the placebo saline infusion will be given on a single day, the duration of the saline run-in (2-4 days) period will be longer (including time for measuring response to run-in placebo). Subjects will receive the placebo saline infusion as an adjunct to their existing antidepressant treatment (up to 2) as specified in the protocol (Section 6.5).

The following evaluations will be done before the placebo saline infusion:

- Assessment by rating scales in the following order: QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, VAS and CGI-S.
- Dissociative symptom test: CADSS.
- Vital signs (blood pressure, pulse, temperature [in °C]).
- Weight measured.
- Serum pregnancy test (serum β-hCG). If the screening and randomization visits are <7 days apart, a repeat pregnancy test is not required before the placebo saline run-in infusion.
- Assess AEs.
- Assess permitted and prohibited concomitant medications.

After the placebo saline infusion, subjects will remain on site for at least 4 hours from start of infusion.

The MADRS will be performed before start of the placebo saline run-in infusion (Time 0 [T_0]) and at least 4 hours after start of the placebo saline run-in infusion (T_4). If the subject has a ≥50% reduction in the MADRS total score after the placebo saline run-in infusion, the subject will be classified as a placebo responder and will not be randomized to the double-blind treatment period of the study (Visit 3).

Qualified subjects will be randomly assigned 2 to 4 days after the placebo run-in infusion to 1 of the 3 treatment arms described below at Visit 3 (Day 1).

4.1.3 Randomization/double-blind treatment period (Weeks 1 to 3)

Week 1: Visits 3, 4 and 5 (Days 1 to 8)

Only qualified subjects will be randomized (Visit 3, Day 1). Two to 4 days after the placebo saline run-in infusion, qualified subjects will return to the study center on Day 1 (Visit 3) of the double-blind treatment period.

Subjects will undergo the study procedures and assessments described for Day 1 (Visit 3) before randomization (Table 3). Assessments conducted before randomization will be considered baseline assessments. The QIDS-SR-16 will be completed daily (including the infusion visits and when subject is at home) during Week 1.

Qualified subjects who meet the inclusion/exclusion criteria and whose HAM-D score is still ≥20, CGI-S score ≥4, and QIDS-SR-16 score ≥16 will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms:

- **Treatment A**: Subjects will receive AZD6765 100 mg (total dose) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min (1.67 mg/min) over 60 minutes.

- **Treatment B**: Subjects will receive AZD6765 150 mg (total dose) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min (2.50 mg/min) over 60 minutes.

- **Treatment C**: Subjects will receive placebo (0.9% saline) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min over 60 minutes.

Subjects should be semi-reclined during the IV infusion. Subjects will receive multiple infusions of AZD6765 (100 or 150 mg) or placebo during the treatment period.

This study includes the option for randomized subjects to participate in optional exploratory genetic research and optional biomarker (inflammatory cytokine and urine) analysis, where permitted. A 9-mL sample of blood will be collected from qualified subjects who have also provided consent for optional exploratory genetic research. The blood sample can be collected anytime after a subject has qualified for the study, but it is preferred that collection be done at the baseline/randomization visit (Visit 3, Day 1). A 2-mL serum sample and a 10-mL urine sample will be collected from qualified subjects who have also provided consent for optional exploratory biomarker research. The serum sample will be collected at the randomization visit and at Week 3 prior to start of infusion. The urine sample can be collected anytime after a subject has qualified for the study, but it is preferred that collection be done at the baseline/randomization visit (Visit 3, Day 1). Another 10-mL urine sample will be collected at Week 4 (Visit 12) from qualified subjects who have provided consent for optional exploratory biomarker analysis.

During Week 1, all subjects will receive 3 infusions as follows, which will be administered on non-consecutive days. Each infusion will be given over 60 minutes.

- **Infusion 1 (randomization)**: The first infusion of randomized drug will be administered on Day 1 (Visit 3), two to 4 days after the single-blind placebo saline run-in infusion.
- **Infusion 2**: The second infusion will be administered on Day 4 (Visit 4), three days after the first (randomization) infusion on Day 1.
- **Infusion 3**: The third infusion will be given 2 to 3 days (Visit 5) following the second infusion.

After Infusions 1 and 2 (Week 1), subjects will remain on site for at least 4 hours after start of infusion (ie, up to T_4). Starting from Infusion 3 (Week 1), subjects will remain on site for at least 2 hours after start of infusion (ie, up to T_2).

Subjects must report by telephone any AEs that occur the day after the first infusion (Infusion 1 after randomization [Week 1]).

Blood samples will be collected for PK analysis (see Table 10 for blood sampling schedule for all subjects during Week 1).

Weeks 2 and 3: Visits 6 to 11

During Weeks 2 and 3, all subjects will receive 3 infusions per week (Infusions 1, 2 and 3) on any non-consecutive day during Weeks 2 and 3 (Visits 6, 7 and 8 and Visits 9, 10 and 11, respectively) (Table 5). The last infusion on Week 3 (Infusion 3) will be administered 2 to 3 days after the previous infusion. The final assessments (efficacy measures), including MADRS, will be conducted within 2 to 4 hours of the last infusion (Infusion 3).

During Weeks 2 and 3, subjects will remain on site for at least 2 hours from the start of infusion (ie, up to T_2).

Subjects will undergo all procedures and assessments at the designated visits per the Study Assessments (Table 3 and Table 5).

Blood samples will be collected for PK analysis (see Table 11 for blood sampling schedule during Week 3).

At Week 3, a 2-mL serum sample will be collected from qualified subjects who have also provided consent for optional exploratory biomarker research. The serum sample will be collected prior to start of infusion.

4.1.4 5-week post-treatment follow-up maintenance period: Weeks 4 to 8 (Visits 12 to 16)

Subjects will continue on the antidepressants that they entered the study on (including SSRIs, SNRIs, bupropion or mirtazapine) for another 5 weeks.

Subjects will be scheduled for a 7-, 14-, 21-, 28- and 35-day follow-up visit (Visits 12, 13, 14, 15 and 16) from last dosing to assess maintenance effects.

Subjects will undergo the study procedures and assessments at the designated visits per the Study Assessments (Table 3 and Table 6).

Another 10-mL urine sample will be collected at Week 4 (Visit 12) from qualified subjects who have provided consent for optional exploratory biomarker analysis.

Table 3 Study assessments

Study Procedures	Screening[a]	Single-blind IV Placebo Run-in Infusion[b,c]	3-Week Double-blind Treatment Period				5-Week Follow-up (Maintenance) Period				
			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Final Visit OR Early DC[e] Week 8
			Randomization[d]								
Visit Day[f]	**-30 to -1**	**-3 to -1[g]**	**1**	**2-8**	**9-15**	**16-22**	**23-29**	**30-36**	**37-43**	**44-50**	**51-57**
Visit Number	**1**	**2**	**3**	**4, 5**	**6, 7, 8**	**9, 10, 11**	**12**	**13**	**14**	**15**	**16**
Informed consent	X										
Medical/medication/ surgical history	X										
Inclusion/exclusion criteria	X		X								
Demographic data	X										
Height[h]	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X					X					X
Digital 12-lead ECG[i]	X		X	X	X	X					X

Table 3 Study assessments

Study Procedures	Screening[a]	Single-blind IV Placebo Run-in Infusion[b,c]	3-Week Double-blind Treatment Period				5-Week Follow-up (Maintenance) Period				
			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Final Visit OR Early DC[e] Week 8
			Randomization[d]								
Visit Day[f]	**-30 to -1**	**-3 to -1[g]**	**1**	**2-8**	**9-15**	**16-22**	**23-29**	**30-36**	**37-43**	**44-50**	**51-57**
Visit Number	**1**	**2**	**3**	**4, 5**	**6, 7, 8**	**9, 10, 11**	**12**	**13**	**14**	**15**	**16**
Vital signs[j]											
Blood pressure and pulse[k] (supine & standing)	X	X	X	X	X	X	X	X	X	X	X
Body temperature (°C)	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[l]	X		X	X	X	X	X				X
Alcohol/Urine drug screen	X										
HIV/HBsAg/HCV screening	X										
Serum β-hCG pregnancy test[m]	X	X				X					X
Randomization			X								

Table 3 Study assessments

Study Procedures	Screening[a]	Single-blind IV Placebo Run-in Infusion[b,c]	3-Week Double-blind Treatment Period				5-Week Follow-up (Maintenance) Period				
			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Final Visit OR Early DC[e] Week 8
			Randomization[d]								
Visit Day[f]	**-30 to -1**	**-3 to -1[g]**	**1**	**2-8**	**9-15**	**16-22**	**23-29**	**30-36**	**37-43**	**44-50**	**51-57**
Visit Number	**1**	**2**	**3**	**4, 5**	**6, 7, 8**	**9, 10, 11**	**12**	**13**	**14**	**15**	**16**
Study drug administration per randomization schedule[d]			X	X	X	X					
PK blood sampling[n] (AZD6765 levels)			X	X	X	X					
Optional genetic blood sampling[o]			X								
Blood sample for optional biomarker (inflammatory cytokine) analysis			X			X					
Urine sample for optional renal biomarker analysis			X				X				
Rating scales[f, r]											
QIDS-SR-16[p]	X	X	X	X	X	X	X	X	X	X	X
HAM-D	X	X	X		X	X	X	X	X	X	X

Table 3 Study assessments

Study Procedures	Screening[a]	Single-blind IV Placebo Run-in Infusion[b,c]	3-Week Double-blind Treatment Period				5-Week Follow-up (Maintenance) Period				
			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Final Visit OR Early DC[e] Week 8
			Randomization[d]								
Visit Day[f]	**-30 to -1**	**-3 to -1[g]**	**1**	**2-8**	**9-15**	**16-22**	**23-29**	**30-36**	**37-43**	**44-50**	**51-57**
Visit Number	**1**	**2**	**3**	**4, 5**	**6, 7, 8**	**9, 10, 11**	**12**	**13**	**14**	**15**	**16**
MADRS[q]	X	X	X	X	X	X	X	X	X	X	X
BSS[c]	X	X	X		X	X	X	X	X	X	X
C-SSRS[c]	X	X	X		X	X	X	X	X	X	X
HAM-A	X	X	X	X	X	X	X	X	X	X	X
VAS		X	X								
CADSS (dissociation)	X	X	X	X	X	X					
Q-LES-Q-SF (quality of life)	X		X		X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X
MINI (including atypical & melancholic depression)[s]	X										

Table 3 Study assessments

Study Procedures	Screening[a]	Single-blind IV Placebo Run-in Infusion[b,c]	3-Week Double-blind Treatment Period				5-Week Follow-up (Maintenance) Period				
			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Final Visit OR Early DC[e] Week 8
			Randomization[d]								
Visit Day[f]	**-30 to -1**	**-3 to -1[g]**	**1**	**2-8**	**9-15**	**16-22**	**23-29**	**30-36**	**37-43**	**44-50**	**51-57**
Visit Number	**1**	**2**	**3**	**4, 5**	**6, 7, 8**	**9, 10, 11**	**12**	**13**	**14**	**15**	**16**
Antidepressant Treatment History Form (ATHF) score card	X										
Assess AEs[t]	X	X	X[u]	X	X	X	X	X	X	X	X
Assess permitted & prohibited concomitant medications	X	X	X	X	X	X	X	X	X	X	X

a Screening period will take place up to 30 days prior to Day 1 (Visit 3) of the treatment period.
b Following administration of the IV placebo saline run-in infusion (Visit 2) and after Infusion 1 (Visit 3) and Infusion 2 (Visit 4) of Week 1, subjects will remain on site for at least 4 h after start of infusion. Starting from Infusion 3 (Visit 5) of Week 1, subjects will remain on site for at least 2 h after start of infusion.
c BSS and C-SSRS will be performed weekly. Note: BSS and C-SSRS will be done before the placebo run-in saline infusion and before randomization.
d Randomization will take place on Day 1 (Visit 3) of the treatment period.
e DC is discontinuation. Subjects who discontinue early from the study will be asked to complete all the required study procedures and assessments from Visit 16 (Week 8).
f See Table 4, Table 5, Table 6, Table 10 and Table 11 for specific timing to perform all procedures, including PK sampling. Rating scales must be performed as specified in Table 4, Table 5, and Table 6 for the specific timing of each assessment.
g Visit 2 (Day -3 to Day -1) evaluations will be done prior to the IV placebo saline run-in infusion.

h Height will be measured once during the screening period; however, weight will be measured at every clinic visit during the 3-week treatment period and during the 5-week post-treatment follow up period.

i ECG will be performed at screening, prior to start of infusion (at randomization, Day 1, T_0 of Visit 3, Week 1), 1 hour after the infusion (T_1, Infusion 1, Visit 3 of Week 1), at the end of Week 1 (Visit 5), end of Week 2 (Visit 8), end of the 3-week treatment period (Visit 11), and at Week 8 (Visit 16).

j Vital signs will be measured as shown in Table 4, Table 5 and Table 6.

k If possible, the same arm should be used for each blood pressure evaluation.

l Clinical laboratory assessments:

Hematology: White blood cell (WBC) with differential, red blood cell (RBC), hemoglobin (Hgb), hematocrit, platelet count. Hematology will be done at screening, randomization (Day 1, Visit 3, Week 1), at Weeks 3 and 8. Hematology will not be done at Visit 6 (Week 2).

Clinical chemistry: Bicarbonate, sodium, potassium, chloride, BUN, creatinine, glucose, calcium, uric acid, cholesterol, triglycerides, total bilirubin (direct and indirect), protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), lithium, Troponin I and Troponin T. Clinical chemistry will be done at screening, randomization (Day 1, Visit 3, Week 1), end of Week 1 (Visit 5), Week 2 (Visit 6), Week 3 (Visit 9), Week 4 (Visit 12), and end of Week 8 (Visit 16). Lithium levels will be assessed at screening, prior to infusion at Weeks 1 (Day 1), 2 and 3, and also at Weeks 4, 6 and 8.

Urinalysis: pH, Hgb, protein, glucose, bilirubin, ketones. If the urine sample is positive for protein or blood, a microscopic examination of the urine sediment will be performed. Urine electrolytes (Na^+, K^+, Cl^-, Ca^{2+}) will be determined as well. Urinalysis will be done at screening, randomization (Day 1, Visit 3, Week 1), end of Week 1 (Visit 5), Week 2 (Visit 6), Week 3 (Visit 9), Week 4 (Visit 12), and end of Week 8 (Visit 16).

Thyroid function tests (T_3, T_4, thyroid stimulating hormone [TSH]**):** Thyroid function tests will only be done at screening and at Week 3 prior to start of infusion. Baseline levels will be obtained at screening to exclude for thyroid disease.

m If the screening and randomization visits are <7 days apart, a repeat pregnancy test is not required before the IV placebo saline run-in infusion.

n The actual sample collection date and time for PK will be recorded in the source documents and eCRF.

o Blood sample for pharmacogenetics will only be collected once during the study, preferably on Day 1 of the treatment period.

p QIDS-SR-16 will be completed daily (including the infusion visits and when subject is at home) during Week 1 and then weekly thereafter. QIDS-SR-16 will be dispensed at Visit 3 (to be returned at Visit 4), Visit 4 (to be returned at Visit 5) and Visit 5 (to be returned at Visit 6).

q For the MADRS evaluation, Day 1, pre-infusion will be considered baseline.

r Subjects will be assessed before randomization and will only be randomized if the HAM-D score is still ≥20, CGI-S score ≥4 and QIDS-SR-16 score ≥16.

s The MINI will be performed at screening only and will include assessments of atypical and melancholic depression.

t AEs will be collected from informed consent signing through the follow-up period.

u Subjects must report by telephone any AEs that occur the day after the first infusion (Infusion 1 after randomization [Week 1]).

Table 4 Placebo run-in period and Week 1: Timing of procedures

	Placebo run-in			Week 1								
Study Visit	**Visit 2**			**Visit 3**			**Visit 4**			**Visit 5**		
Study Day	**Day -3 to Day -1[a]**			**Day 1 Randomization[b, c]**			**Day 4**			**Day 6 or 7**		
Infusion	**Saline infusion**			**Infusion 1**			**Infusion 2**			**Infusion 3**		
Time	T_0	T_1	T_4	T_0	T_1	T_4	T_0	T_1	T_4	T_0	T_1	T_2
Procedures[d]												
QIDS-SR-16[g]	√			√			√			√		
HAM-D	√			√								
MADRS	√		√	√		√	√		√			√
BSS[h]	√			√								
C-SSRS[h]	√			√								
HAM-A	√			√								√
VAS[i]			√	√	√	√						
CADSS	√	√	√	√	√	√		√	√			
Q-LES-Q-SF				√								
CGI-S	√			√			√					√
CGI-I						√	√					√
Vital signs[e]	√	√	√	√	√	√	√	√	√	√	√	√
ECG[f]				√	√						√	
Lab samples	√			√			√			√		

a Subjects with ≥50% reduction in MADRS total score after the IV placebo saline run-in infusion will be classified as placebo responders and will not be randomized to the treatment period of the study.

b Subjects will be assessed before randomization. Day 1 (Visit 3) pre-infusion depression scales will serve as the baseline. For Infusions 1 and 2 (Week 1), subjects will remain on site for at least 4 h after start of infusion (T_4). For Infusion 3 (Week 1), subjects will remain on site for at least 2 h after start of infusion (T_2).

c Randomization will occur 2-4 days after the IV placebo saline run-in infusion. Week 1 (Days 1-7) starts with randomization of study drug on Day 1 of the treatment period.

d Procedures will be completed in the order listed in this table.

e Vital signs will be measured at time 0 (T_0 before infusion), 1 h after start of infusion (T_1), and at least 2 h (T_2) or 4 h after start of infusion (T_4).

f ECG will be performed prior to start of infusion (T_0 of Visit 3, Day 1) and will be considered the baseline value. ECG will also be performed to capture any ECG changes at the maximum plasma AZD6765 concentration (C_{max}) at 1 h after start of infusion (T_1).

g QIDS-SR-16 will be the first procedure performed in the morning before start of infusion and will be completed daily by the subject for the first 7 days (Week 1) and then weekly thereafter.

h BSS and C-SSRS will be performed once weekly. BSS and C-SSRS will be done before the IV placebo saline run-in infusion (Visit 2) and before randomization (Visit 3).

i The specific VAS scale to be used is the Bond-Lader VAS.

Table 5 Weeks 2 and 3: Timing of procedures

Infusion	**Infusion 1**			**Infusion 2**			**Infusion 3**		
Time[a]	**T_0**	**T_1**	**T_2**	**T_0**	**T_1**	**T_2**	**T_0**	**T_1**	**T_2**
Procedures[b]									
QIDS-SR-16									√
HAM-D									√
MADRS[d]									√
BSS									√
C-SSRS									√
HAM-A									√
CADSS									√
Q-LES-Q-SF									√
CGI-S									√
CGI-I									√
Vital signs	√	√		√	√		√	√	
ECG[c]								√	
Lab samples	√			√			√		

a Subjects will receive 3 infusions/week for Weeks 2 and 3. Subjects will remain on site for at least 2 h after start of infusion (T_2). T_0 is time before start of infusion, T_1 is 1 h after start of infusion, and T_2 is 2 h after start of infusion.

b Procedures will be completed in the order listed in this table.

c ECG will be performed to capture any ECG changes at the maximum plasma AZD6765 concentration (C_{max}) at 1 h after start of infusion (T_1) at the end of Week 2 (Visit 8) and Week 3 (Visit 11).

d MADRS will be done within 2-4 h of Infusion 3 at Weeks 2 and 3.

Note: Week 2: Infusions 1, 2 and 3 (Visits 6, 7 and 8, respectively); Week 3: Infusions 1, 2 and 3 (Visits 9, 10 and 11, respectively).

Table 6 Weeks 4, 5, 6, 7 and 8: Follow up period and timing of procedures

Study Week	**Week 4[a]**	**Week 5[a]**	**Week 6[a]**	**Week 7[a]**	**Week 8[a]**
Visit Number	**12**	**13**	**14**	**15**	**16**
Procedures					
QIDS-SR-16	√	√	√	√	√
HAM-D	√	√	√	√	√
MADRS	√	√	√	√	√
BSS	√	√	√	√	√
C-SSRS	√	√	√	√	√
HAM-A	√	√	√	√	√
Q-LES-Q-SF	√	√	√	√	√
CGI-S	√	√	√	√	√
CGI-I	√	√	√	√	√
Vital signs[a]	√	√	√	√	√
ECG					√
Lab samples	√				√

a Vital signs will be performed after the rating scales. Rating scales will be performed on scheduled visit days during the 5-week post treatment follow-up period in the order presented in this table.

Figure 1 Dosing flow chart

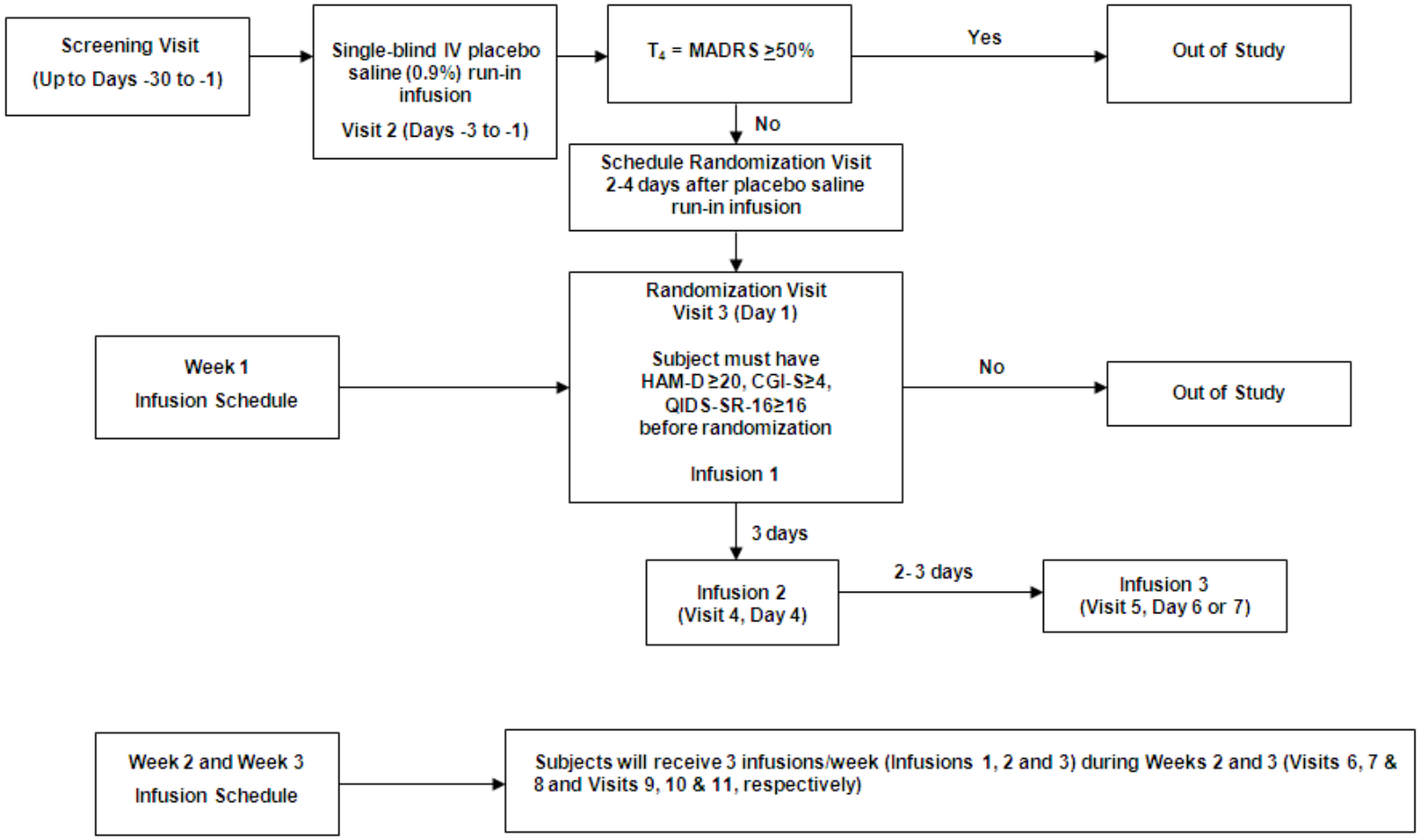
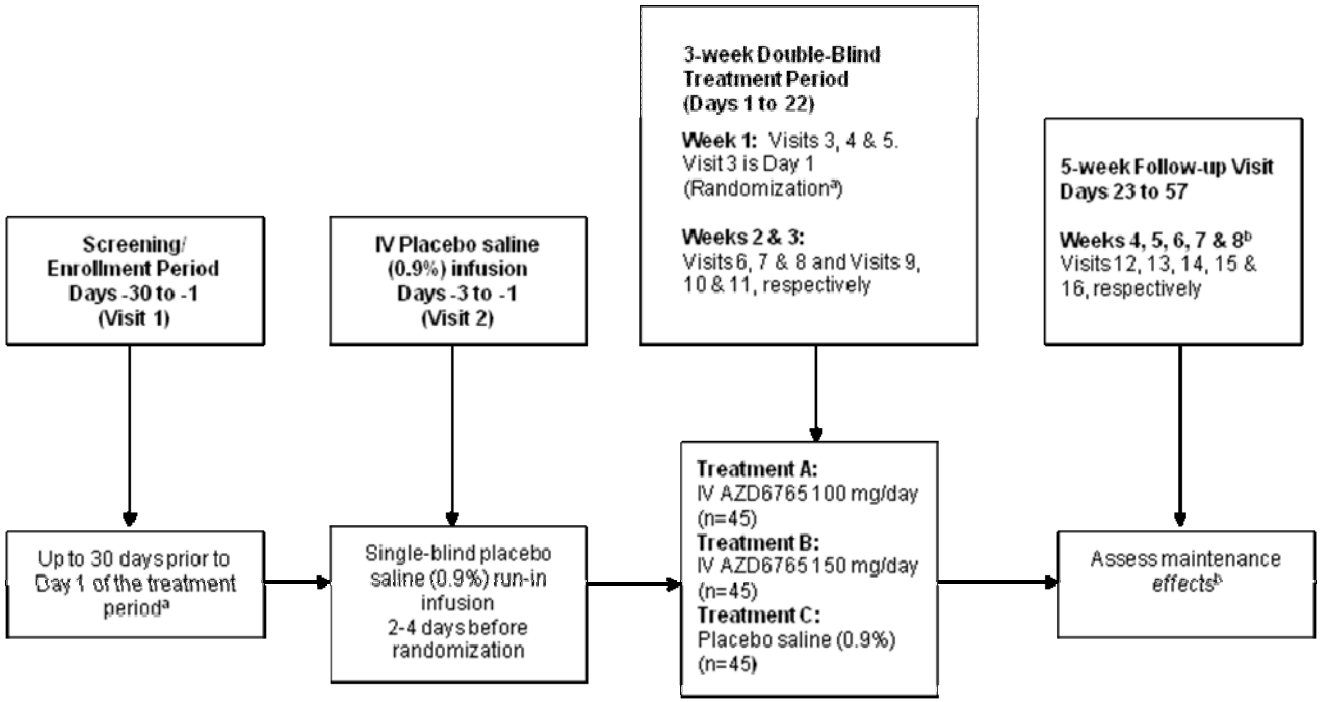


Figure 2 Study flow chart



a Approximately 150 subjects will be randomized to obtain 135-140 evaluable subjects. Subjects will be randomized to either IV AZD6765 100 or 150 mg/infusion or placebo saline (0.9%) based on the randomization schedule. Randomization will take place on Day 1 (Visit 3) of the double-blind treatment period.

b Subjects will be scheduled for a 7-, 14-, 21-, 28- and 35-day follow-up visit from last dosing (Visits 12, 13, 14, 15 & 16) to assess maintenance effects during the 5-week follow-up post-treatment period.

4.2 Rationale for study design, doses and control groups

The primary objective of the study is to determine whether a superior antidepressant effect can be achieved with multiple infusions of AZD6765 100 or 150 mg versus placebo when given adjunctively with selected FDA-approved antidepressants (including SSRIs, SNRIs, bupropion or mirtazapine) for subjects suffering from MDD with a history of poor response to other antidepressant therapies.

The results from this study will build upon existing clinical data observed with the use of NMDA receptor antagonists. A growing body of preclinical research suggests that brain glutamate systems may be involved in the pathophysiology of major depression and the mechanism of action of antidepressants. A double-blind, placebo-controlled trial to assess the treatment effects of a single dose of ketamine, an NMDA receptor agonist was associated with decreases in depressive symptoms when compared with placebo (Berman et al 2000). However, studies with memantine in MDD have been negative.

The dose and study design chosen for this study are based on results of information gained from previous AstraZeneca clinical studies, the Phase IIa study as well as toxicological, pharmacological and PK studies in different animal species and in vitro human data.

An enrollment period of up to 30 days is required to allow the investigator to review the results of laboratory assessments which would confound the results of the study and also to ensure the safety of subjects.

Please see the IB for further information.

5. SUBJECT SELECTION CRITERIA

The subject population should be selected without bias.

Investigator(s) must keep a record of subjects who entered pre-trial screening but were never enrolled, eg, subject screening log. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

For inclusion in the study, subjects must fulfill the following criteria:

1. Provision of informed consent before initiation of any study-related procedures.

2. Male and female subjects aged 18 to 65 years, inclusive. All females must have a negative serum pregnancy test. Women of child-bearing potential must use (confirmed by the investigator) a highly effective form of birth control. The highly effective form of birth control includes but is not limited to: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion,

IUD/IUS (copper coils), Depo-Provera injections, low dose combined oral contraceptive only if used in TriCycle regime, and Evra Patch or Nuvaring use in TriCycle regime. Women should be on a stable method of birth control for a minimum of 3 months prior to study entry.

3. Documented clinical diagnosis meeting criteria from the DSM-IV-TR confirmed by the MINI:

   – 296.2x Major Depressive Disorder, Single Episode or 296.3x Major Depressive Disorder

   – and with a HAM-D score ≥20, CGI-S ≥4 and QIDS-SR-16 ≥16 at screening, Visit 2, and Visit 3/randomization (Subjects who were considered screen failures under the entrance criteria outlined in the original protocol, but who would have qualified under these current criteria, may be considered for re-screening.)

   – HAM-D item 3 ≤2 (some suicidal ideation but no plans)

4. Currently taking one FDA-approved antidepressant (per US label) for at least 6 weeks (on day of IV placebo saline run-in infusion):

   – The daily dose must be within label.

   – The subject must be on minimally effective dose (per label) for at least 4 weeks (on day of IV placebo saline run-in infusion).

   A second drug is allowed if prescribed for depression, for a duration of at least 6 weeks. There must not be any change in the dose of this drug in the last 4 weeks. The dose of this drug must be appropriate in the judgement of the investigator. The second drug for depression must be one of the following (Table 8):

   – FDA-approved antidepressant (except the excluded drugs such as monoamine oxidase inhibitors [MAOIs], tricyclic antidepressants [TCAs], antipsychotics). Acceptable combination of 2 FDA-approved antidepressants (SSRI/SNRI+bupropion, SSRI/SNRI+mirtazapine)

   – Buspirone

   – Triiodothyronine

   – Lithium

5. History of poor response to 1 or more antidepressants (in addition to the antidepressant subject is taking at enrollment) after exposure at adequate doses or maximum tolerated doses for ≥4 weeks.

6. Be able to understand and comply with the requirements of the study, as judged by the investigator.

7. Outpatient status at screening and enrollment (randomization) visits.

For inclusion in the optional exploratory genetic sample collection, subjects must fulfill the following criterion:

1. Provision of informed consent for genetic research.

If a subject declines to participate in the optional genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in this CSP, so long as they consent.

5.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. Subjects with a lifetime history of DSM-IV Axis I disorder other than MDD with the exception of generalized anxiety disorder (GAD), co-morbid panic disorder and simple phobias. Subjects with co-morbid GAD are eligible to be enrolled provided that MDD is the primary diagnosis.

2. Subjects with a DSM-IV Axis II disorder which has a major impact on the subject's current psychiatric status.

3. Subjects with a DSM-IV Axis II borderline or antisocial personality disorder.

4. Lifetime history of schizophrenia, bipolar, psychosis or psychotic depression.

5. Length of current episode of depression is ≤12 weeks prior to enrollment.

6. Length of current episode of depression exceeds ≥5 years.

7. Use of mood stabilizers, other antipsychotic drugs or TCAs within 7 days of Day 1, or MAOIs within 14 days of Day 1 of the treatment period (Table 8).

8. Lifetime history of failure to ECT therapy.

9. Lifetime history of vagal nerve stimulation and deep brain stimulation.

10. Lifetime use of depot antipsychotics.

11. History of substance or alcohol abuse in the past 6 months or dependence within 1 year (except for caffeine or nicotine dependence), as defined in DSM-IV criteria. Subjects with a positive urine toxicology screen (UTS) for methamphetamines benzodiazepines, cocaine and/or metabolites, amphetamines, tetrahydrocannibinol (THC), opiates, PCP, and barbiturates will be excluded except for subjects testing

positive for prescribed medications. Subjects can be re-tested only if the initial THC result is positive, but should be excluded if the result is still positive for THC at the second test. Subjects with positive UTS for a drug(s) legally available by prescription must provide evidence of prescription for the drug(s).

12. Use of drugs that induce or inhibit the hepatic metabolizing CYP3A4 enzymes within 2 weeks prior to randomization:

    - Inducers: carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort.

    - Inhibitors: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir.

    Subjects will also be excluded if they need to use these drugs during the study.

13. Pregnancy or lactation.

14. Evidence of clinically relevant disease, eg, renal or hepatic impairment, symptomatic or significant coronary artery disease, cerebrovascular disease, viral Hepatitis B or C, syphilis, or acquired immunodeficiency syndrome (AIDS). Hypothyroidism is permitted if corrected and the subject is on a stable regimen for a minimum of 6 months.

15. QT interval corrected by the Fridericia formula (QTcF) on Visit 1/screening and Visit 3 pre-infusion ECG of ≥450 (msec).

16. Systolic blood pressure (standing and supine) <95 mmHg or >140 mmHg at Visit 1/screening, Visit 2 and Visit 3/prior to randomization.

17. Heart rate <50 or >100 beats per minute at Visit 1/screening, Visit 2 and Visit 3/prior to randomization.

18. Subjects who have a thyroid stimulating hormone (TSH) concentration more than 10% above the upper limit of normal (ULN) of the range of the laboratory used for the TSH sample analysis at screening whether or not the subject is being treated for hypothyroidism.

19. A clinical finding that is unstable (eg, hypertension, poorly controlled diabetes, unstable angina) or that, in the opinion of the investigator, would be negatively affected by the study medication or that would affect the study medication.

20. Conditions that could affect metabolism of study medication (eg, liver disease).

21. A current diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years.

22. Current or past diagnosis of stroke or transient ischemic attack.

23. History of head trauma, including closed head injury in which loss of consciousness occurred that could interfere with the conduct of the study or the interpretation of results in the judgement of the investigator.

24. History of epilepsy or history of epilepsy in first degree relative.

25. Receipt of ECT within 90 days prior to randomization.

26. Subjects who, in the investigator's judgement, pose a current serious suicidal or homicidal risk, have a HAM-D item 3 score of ≥3 or have made a suicide attempt within the past 6 months.

27. Clinically significant deviation from the reference range in clinical laboratory test results as judged by the investigator or sponsor.

28. ECG results considered being clinically significant as determined by the investigator or an experienced cardiologist interpreting the ECG.

29. Known history of intolerance or hypersensitivity to any medication required by this protocol (or 3 or more classes of pharmaceuticals) or current manifestation of any allergic disorder (other than seasonal allergies) as judged by the investigator.

30. Involvement in the planning and conduct of the study (applies to all AstraZeneca, investigational site or third party vendor staff).

31. Participation in another clinical study or compassionate use program within 60 days of randomization.

For the subject to be qualified for the optional genetic research, the subject must not:

1. Have had previous bone marrow transplant.

2. Received whole blood transfusion within 120 days prior to the date of genetic sample collection.

If either of these two exclusion criteria is present, the subject cannot participate in the optional genetic research.

5.3 Procedures for handling incorrectly included subjects

Subjects who do not meet the inclusion/exclusion criteria for the study should not, under any circumstances, be enrolled–there can be no exceptions to this rule.

Procedures included in the protocol for the discontinuation of incorrectly enrolled subjects must be followed. These procedures must take into consideration ethical and safety factors and how these subjects will be treated in the analyses.

When an incorrectly enrolled subject is identified, the AstraZeneca Study Team Physician or representative and the investigator will participate in a discussion to determine whether or not to continue the subject in the study. The AstraZeneca Study Team Physician or representative will ensure all such decisions are appropriately documented.

5.4 Withdrawal of subjects

5.4.1 Criteria for discontinuation from the study

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject are:

- Voluntary discontinuation by the subject who is at any time free to discontinue the subject's participation in the study, without prejudice to further treatment.
- Severe non-compliance to protocol.
- Incorrectly enrolled subjects.
- Subject is lost to follow-up.
- The subject has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca or representative, or the subject.
- Safety reasons as judged by the investigator, particularly if subject becomes pregnant.
- The condition under investigation worsened.
- The subject is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 6.1.
- The subject is unable to tolerate the assigned dose of study medication.
- The subject has a clinically significant deviation from the reference range in Troponin I, T, serum or urine potassium levels; or any other finding suggestive of clinically significant deterioration in cardiac or renal function as judged by the investigator or sponsor.

Specific reasons for discontinuing a subject from the optional genetic research when genetics is a secondary objective of the study are:

- Withdrawal of consent for genetic research. A subject may withdraw from this optional genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the subject will not prejudice further treatment.

5.4.2 Procedures for discontinuation of a subject from the study

Subjects who discontinue from the study should always be asked about the reasons for discontinuation and the presence of any AEs. If possible, the subject will be seen and assessed by an investigator during the study discontinuation visit. AEs will be followed up (see Sections 7.3.3 and 7.3.4).

If a subject discontinues from the study before completion, all assessments and procedures required at Week 8/Visit 16 in Table 3 and Table 5 will be conducted whenever possible. Every effort should be made to follow-up with subjects who discontinue from the study prior to Week 8.

The investigator must notify AstraZeneca or representative of any hospitalization. Hospitalization is an SAE and should be reported as described in Sections 7.3.2 and 7.3.4. If a subject is hospitalized, the subject will be discontinued from the study and all assessments and procedures required at Week 8/Visit 16 in Table 3 and Table 5 will be conducted.

Subjects who discontinue from the study will not be replaced.

5.4.2.1 Procedures for discontinuation from optional genetic aspects of the study

Subjects who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this linked genetic research. It must be established whether the subject:

- Agrees to the optional genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.

- Withdraws consent for the sample to be kept for the optional genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The PI is responsible for providing written notification to AstraZeneca or representative of any subject who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca or representative will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

In the case of any subject withdrawing consent for the genetic research, the PI must notify the monitor using the "Withdrawal of Consent Form" (to be supplied). Requests for sample

destruction should be forwarded by the monitor to the head of Clinical Genotyping Group (CGG) along with copies of the relevant documentation detailing study code and subject enrollment code. AstraZeneca or representative and the PI will receive written confirmation from the CGG that the genetic sample has been destroyed.

6. STUDY CONDUCT

6.1 Restrictions during the study

Use of concomitant medications is restricted as detailed in Section 6.5, Table 8.

6.2 Subject enrollment and randomization

The PI will:

1. Obtain signed informed consent from the subject before any study specific procedures are performed.

2. Assign potential subject a unique enrollment number, beginning with "E#" (for example, 1100101).

3. Determine subject eligibility. See Sections 5.1 and 5.2.

4. Assign an eligible subject unique randomization code (subject number), beginning with "#".

As subjects are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number (4-digits) and the subject number within that particular center (3-digits) (for example, E-1100-101).

6.2.1 Procedures for randomization

Subjects with or without a diagnosis of co-morbid GAD (as defined by the MINI) are eligible for enrollment. Because co-morbid GAD is potentially a prognostic factor for efficacy, the randomization will be stratified by co-morbid GAD. Up to 30% of randomized subjects can be diagnosed with co-morbid GAD.

Eligible subjects will be randomized in balanced blocks to receive IV AZD6765 100 or 150 mg, or placebo saline infusion in a 1:1:1 ratio. The actual treatment given to individual subjects will be determined by a randomization scheme that has been loaded into the IVRS database. If a subject is discontinued from the study, his/her randomization or enrollment number will not be reused, and the subject will not be allowed to re-enter the study. Subjects who discontinue from the study will not be replaced.

If a randomization number is allocated incorrectly, no attempt should be made to remedy the error once study material has been dispensed. The subject will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the

error is discovered. Subsequent subjects will continue using the first unallocated randomization number in the original numbering sequence.

6.3 Blinding and procedures for unblinding the study

6.3.1 Methods for ensuring blinding

The investigator, subject and study staff will be blinded. The pharmacist will be unblinded. For the single-blind placebo saline infusion prior to randomization, only the subject will be blinded.

Both AZD6765 and 0.9% placebo saline will be prepared by the pharmacist in advance and provided to the study staff on the morning of the dosing. Packaging and labeling of the investigational products will be performed in a way to ensure blinding throughout the study.

No member of the study team in AstraZeneca, at investigational centers or any contract research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Products (IPS) and Patient Safety.

The randomization schedule for blinding of randomized treatment will be maintained by AstraZeneca and will not be disclosed until after database lock.

6.3.2 Methods for unblinding the study

Individual treatment codes from the IVRS, indicating the treatment randomization for each randomized subject, will be available to the investigator or pharmacist at the study center. Each center will be provided an IVRS user manual which describes this.

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. If the treatment code is broken, then the investigator must document and report to AstraZeneca or representative immediately.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

6.4 Treatments

AstraZeneca will supply AZD6765 in bulk supply as a 15 mg/mL (free base concentrate), in a glass vial with a bromobutyl rubber stopper and aluminum cap (Table 7). Each vial will contain a nominal volume of 10.7 mL hydrochloride concentrate. The pharmacist for the investigational site will be responsible for diluting the concentrate to obtain the desired dosing.

Isotonic sterile saline (to be used as the placebo as well as a diluent for AZD6765), will be supplied by the site.

Instructions will be provided to the site pharmacist regarding dose preparation and administration.

AZD6765 or placebo should be infused using a syringe pump.

Table 7 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer	Formulation
AZD6765	15 mg/mL for IV infusion	AstraZeneca	6765/375/A/251, 2729-x-1 or H2101-01-01

The batch numbers will be recorded in the Study Master File (SMF) and identified in the Clinical Study Report (CSR).

6.4.1 Doses and treatment regimens

Subject will be randomized to receive either Treatment A (AZD6765 100 mg), B (AZD6765 150 mg) or C (placebo saline) by IV infusion in a 1:1:1 ratio. Subjects should be semi-reclined during the IV infusion.

- **Treatment A**: Subjects will receive AZD6765 100 mg (total dose) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min (1.67 mg/min) over 60 minutes.
- **Treatment B**: Subjects will receive AZD6765 150 mg (total dose) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min (2.50 mg/min) over 60 minutes.
- **Treatment C**: Subjects will receive placebo (0.9% saline) intravenously once per dosing day at the study center. The infusion will be a final volume of 30 mL given at an infusion rate of 0.5 mL/min over 60 minutes.

Subjects will receive multiple infusions of AZD6765 (100 or 150 mg) or placebo during the treatment period.

6.4.2 Labeling

AstraZeneca will provide the investigational product to the study sites. Labeling of the investigational products will be performed in accordance with Good Manufacturing Practice. The labels will be produced in the local language and in accordance with local regulations for each participating country.

All clinical trial material will be packaged and labeled by AstraZeneca. The clinical trial material will be clearly marked according to national requirements regarding use for clinical trial investigation only and will also be labeled with the drug name, study reference number and storage conditions. It is the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study. The study site dispensary staff will dilute and dispense the investigational product according to the randomization scheme. Individual dosing containers will be labeled with the study number, subject number and study day.

6.4.3 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The investigational product label on the treatment vials and the IB specifies the appropriate storage and shipment.

6.5 Concomitant and post-study treatments

6.5.1 Concomitant medications

Medications prohibited, permitted with restrictions, or permitted during the treatment period are specified in Table 8. Subjects are allowed to be on up to 2 antidepressants during the study as permitted in the protocol.

A second drug is allowed if prescribed for depression, for a duration of at least 6 weeks. There must not be any change in the dose of this drug in the last 4 weeks. The dose of the adjunctive antidepressants will not be changed after randomization. The dose of this drug must be appropriate in the judgement of the investigator. The second drug for depression must be one of the following (Table 8):

- FDA-approved antidepressant (except the excluded drugs such as MAOIs, TCAs and antipsychotics). Acceptable combination of 2 FDA-approved antidepressants (SSRI/SNRI+bupropion, SSRI/SNRI+mirtazapine)

- Buspirone, Triiodothyronine, Lithium

Subjects who have been on long-term diazepam and/or benzodiazepines will be allowed to enroll in the study. Benzodiazepines are permitted only if the subject has been taking a stable dose every day since 30 days prior to randomization. Hypnotics are allowed only if ongoing for 30 days and taken daily.

Any medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be recorded in the appropriate sections of the source documentation and electronic case report form (eCRF). The subject must be instructed to report all medications given to the subject, in addition to those prescribed by the investigator.

Lithium plasma concentration

In subjects receiving chronic lithium therapy, any routine assays of lithium plasma levels should be captured in the eCRF. In addition to plasma lithium concentration levels, sampling dates, dosing history prior to the sampling should be recorded (ie, date and approximate time of drug intake for the 2 prior doses, captured as accurately as possible, based on the subject's memory/or diary notes). Lithium dosing may be reduced after screening at the investigator's discretion only if serum lithium values are above the therapeutic range. Lithium dosing should otherwise remain unchanged.

Lifetime use of drugs for depression (collected on the ATHF score card) and pre-study medications for all other concomitant medication use from up to 60 days prior to randomization will be recorded in the appropriate sections of the source documentation and eCRF.

Table 8 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
Prohibited	MAOIs	
	Vagal nerve stimulation, ECT, deep brain stimulation	
	Psychostimulants	
	Lamotrigine	
	Valproate	
	Nefazodone	
	Divalproex	
	Antipsychotics (except study medication) and TCAs	
	CYP3A4 inducers (potent)	eg, phenytoin, carbamazepine, barbiturates, rifampin, rifabutin, glucocorticoids, thiorizadine and St. John's Wort
	CYP3A4 inhibitors (potent)	eg, ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir

Table 8 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
Permitted with restrictions	Benzodiazepines (stable dose)	Benzodiazepines are permitted only if the subject has been taking a stable dose every day since 30 days prior to randomization. A stable dose is defined as no change in dose 30 days prior to randomization. The dosage in the past 30 days should be no more than lorazepam maximum dose 2 mg/day or equivalent, which includes the following: • Alprazolam 1.0 mg/day • Estazolam 4.0 mg/day • Oxazepam 30 mg/day • Temazepam 60 mg/day • Clonazepam 1.0 mg/day • Diazepam 10 mg/day It should be noted this is not an exhaustive list.

Table 8 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
	Hypnotics	Hypnotics are allowed only if ongoing for 30 days and taken daily. One of the following medications can be used for insomnia at the restricted and maximum allowable dose of: • up to 150 mg/day trazodone • 10 mg Zolpidem tartrate • 12.5 mg Ambien CR • 3 mg eszopiclone • 1 gram chloral hydrate • 20 mg zaleplon, or • 8 mg ramelteon (in the evening) up to the specified dosage per night if treatment has been ongoing on a regular basis since 30 days prior to enrollment.
Permitted	SSRIs[a]	Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine
	SNRIs[a]	Venlafaxine, desvenlafaxine, duloxetine
	Triiodothyronine[a]	
	Lithium[a]	
	Buspirone[a]	
	Mirtazapine[a]	
	Bupropion[a]	
	Combination antidepressants[a]	eg, mirtazapine + venlafaxine. Combination of 2 antidepressants will be allowed (or 2 drugs that in the judgement of the investigator are used for treatment of depression)

Table 8 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
	Stable psychotherapy	
	nonpsychoactive medications, including over-the-counter counter medications, taken by the subjects before entry into the study	
	medications required to treat illnesses or complaints that occur during the study	may be used at the discretion of the investigator
	medications which are considered necessary for the subject's safety and well-being	may be given at the discretion of the investigator. Includes medication and devices for contraception.

a These concomitant medications are allowed if prescribed within label.

6.6 Treatment compliance

Treatment compliance will be assured by supervised administration of the study drugs by the investigator or his/her designee.

6.6.1 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the investigator's/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca or representative are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Study treatments are only dispensed to study subjects in accordance with the protocol.

The pharmacist will prepare AZD6765 infusions unblinded and will account for all study medications dispensed.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded in the subject's source documentation and in the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed by the pharmacist, and copies retained in the investigator site file.

7. COLLECTION OF STUDY VARIABLES

7.1 Recording of data

The investigator will ensure that all data collected in the study are provided to AstraZeneca or representative. The investigator will ensure the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided.

The PI will provide AstraZeneca or representative with all data produced during the study from the scheduled study assessments. The PI will ensure the accuracy, completeness, legibility, and timeliness of the data reported to AstraZeneca or representative in the eCRF and in all required reports.

Data will be entered in the eDC system at the study site. Trained study personnel will be responsible for entering data specified in the protocol into the eDC system and according to the eCRF instructions. When data have been entered reviewed, edited and Source Data Verification (SDV) performed by AstraZeneca or representative, the data will be frozen to prevent further editing. The PI will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

7.2 Screening and demography procedures

The following study measurements will be obtained. The timing of these measurements is detailed in the Table 3 (Study Assessments). The following "priority order" will be in effect when more than one assessment is required at a particular timepoint:

- Depression scales
- Suicidality
- Dissociative testing
- QoL
- Vital signs.
- Digital ECGs.
- Clinical laboratory assessments and PK blood sampling (Note: PK sampling must be performed at the precise protocol scheduled time and this time will be recorded in the eCRF.)

The following data will be collected at the screening visit (Visit 1) prior to the treatment period/randomization (Visit 3):

- Informed consent will be collected prior to any study-related procedure being performed.
- Medical, medication, and surgical history.
- Inclusion/exclusion criteria (will be reviewed at screening and at admission to the treatment period).
- Demography (date of birth, sex, and race).
- Vital signs (supine and standing BP and pulse [heart rate]) and oral body temperature (°C).
- Physical examination (including height and weight).

- Digital 12-lead ECG.
- Diagnosis of depression by use of the MINI (including assessments of atypical and melancholic depression) and severity of depression evaluated by HAM-D.
- Assessment of depression and suicidality by scales: QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, and CGI-S.
- Dissociative symptom test: CADSS.
- QoL: Q-LES-Q-SF.
- Review of concomitant medications for general use and use for depression. The ATHF card will be used for review of medications for depression.
- Laboratory assessments, including hematology, clinical chemistry (including lithium levels in subjects taking lithium, and Troponin I and T levels), urinalysis, serum β-hCG pregnancy test, and thyroid function tests.
- Blood sample for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) serology.
- Alcohol and urine drug screen.
- Assess AEs.
- Assess permitted and prohibited concomitant medications.

The data listed above will be recorded on specifically designed eCRFs.

Visit 1 may be conducted up to 30 days prior to Day 1 (Visit 3) of the treatment period/randomization.

7.2.1 Follow-up procedures

Subjects will continue on the antidepressants that they entered the study on (including SSRIs, SNRIs, bupropion or mirtazapine) for another 5 weeks.

Subjects will be scheduled for a 7-, 14-, 21-, 28- and 35-day follow-up visit (Visits 12, 13, 14, 15 and 16) from last dosing to assess maintenance effects.

At Weeks 4, 5, 6, and 7 (Visits 12, 13, 14 and 15), the following data will be collected:

- Vital signs (supine and standing BP and pulse rate) and oral body temperature (°C).
- Weight.

- Assessment of depression and suicidality by scales: QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, CGI-S and CGI-I.
- QoL: Q-LES-Q-SF.
- Assess AEs.
- Assess permitted and prohibited concomitant medications.
- At Week 4 (Visit 12), clinical chemistry assessments (including lithium levels in subjects taking lithium, and Troponin I and T levels) and urinalysis will be performed.
- At Week 4 (Visit 12), a urine sample will be collected for optional biomarker research from qualified subjects who have provided consent for optional exploratory biomarker analysis.
- At Week 6 (Visit 14), blood samples will be collected to assess only lithium levels in subjects taking lithium.

At Week 8 (Visit 16), the following data will be collected:

- Vital signs (supine and standing BP and pulse [heart rate]) and oral body temperature (°C).
- Digital 12-lead ECG.
- Physical examination, including measurement of weight.
- Laboratory assessments, including hematology, clinical chemistry (including lithium levels in subjects taking lithium, and Troponin I and T levels), urinalysis, and serum β-hCG pregnancy test.
- Assessment of depression and suicidality by scales: QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, CGI-S and CGI-I.
- QoL: Q-LES-Q-SF.
- Assess AEs.
- Assess permitted and prohibited concomitant medications.

The data listed above will be recorded on specifically designed eCRFs.

7.3 Safety

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The PI is responsible for ensuring this.

7.3.1 Definition of adverse events (AEs)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including the run-in period, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

7.3.2 Definitions of serious adverse events (SAEs)

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

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

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

Psychiatric hospitalization is at times required and is expected for MDD. If hospitalization is needed due to the exacerbation of, or for the stabilization of for MDD, it will be reported as an SAE. The psychiatric assessments will reflect the worsening of the subject's condition and the need for hospitalization. These hospitalizations will be reported in the eCRF. Further guidance on the reporting of deterioration of the subject's condition with respect to MDD is contained in the following Section 7.3.3.

7.3.3 Recording of AEs

All AEs that occur after consent has been signed, during the placebo saline run-in period, treatment period, or the 5-week follow-up post-treatment period, whether or not related to the study drug, must be recorded on the eCRF. Unsolicited AE reports occurring up to 1 week after the last dose of investigational product should be recorded together with concomitant medications in the appropriate sections of the eCRF.

Variables

The following variables will be recorded in the eCRF for each AE; description of the AE, the date when the AE started and stopped (duration of AE), maximum intensity, whether the AE is serious or not, causality rating (yes or no), action taken with regard to investigational product (eg, AE caused subject to discontinue study, etc) and outcome.

Intensities will be reported for each AE in the following categories:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The Investigator will assess the causal relationship (ie, the relationship to study treatment) between the investigational product and AEs, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Worsening symptoms of the primary study condition (ie, MDD) should not be recorded as an AE. However, if hospitalization results from worsening psychiatric symptoms, the hospitalization should be recorded as an SAE in the eCRF.

Study drug abuse is an SAE, even when there are no symptoms or additional AEs, and should be reported according to the guidelines in Section 7.3.4. Misuse of study drug is an AE but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose of investigational product occur, it must be reported in accordance with the procedures described in Section 1.2, Overdose. All overdoses, with or without associated symptoms, should be reported as AEs.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of study drug, should be reported as AEs (serious or nonserious). This event should be identified as suicide or attempted suicide, and the method of the suicide or attempt should be provided. If an attempted suicide meets the criteria for an SAE, the event must be reported according to the guidelines in Section 7.3.4. Suicidal thoughts should also be regarded as AEs.

All events of suicidality will be carefully monitored. These include events of suicide attempts, suicidal ideation, completed suicides, and suicidal behavior. The last category includes behavioral AEs or SAEs in which the investigator cannot rule out underlying suicidal thinking, eg, motor vehicle accident or behaving in a dangerous or unsafe way, and other self-injurious behaviors.

Investigators are required to provide detailed accounts of AEs related to, or possibly related to, suicidality as described above, to AstraZeneca or representative promptly according to the guidelines for SAEs in Section 7.3.4 and preferably within 5 days for nonserious AEs. Requested information about these events includes the exact nature of the event and the circumstances of the subject at the time of the event. In addition to the usual information required to document AEs or SAEs, data on all of the above will be collected on separate eCRF pages.

Any subject who, based on the investigator's judgement, poses an imminent risk of suicide should be discontinued from the study (see Section 5.4.1 and Section 5.4.2). All efforts should be taken to minimize the risk of suicide and the investigator should carefully monitor the subject.

The latest version of the AE dictionary, Medical Dictionary for Regulatory Activities (MedDRA), will be used by the CRO staff for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be processed in the Global Patient Safety Database Clintrace and coded using MedDRA.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 1.3, Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

AEs based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "*Have you had any health problems since the previous visit?*", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs based on examinations and tests

Deterioration as compared to baseline in the protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AEs.

Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (eg, anemia vs. low hemoglobin value).

Follow-up of unresolved AEs

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

7.3.4 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. SAEs will be recorded from the time of informed consent. All SAEs must be reported within **one business day** to AstraZeneca or representative.

The investigator and/or AstraZeneca or representative are responsible for informing the Ethics Committee (EC) and/or the Regulatory Authority of the SAE as per local requirements.

If any SAE occurs in the course of the study, then the investigator or other site personnel must inform AstraZeneca or representative immediately but no later than the end of the next business day of when the investigator or site personnel becomes aware of it.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform the appropriate AstraZeneca representative of any follow-up information on a previously reported SAE immediately but no later than the end of the next **business day** of when the investigator or site personnel becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the appropriate AstraZeneca clinical patient safety data entry site within **one business day** for fatal and life threatening events and within **five calendar** days for other SAEs. If the report arrives late in the day, it can be sent the following morning. If the report arrives during a weekend or public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

7.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times given in the study assessments (Table 3).

The following clinical laboratory tests (Table 9) will be performed at the screening visit, at the end of the Week 3 visit (final visit or at early study discontinuation), and at Week 8. The date and time of each collection will be recorded on the appropriate source documentation and eCRF.

Table 9 Laboratory assessments

Hematology	Clinical chemistry	Urinalysis
B-Hemoglobin	S-Creatinine	Specific gravity
B-Leukocyte (WBC) differential count	S-Uric acid	pH
B-Platelet count	S-Total bilirubin (direct and indirect)	Glucose
B-Hematocrit	S-Albumin	Protein
B-RBC	S-Alkaline phosphatase	Ketones
	S-ALT	Blood/hemoglobin
HIV	S-AST	Leukocytes
HBsAg	S-Potassium, S-Calcium, S-Sodium	Nitrates
HCV	S-Chloride	Bilirubin
	S-Bicarbonate	Urobilinogen
	S-Glucose	Urine osmolality

Table 9 Laboratory assessments

Hematology	Clinical chemistry	Urinalysis
	Blood urea nitrogen (BUN)	Microscopic examination (if the urine dipstick is abnormal for leukocytes or blood. Urine electrolytes [Na^+, K^+, Cl^-, Ca^{2+}] will be determined as well)
	Protein	
	Lactate dehydrogenase (LDH)	**Urine drug screen**[a]
	Lithium	Cocaine
	S-Troponin I and T	Cannabinoids
	S-Lipids	PCP
	Total cholesterol	Amphetamines class
	Triglycerides	Benzodiazepines class
	High density lipoprotein (HDL) cholesterol	Barbiturates class
	Low density lipoprotein (LDL) cholesterol	Opiates class
		Propoxyphene
	S-Thyroid function tests[a]	Methaqualone
	Free triiodothyronine (T_3)	Methadone
	Free thyroxine (T_4)	Ethanol
	TSH	
	S-β-hCG pregnancy test	

Prefix: B for blood and S for serum.
a HIV, HBsAg, HCV, and urine drug screen will be conducted at the screening visit only.

Samples should be taken by adequately trained study personnel and handled in accordance with given instructions. Volumes of blood samples are described in Section 8.1. The central laboratory (see Section 1) will perform all clinical laboratory determinations as listed in Table 9. Up-to-date reference lists will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range. The investigator should make an assessment of the available results with regard to clinically significant abnormalities. The paper copy should be signed and archived in the eCRF and is the source data for laboratory variables at site.

Blood samples for laboratory assessments will be collected from subjects in non-fasting state.

7.3.6 Physical examination, height and weight

A complete physical examination should be completed by a physician or any qualified licensed staff at the screening visit, Week 3 (Infusion 3) and Week 8, and recorded by body system on the appropriate sections of the source documentation and eCRF.

The complete physical examination will include assessments of the following: general appearance, skin, head, neck (including eyes, ears, nose and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems. Complete physical examination data to be recorded on the eCRF will include: 1) normal/abnormal and 2) a description of the abnormalities.

Height will be measured at the screening visit only. Weight will be measured at the screening visit and at every visit through Week 8 (Visit 16). Height will be measured in centimeters (cm) and weight will be measured in kilogram (kg) with the subject wearing light clothing and without shoes. If possible, weight should be recorded using the same scale at each visit.

7.3.7 ECG

7.3.7.1 Resting digital 12-lead ECG

Digital ECGs for all subjects at all centers will be conducted at the center using a machine provided by the central ECG laboratory (eRT) and will be transmitted to eRT (Section 1). Digital ECG will be performed at screening, prior to start of infusion (at randomization, Day 1, T_0 of Visit 3, Week 1), 1 hour after the infusion (T_1, Infusion 1, Visit 3 of Week 1), at the end of Week 1 (T_1 of Visit 5), end of Week 2 (Visit 8 [Infusion 3]), end of Week 3 (Visit 11 [Infusion 3]), and at Week 8 (Visit 16). The ECG at T_0 of Visit 3 (Day 1) will be considered the baseline value.

Digital ECGs will be obtained after the subject has been resting in a semi-reclining position for at lest 10 minutes.

All digital ECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT and QTcF. QTcF intervals will be calculated using the Fridericia formula (Puddu et al 1988).

If indicated, additional ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment on the appropriate eCRF.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF. Abnormal values shall not be recorded as AEs unless deemed clinically significant.

Quality assurance of the ECG waveform and subject demographics will be conducted by a central laboratory operator at eRT. Digital ECGs will be processed through a computer interpretation program and then reviewed, first by an ECG analyst and then by a board-certified cardiologist. Results will be faxed and a hard copy report mailed to the center.

7.3.8 Vital signs

7.3.8.1 Blood pressure, pulse and temperature

Blood pressure (supine and standing), pulse rate (supine and standing), and oral body temperature will be measured at the screening visit, placebo saline run-in infusion, randomization (Day 1), and at each scheduled weekly visit (Table 3, Table 4, Table 5 and Table 6). Oral body temperature will be measured in °C.

An appropriately sized cuff will be used to obtain systolic and diastolic BP. The assessment will be done first with the subject in the supine position for 3 minutes and again within 3 minutes of the subject attaining a standing position. Standing and supine BP and pulse rate should be measured with the right arm at heart level.

7.3.9 Other safety assessments

7.3.9.1 Medical/medication/surgical history

A detailed medical surgical history including medication history will be recorded for each subject during the screening visit. Significant medical conditions that have occurred within the past two years or conditions that are ongoing (ie, headache, backache, indigestion) will be recorded (Table 3).

7.3.9.2 Pregnancy test

A serum pregnancy test will be performed on all women at the screening visit (Visit 1), before the single-blind IV placebo run-in infusion (Visit 2), at Week 3 (Visit 11) and Week 8 (Visit 16). If a pregnancy test is found to be positive at anytime, the subject will not be able to continue participation in the study (see Table 3 for the timing of pregnancy testing and Section 1.3 for procedures in case of pregnancy).

7.3.9.3 Urine drug screen

A urine sample will be evaluated only during the screening visit. The sample will be tested for the drugs of abuse including methamphetamines (including ecstasy), benzodiazepines, cocaine and/or metabolites, amphetamines, THC, opiates, PCP, barbiturates, and ethanol (Table 9).

If a subject only tests positive for THC during the initial drug screen, they can be retested but should be excluded if the second test is still positive. Subjects who have a positive UDS for a drug(s) legally available by prescription must provide evidence of the prescription for the drug(s).

Note: Although the results of the UDS must be documented in the subject's file, the results will not be collected on the eCRF and will therefore not be recorded in the study database.

7.3.9.4 Serology testing

Serology testing for HIV antibody, HBsAg and HCV antibody will be performed on all subjects during the screening visit only (Table 3). If a test is positive, the subject will not be allowed to participate in the study.

Note: Although the results of the HIV and hepatitis serology testing must be documented in the subject's file, the results will not be collected on eCRFs and will therefore not be recorded in the study database.

7.3.9.2.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality (Posner et al 2007). It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be administered at the screening visit and at each scheduled visit throughout the study by a trained rater. The trained rater will record the clinical observation on the scale which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

The timing of the C-SSRS evaluations is found in Table 3, Table 4, Table 5 and Table 6.

7.4 Efficacy

7.4.1 Rating scales

The following scales, MADRS, HAM-D, HAM-A, VAS, CADSS, CGI-S and CGI-I will be utilized in this study and will be rated by the investigator or delegate, according to the schedule of events in Table 3.

When multiple scales are being performed at the same timepoint, scales should be performed in the following order: QIDS-SR-16, HAM-D, MADRS, BSS, C-SSRS, HAM-A, VAS, CADSS, Q-LES-Q-SF, CGI-S and CGI-I.

To ensure consistency throughout the study, all site personnel (eg, physician, PhD, RN, or other healthcare professional skilled and experienced in the care of this patient population) administering the MADRS, HAM-D, BSS, C-SSRS, HAM-A, CADSS, CGI-I and CGI-S, will receive training in conducting these assessments. In addition, certification will be required for MADRS and CGI scale administration (prior to rating these scales for this study).

To reduce scoring variability, it is important that the same rater conduct the rater assessments for a given subject for a specific scale throughout the course of the study. The back-up rater

must meet the same qualifications as the primary rater and be authorized by the PI and approved by AstraZeneca or representative to conduct the ratings.

The scores in each of the scales will be recorded on the appropriate sections of the eCRF. Signs and symptoms revealed and recorded during the ratings should only be reported as AEs if they fulfill the criteria for a SAE or are the reason for discontinuation from treatment with the investigational product.

Please see Table 4, Table 5 and Table 6 for the timing of evaluations.

7.4.2 Primary efficacy variable

The primary efficacy endpoint is the change from baseline in MADRS total score at Week 3.

7.4.2.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale for the evaluation of depressive symptoms (Montgomery and Åsberg 1979). The MADRS will be administered by a physician, PhD, RN, or other healthcare professional skilled and experienced in the care of this subject population. Each rater administering the MADRS must receive training and certification on the use of the MADRS and must be approved by AstraZeneca or representative.

Each MADRS item is rated on a 0 to 6 scale. Higher MADRS scores indicate higher levels of depressive symptoms. The individual item scores will be recorded on the eCRF. A subject will be classified as in remission if their MADRS total score is ≤10. The timing of the MADRS measurements can be found in Table 3, Table 4, Table 5 and Table 6.

7.4.3 Secondary efficacy variables

7.4.3.1 Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16)

The QIDS-SR-16 is designed to assess the severity of depressive symptoms (Rush et al 2003). It is a 16-question self-test done by the subject to help the subject become aware of some signs and symptoms of depression. The test measures 9 different criterion domains of major depression.

The timing of QIDS-SR-16 is found in Table 3, Table 4, Table 5 and Table 6.

7.4.3.2 Beck Scale for Suicide Ideation (BSS)

The BSS is a 21-item report scale to assess the severity of suicidal ideation in adults and adolescents (Beck et al 1979). Only the first 19 items are graded in severity on a 0 to 2 scale, which are added to produce a total score. The last two items are the number of previous suicide attempts and the seriousness of the intent to die associated with the last attempt. The timing of BSS evaluations is found in Table 3, Table 4, Table 5 and Table 6.

7.4.3.3 Clinical Global Impressions: CGI-I and CGI-S

The Clinical Global Impressions (CGI) scale is a 3-part, clinician-administered scale that assesses global illness severity and change (Guy 1976). For the purposes of this study, only the first two parts of the scale will be used.

The first part, Severity of Illness (CGI-S), is scored to rate the subject's current clinical state. The second part, Global Improvement (CGI-I), is scored to rate the subject's change post-treatment.

Each CGI item is scored on a scale from 1 to 7. A CGI-S score of 1 indicates that a subject is "Normal, not ill" and a score of 7 indicates that a subject is "Among the most extremely ill subjects". A CGI-I score of 1 indicates that a subject is "Very much improved" and a score of 7 indicates that a subject is "Very much worse." The CGI is administered at various times during the course of the study to assess subject progress. Higher CGI-S scores indicate greater illness severity. CGI-I scores greater than 4 indicate worsening, while scores less than 4 indicate improvement. The individual item scores will be recorded on a specifically designed eCRF.

CGI-I will be evaluated at each assessment following randomization, and will be summarized by each rating as well as dichotomized into "Much or Very Much Improved" (a CGI-I rating $\leq$2), or "Not Much Improved" (a CGI-I >2). The timing of the CGI measurements is found in Table 3, Table 4, Table 5, and Table 6.

7.4.3.4 Hamilton Depression Rating Scales (HAM-D and HAM-A)

The HAM-D is a 21-item observer rated scale that assesses depressive symptoms (Hamilton 1960) each of which is rated from 0-2 to 0-4, where 0 is none/absent. Depressive symptoms include depressed mood, feelings of guilt, suicide, insomnia-early, insomnia-middle, insomnia-late, work and activities, retardation, agitation, anxiety psychic, anxiety somatic, somatic symptoms-gastrointestinal (GI), somatic symptoms-general, genital symptoms, hypochondriasis, loss of weight, loss of insight, diurnal variation, depersonalization and derealization, paranoid symptoms, and obsessional symptoms. The first 17 items contribute to the total score. Items 18 to 21 are recorded to give further information about the depression, but are not part of the scale. The HAM-D will be performed during the screening visit and throughout the study to determine depression severity.

The HAM-A (Hamilton 1959) is a widely used interview scale that measures the severity of a subject's anxiety, based on 14 parameters, including anxious mood, tension, fears, insomnia, somatic complaints and behavior at the interview. Each item is rated on a 5-point scale - 0 (not present) to 4 (severe).

The timing of HAM-D and HAM-A evaluations is found in Table 3, Table 4, Table 5 and Table 6.

7.4.3.5 Visual Analogue Scale (VAS)

The modified Bond-Lader VAS is a questionnaire completed by the subject consisting of 16 scales that assess changes in subjective alertness, subjective calmness and subjective contentment (Bond and Lader 1974).

Each scale is a 100-mm line anchored at the ends by antonyms. Subjects mark their current subjective state between the antonyms on the line and each line is scored as millimeter to the mark from the negative antonym. The timing of the VAS measurement is found in Table 3 and Table 4.

7.4.3.6 Dissociative state

7.4.3.6.1 Clinician Administered Dissociative States Scale (CADSS)

The CADSS is a 23-item self-report scale (Bremner et al 1998). It is a reliable, valid self-report instrument designed to assess state symptoms of dissociation in response to a specified stressor. Severity of each dissociative symptom can range from 0 (not present) to 4 (extreme).

The timing of CADSS evaluations is found in Table 3, Table 4 and Table 5.

7.4.4 Patient reported outcomes (PRO)

The patient-reported outcomes of QIDS-SR-16, BSS and VAS are discussed in Section 7.4.3, along with the other secondary efficacy variables.

7.4.4.1 Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q–SF)

The Q-LES-Q-SF measures QoL in key domains (Endicott et al 1993). The short form employs the 14 general activities of the long form, as well as 2 global items. Five-point item scores are aggregated, with higher scores indicative of greater enjoyment or satisfaction in each domain.

The timing of Q-LES-Q-SF is found in Table 3, Table 4, Table 5 and Table 6.

7.5 Pharmacokinetics

For timing of individual samples, refer to Table 10 and Table 11. The actual date and time of the sample collection must be recorded on the appropriate eCRF page.

7.5.1 Determination of drug concentration in biological samples

Samples for determination of AZD6765 concentration in plasma will be analyzed by Bioanalytical Systems, Inc. (BASi) on behalf of AstraZeneca. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report. Blood samples will be collected, labeled and shipped as detailed below.

Additional analyses may be conducted on the biological samples to further investigate reproducibility of incurred samples. Any results from such analyses will be included in the bioanalytical study contribution report.

Venous blood samples (6 mL) will be taken at the times presented in Table 3, Table 10 and Table 11. Individual venipunctures for each timepoint may be performed or an in-dwelling catheter may be used. If the site chooses to use an in-dwelling catheter, the first 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Heparin may **not** be used to flush the catheter.

Six milliliter (6 mL) samples of whole blood will be collected into ethylenediamine tetraacetic acid (EDTA) spray-dried tubes for the determination of AZD6765 in human plasma as follows:

- Week 1: Visits 3, 4 and 5.
- Weeks 2 and 3: Visits 6 7, 8, 9, 10 and 11.

All samples will be immediately placed on ice until centrifugation, which will begin within 30 minutes of sample collection. The sample will be centrifuged for 10 minutes at 2°C to 8°C at 1500Xg (a refrigerated centrifuge is not required but the site must use a cooled centrifuge). The resulting plasma will be divided into 2 transfer tubes (2.0 mL Microcentrifuge Micro Tubes-Sterilized, Cat #4204S, Bio Plas, Inc., USA, or a tube approved by AstraZeneca) and immediately frozen upright at -20°C or below within 15 minutes of plasma preparation and kept frozen at this temperature before, during and after transport to the designated laboratory. One of the samples will be retained at the site. AstraZeneca will instruct the site when to ship the retention sample.

At each visit, one or two samples will be drawn. Samples will be drawn at random according to the PK sample schedule in Table 10 and Table 11. A maximum of 16 blood samples (approximately 96 mL) will be collected from each subject for PK assessments depending on dosing regimen.

It is important that the time and date of the PK sample collection as well as the time and date of the last two doses of study medication are recorded in the eCRF.

If a subject refuses blood collection for PK assessment, this will not be considered a protocol violation as the PK analysis is a secondary objective.

Table 10 Week 1: Timing of PK sampling

Week	Visit	Infusion	1st Sample[a]	2nd Sample[a]	No. of Samples
1	3	Infusion 1	1-2 h (T_{1-2})	2 h - until discharge ($T_{2\text{-discharge}}$)	2
	4	Infusion 2: 3 days from Infusion 1	0 h (T_0)	1-2 h (T_{1-2})	2
	5[b]	Infusion 3: 2 days from Infusion 2	0 h (T_0)	2 h - until discharge ($T_{2\text{-discharge}}$)	2
	5[b]	Infusion 3: ≥3 days from Infusion 2	1 h (T_1)	2 h - until discharge ($T_{2\text{-discharge}}$)	
				Total	**6**

a Samples should be collected randomly within the sample collection window provided, and all efforts should be made to avoid collecting samples at a single scheduled timepoint (except where an exact timepoint is indicated). In addition, attempt should be made to vary sample collection timepoints for each subject as often as possible over the 3-week dosing period.

b Visit 5: Subjects will have blood samples collected at either 2 days from Infusion 2 or ≥3 days from Infusion 2.

Table 11 Weeks 2 and 3: Timing of PK sampling

Week	Visit	Infusion	1st Sample[a]	2nd Sample[a]	No. of Samples
2	6	Infusion 1	0.5-1 h ($T_{0.5-1}$)	1 h - until discharge ($T_{1\text{-discharge}}$)	2
	7[b]	Infusion 2: 2 days from Infusion 1	0 h (T_0)	1 h - until discharge ($T_{1\text{-discharge}}$)	2
	7[b]	Infusion 2: ≥3 days from Infusion 1	1 h (T_1)	1 h - until discharge ($T_{1\text{-discharge}}$)	
	8[c]	Infusion 3: 2 days from Infusion 2	0 h (T_0)		1
	8[c]	Infusion 3: ≥3 days from Infusion 2	1 h - until discharge ($T_{1\text{-discharge}}$)		
3	9	Infusion 1	0.5-1 h ($T_{0.5-1}$)	1 h - until discharge ($T_{1\text{-discharge}}$)	2
	10[b]	Infusion 2: 2 days from Infusion 1	0 h (T_0)	1 h - until discharge ($T_{1\text{-discharge}}$)	2
	10[b]	Infusion 2: ≥3 days from Infusion 1	1 h (T_1)	1 h - until discharge ($T_{1\text{-discharge}}$)	
	11[c]	Infusion 3: 2 days from Infusion 2	0 h - until discharge ($T_{0\text{-discharge}}$)		1
	11[c]	Infusion 3: ≥3 days from Infusion 2	1 h - until discharge ($T_{1\text{-discharge}}$)		
				Total	**10**

a Samples should be collected randomly within the sample collection window provided, and all efforts should be made to avoid collecting samples at a single scheduled timepoint (except where an exact timepoint is indicated). In addition, attempt should be made to vary sample collection timepoints for each subject as often as possible over the 3-week dosing period.

b Visits 7 and 10: Subjects will have blood samples collected at either 2 days from Infusion 1 or at ≥3 days from Infusion 1.

c Visits 8 and 11: Subjects will have blood samples collected at either 2 days from Infusion 2 or at ≥3 days from Infusion 2.

7.5.1.1 Labeling of AZD6765 plasma samples

Freezer compatible labels will be applied to the plasma sample tubes. The labels should contain the following information:

Study Number: D6702C00009
Subject Number
Site Number
Sample Number (Tube and Set Number)

Week
Visit
Protocol Sampling Time

Dose Number
Analyte: AZD6765
Matrix: Plasma

7.5.1.2 Shipment of AZD6765 plasma samples

All AZD6765 plasma samples accompanied by the sample shipment logs will be shipped via an agreed upon courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for delays in the shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment.

The primary contact, [redacted] and the primary monitoring scientist at AstraZeneca, [redacted] must be notified by email and fax at the time that the samples are shipped. The fax notification should include a copy of the sample shipment log and courier tracking numbers.

Samples should only be shipped on Monday through Tuesday. Do not ship on or within two days prior to a legal holiday.

Plasma samples should be shipped to:

[redacted]

7.6 Pharmacodynamics

7.6.1 Collection and processing of serum and urine samples for the determination of biomarkers

Venous blood samples (2 mL) (Table 12) and urine samples (10 mL) for determination of biomarkers will be collected at the times presented in Table 3. Blood and urine samples will be collected, labeled and shipped as detailed below. The date and time will be recorded on the appropriate eCRF.

Serum sample

Blood will be collected according to site procedure. Individual venipunctures for each timepoint may be performed or an indwelling catheter may be used. If a sample is taken through a catheter, the first 1 mL of blood will be discarded, and the catheter flushed **after** sampling with 2 mL of normal saline to keep it patent. Heparin may **not** be used to flush the catheter.

The blood samples (2 mL) will be collected into red top tubes and processed according to standard laboratory procedures. The sample will be centrifuged for 10 minutes at 2°C to 8°C at a relative centrifugal force of 1500Xg (a refrigerated centrifuge is not required but the site must use a cooled centrifuge). The resulting serum will be transferred to two 1.8 mL (Nunc Cryovial, Fisher Scientific No 12-565-163N, NNI No. 375418) or a tube approved by AstraZeneca) and immediately frozen upright at -20°C or below within 15 minutes of serum preparation and kept frozen at this temperature before, during and after transport to the designated laboratory. One of these samples will be retained at the site until instructed by AstraZeneca. This retention sample will be retained until analysis is completed on the original sample and it is decided that the retention sample can be destroyed.

Urine sample

Urine will be collected according to site procedure. The urine samples (10 mL) will be collected into purple top tubes and processed according to standard laboratory procedures. The resulting urine will be immediately frozen upright at -20°C or below within 15 minutes of urine collection and kept frozen at this temperature before, during and after transport to the designated laboratory. One of these samples will be retained at the site until instructed by AstraZeneca. This retention sample will be retained until analysis is completed on the original sample and it is decided that the retention sample can be destroyed.

The 10-mL urine sample will be collected in two 5-mL aliquots. One of the 5-mL aliquots at each timepoint will be labeled and frozen undiluted for possible future biomarker analysis; the second 5-mL aliquot will be buffered for potential future assays. Aliquots will be labeled as described in Section 7.6.2.

Please see Section 8.5 for withdrawal of informed consent for donated biological samples.

7.6.2 Labeling of serum and urine samples for determination of biomarkers

Freezer compatible labels will be applied to the cryovials. The labels should contain the following information:

Study Number: D6702C00009
Subject Number
Site Number
Sample Number (Tube and Set Number)

Week
Visit
Protocol Sampling Time

Dose Number
Analyte: AZD6765
Matrix: Serum OR Urine

7.6.3 Shipment of serum and urine samples to Rules Based Medicine Laboratories

All serum and urine samples accompanied by the specimen shipment logs will be shipped via an agreed upon overnight courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 96 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included in the shipment.

[redacted] t the time samples are shipped. The fax notification should include a copy of the specimen shipment log.

Samples should only be shipped on Monday through Wednesday. Do not ship on or within two days prior to a legal holiday.

Serum and urine samples should be shipped to:

[redacted]

7.7 Pharmacogenetics

7.7.1 Collection of samples

The blood sample for genetic research will be obtained from the subjects after randomization. Samples will be collected, labeled stored and shipped as detailed in the laboratory manual.

For blood volume, see Section 8.1.

7.8 Health economics-Not applicable

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 12 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including lipid panel, serum pregnancy, thyroid and lithium)	**8.5**	**8**	**68**
	Troponin I and T (separate sample)	**3.5**	**7**	**24.5**
	Bicarbonate (this tube cannot be opened so must be a separate aliquot)	**3.5**	**7**	**24.5**
	Hematology	**2**	**4**	**8.0**
HIV, HBsAg, HCV		**8.5**	**1**	**8.5**
Pharmacokinetics (AZD6765 levels)		**6**	**16**	**96**
Pharmacodynamics (optional inflammatory cytokine biomarker analysis)		**2**	**2**	**4**
Pharmacogenetics (optional)		**9**	**1**	**9**
Total			**46**	**242.5**

The Troponin testing will require an addition of 3.5 mL at each time on **7** occasions, in total 24.5 mL.

For subjects who participate in optional genetic sampling, an additional 9-mL blood sample will be collected after randomization.

For subjects who participate in optional serum biomarker (inflammatory cytokine) analysis, an additional 2-mL blood sample will be collected at randomization and at Week 3.

8.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed after analyses or retained for further use as described here.

The laboratory will provide detailed instructions of all laboratory procedures, handling and shipment of laboratory samples before the study start. The samples should be properly taken, handled, labeled and shipped in accordance with the instructions provided by the laboratory. Samples should be shipped to the laboratory by courier unless otherwise agreed.

The analyte stability limits defined by the laboratory will be applied to all analyses performed on behalf of AstraZeneca. The laboratory will not analyze samples that fall outside these stability limits. Analytical data found to have been derived from a sample that fell outside these stability limits would not be reported. The standards of procedures followed by the laboratory may be amended in accordance with their Standard Operating Procedures. The laboratory will inform AstraZeneca of the stability limits relevant to this study before the first subject gives informed consent to take part in the study.

8.2.1 Pharmacokinetics and/or pharmacodynamics samples

Additional analysis may be conducted on the biological samples to further investigate incurred sample reproducibility/stability. Any results from such analyses will be reported in the Bioanalytical contribution report.

8.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee or representative working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. The link between the subject enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

8.3 Labeling and shipment of biohazard samples

The PI ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria (see International Airline Transportation Association [IATA] 6.2 Regulations Guidance in Appendix C).

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the subject unless agreed with AstraZeneca or representative and appropriate labeling, shipment and containment provisions are approved.

8.4 Chain of custody of biological samples

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

The PI at each center keeps full tractability of collected biological samples from the subjects while in storage at the center until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full tractability of the samples while in storage and during use until used or disposed.

AstraZeneca or representative will keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in AstraZeneca's bio bank system during the entire life cycle.

8.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated, the samples will be disposed/destroyed, if not already analyzed and documented.

If collection of the biological samples is a voluntary part of the study, then the subject may continue in the study.

The PI will ensure:

- Subject's withdrawal of informed consent is notified immediately to AstraZeneca or representative.
- Biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- The laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

AstraZeneca or representative will ensure the central laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1 Ethical conduct of the study

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

9.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

For study centers within the US or in studies where non-US subjects' protected health information (subject data) will come into the US through a covered entity (eg, Central lab/Reader), the Informed Consent Form will incorporate, or be accompanied by, a separate document incorporating Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which subjects authorize the use and disclosure of their Protected Health Information by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer-processed by AstraZeneca or representative will be identified by subject enrollment number, randomization number, and study code. The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may require direct access to parts of the hospital or practice records relevant to the study, including the subject's medical history.

9.3 Ethics and regulatory review

An EC/IRB must approve the final study protocol, including the final versions of the Informed Consent Form and any other written information to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

The opinion of the EC/IRB must be given in writing. The investigator must submit the written approval to AstraZeneca or representative before enrollment of any subject into the study. Study investigational product will not be distributed to the site until such approval is in place.

The EC/IRB must approve all advertising used to recruit subjects for the study.

AstraZeneca must approve any modifications to the Informed Consent Forms that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the EC/IRB annually.

Before enrollment of any subject into the study, the final study protocol, including the final versions of the Informed Consent Forms, a notification to the national regulatory authority is done and is approved by the national regulatory authority according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

In the US, the PI is also responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca or representative will provide this information to the PI.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the EC/IRB according to local regulations and guidelines.

9.4 Informed consent

The PI at each center will:

- Ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure that the subjects are notified that they are free to discontinue from the study at any time.
- Ensure that the subjects are given the opportunity to ask questions and allowed time to consider the information provided.
- Obtain and document the subject's signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Forms are stored in the Investigator's Study File.
- Ensure that copies of the signed Informed Consent Forms are given to the subject.

Where genetic analyses are included, special account of these will be made in the consent forms, as it is recognized that special provisions need to be made to retain confidentiality of medical information. These factors have been taken into account in the design of the consent forms. Forms specific for giving consent for taking samples for genotyping will be used. The subject's signed and dated Informed Consent must be obtained before conducting any procedure specifically for the genetic sampling. The PI must store the original, signed Informed Consent Forms. A copy of the signed Informed Consent Forms must be given to the subject.

If modifications are made according to local requirements, the new versions of the Informed Consent Forms have to be approved by AstraZeneca.

9.5 Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and in a new version of the study protocol (Amended Protocol).

The amendment must be approved by each EC/IRB and if applicable, also the national regulatory authority, before implementation. Local requirements must be followed for amended protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the EC/IRB, see Section 9.3.

If a protocol amendment requires a change to a center's Informed Consent Forms, AstraZeneca and the center's EC/IRB must approve the revised Informed Consent Forms before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

9.6 Audits and inspections

Authorized representatives of AstraZeneca, the regulatory authority, or the EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca or representative immediately if contacted by a regulatory agency about an inspection at the center.

10. STUDY MANAGEMENT

10.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for an AstraZeneca representative or representative to discuss with and/or visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the investigator.

10.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative or representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the eDC system utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.3 Monitoring of the study

It is understood that AstraZeneca or its representative will contact and visit the Investigator regularly for monitoring purposes. During this study, there will be on-site monitoring visits to review source documentation and eCRFs to evaluation them for completeness, legibility, and consistency.

The Study Monitor will be allowed, on request, to inspect the various records of the trial (eCRFs, source documents, signed Informed Consent Forms, and any other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. It will be the Study Monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The Study Monitor must have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or her/his designee[s]) agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

During the monitoring visits, the Study Monitor will also:

- Provide information, support and training to the investigator and investigational staff (as needed).
- Confirm that investigational facilities are adequate and remain acceptable throughout the trial.
- Confirm that the investigational team is adhering to the protocol, data are being recorded accurately and timely in the eCRFs, and that investigational product accountability checks are being performed.
- Verify subject existence for all subjects who sign the Informed Consent Forms.
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the subject.

Source documents

The Investigator shall permit the authorized sponsor, agents of the sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect and copy all records relating to an investigation, including subject records. Completed eCRFs must be made available by the investigator for review by the sponsor, agents of the sponsor, the Study Monitor and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the sponsor and of the regulatory agencies have direct access to source documents (eg, subject medical records, charts, laboratory reports, and signed Informed Consent Forms). The eCRFs will be compared with the source documents to ensure that there are no discrepancies between critical data. Subject confidentiality will be protected at all times.

10.3.1 Source data

The location of source data is described in the CSA.

10.4 Study agreements

The PI at each center must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail.

Agreements between AstraZeneca and the PI must be in place before any study-related procedures can take place, or subjects be enrolled.

10.5 Study timetable and end of study

The end of the entire study is defined as the date of the last subject completing last visit. The study is expected to start in [redacted]

Before a subject's enrollment in the study and any study-related procedures are undertaken, the following should be fulfilled:

- signed CSP and other agreements between AstraZeneca and the PI/study center
- written approval of the study by the IRB/IEC
- written approval of the study, if applicable, by the regulatory authority
- signed and dated FDA Form 1572 (US centers only)
- signed and dated Financial Disclosure forms for all study personnel listed on the most recent version of FDA Form 1572 (US centers only)

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD6765.

11. DATA MANAGEMENT

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the subject's data will be locked.

Electronic case report form (eCRF)

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the eDC system. All sites will need internet access to access the eCRFs and will only have access to data for subjects at their own sites. Data Management (DM) and other co-ordinator teams will have access to data at all sites.

All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the subject's eCRF correspond to the entries on the subject's medical records.

The eCRFs for any subject leaving the study should be completed at the time medication is terminated for whatever reason.

eCRFs must accurately reflect data contained in subject's records (eg, source documents).

Dataflow

After data is entered into the eCRF by site, autoqueries that are generated by the eDC system should be addressed by site. At the monitoring visit, the Study Monitor must perform the SDV of the required fields on completed forms and if there are no open queries, freeze the form. DM will run manual consistency checks outside of the eDC system and will raise manual queries for sites to address; if the form is frozen, DM will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data is entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

Database lock

Once all subject casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

Coding

All AEs and Medical Histories recorded in the eCRF will be coded using MedDRA and all Medications coded using AstraZeneca's Drug Dictionary (AZDD). The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

Investigator site file

At the beginning of the study, an Investigator's study file will be established at the study center. The Investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The Investigator/institution must take measures to prevent accidental or premature destruction of these documents.

SAE reconciliation

The CRO will perform SAE reconciliation between the CRO Clinical Study database and the AZ Clinical Patient Safety database.

Biological samples

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

ECG data

ECG data will be processed by a central laboratory and the results will be sent electronically to AstraZeneca or its representative.

Genetic data

In the case of genotypic data, only the date the subject gave consent to participation in the genetic research and the date the blood sample was taken from the subject will be recorded in the eCRF and database.

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the CSR for the main study.

12. EVALUATION AND CALCULATION OF VARIABLES

12.1 Calculation or derivation of safety variables

12.1.1 Adverse events

A treatment-emergent AE (TEAE) is defined as any AE that started on or after the first dose of study medication up to 30 days after the last dose of study medication. An AE already present at the time of the first dose of study medication that worsens in intensity following exposure to study medication or an AE with an unknown/not reported onset date will also be considered as treatment-emergent.

12.1.2 Other significant adverse events (OAE)

During the evaluation of the AE data, AstraZeneca or representative will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR.

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

12.1.3 Laboratory safety assessments

Change from baseline at each visit will be calculated as the visit value minus the baseline value for each continuous clinical chemistry, hematology, and urinalysis measurement.

12.1.4 Weight and BMI

A baseline BMI will be calculated. Change from baseline at each visit will be calculated as the visit value minus the baseline value. Also, the proportions of subjects who have a weight gain $\geq$7% compared to baseline will be tabulated.

12.1.5 ECG

Change from baseline at each visit will be calculated as the visit value minus the baseline value for each ECG parameter: heart rate, QRS duration, PR interval, RR interval, QT and QTcF interval.

12.1.6 Vital signs

Change from baseline at each visit will be calculated as the visit value minus the baseline value for each vital sign: blood pressure, pulse rate (supine and standing), and oral temperature.

12.1.7 Other safety assessments

12.1.7.1 C-SSRS

Occurrence of suicidal behavior after baseline up to Week 3 will be defined as having answered "yes" to at least one of the four suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

Occurrence of suicidal ideation after baseline up to Week 3 will be defined as having answered "yes" to at least one of the five suicidal ideation subcategories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any post-baseline evaluation.

12.2 Calculation or derivation of efficacy variables

12.2.1 MADRS

The MADRS total score will be calculated as the sum of the 10 individual item scores; the total score can range from 0 to 60. Change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.2 QIDS-SR-16

The QIDS-SR-16 total score is derived by summing the scores for the 16 individual items as instructed on the instrument scoring sheet. The change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.3 BSS

The BSS total score is derived by summing the scores for the first 19 individual items. Items 20 and 21 will be regarded as individual items. The change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.4 CGI-I and CGI-S

For CGI-S, the change from baseline to each assessment will be calculated as the visit score minus the baseline score.

CGI-I will be evaluated at each assessment following randomization. Also, a CGI-I score category will be calculated as ≤2 (very much or much improved) vs. >2.

12.2.5 HAM-D and HAM-A

The HAM-D total score will be calculated as the sum of the first 17 individual item scores on the HAM-D GRID score sheet; the total score can range from 0 to 50. Items 18 to 21 will be regarded as single items.

The HAM-A total score will be calculated as the sum of the 14 individual item scores. The HAM-A psychic anxiety factor score will be calculated as the sum of the following 7 items: anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behavior at interview. The HAM-A somatic anxiety factor score will be calculated as the sum of the following 7 items: somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, and autonomic system.

For these variables, change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.6 VAS

The VAS total score is derived as the average of the number of millimeters (maximum 100) from the negative antonym for each individual scale. Change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.7 CADSS

The CADSS total score will be calculated as the sum of the individual item scores. For CADSS, change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.2.8 Calculation and derivation of patient reported outcome variables

12.2.8.1 Q-LES-Q-SF

The Q-LES-Q-SF total score is derived by summing item scores 1 to 14. For these variables, the change from baseline to each assessment will be calculated as the visit score minus the baseline score.

12.3 Calculation or derivation of pharmacokinetics variables

The population PK analysis will be performed by AstraZeneca. AZD6765 plasma concentration-time data from this study and other prior and/or future studies may be pooled and subjected to analysis using non-linear mixed effects modelling, in order to build a population model to describe the PK of AZD6765 in patients with MDD. Together with safety data and efficacy/PD data, this may be subjected to exploratory population PK/PD analyses. A population PK analysis plan will be produced prior to any such investigations, and the analysis will be reported separately.

12.3.1 Pharmacokinetics analysis method

Population PK will be performed on the plasma concentrations of AZD6765 using the "population PK approach."

12.4 Calculation or derivation of pharmacodynamic variables-Not applicable

12.5 Calculation or derivation of pharmacogenetic variables-Not applicable

12.6 Calculation or derivation of health economics variables-Not applicable

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 Description of analysis sets

13.1.1 Safety analysis set

The safety analysis set will include all randomized subjects who were given study treatment, classified according to the treatment actually received. That is, erroneously treated subjects (eg, those randomized to Treatment A but actually given Treatment B) will be accounted for in their actual treatment group. The safety analysis set will be used to assess safety and tolerability variables.

13.1.2 Modified intent-to-treat (mITT) analysis set

The mITT analysis set will include all randomized subjects, classified according to randomized treatment, who took investigational product and who have a randomization (baseline) MADRS total score assessment and at least 1 MADRS total score post-randomization. The mITT analysis set will be used for the efficacy analyses.

13.1.3 Completers analysis set

The Completers analysis set will include only those mITT subjects who complete 3 weeks of treatment and proceed into the post-treatment period, and who receive the treatment to which they were randomized. The Statistical Analysis Plan (SAP) will outline additional efficacy analyses that may be based on this analysis set.

13.1.4 Per-protocol (PP) analysis set

The PP analysis set will include only those mITT subjects who have no major protocol violation, who complete 3 weeks of treatment and proceed into the post-treatment period, and who receive the treatment to which they were randomized. The SAP will provide the exact criteria for defining the PP analysis set. Additional analyses of efficacy variables may be performed using the PP analysis set to check the robustness of the treatment effects.

13.2 Methods of statistical analyses

A comprehensive SAP will be prepared and finalized prior to unblinding. All statistical comparisons will be based on a 2-sided $\alpha = 5\%$ level of significance. The primary analysis will use Dunnett's procedure for multiplicity adjustment; for the secondary analyses, no corrections to the p-values will be made and unadjusted 95% confidence intervals will be presented where appropriate.

Descriptive statistics for continuous data will include n, mean, median, standard deviation, minimum and maximum. Descriptive statistics for categorical data will include n, frequency, and percentage.

For all change from baseline variables, baseline will be defined as the last non-missing value prior to or on the day of randomization—although it must be prior to dosing.

Two types of datasets, both derived from the mITT analysis set, will be used for efficacy analyses: the observed case (OC) dataset and the last observation carried forward (LOCF) dataset. In general the OC data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing—no data imputation will be performed. The LOCF data will be the corresponding OC data or, if that is missing, the last non-missing data carried forward from the most recent preceding visit. However, baseline values will not be carried forward for LOCF imputation. The calculation of total scores when there are missing item scores will be described in the SAP. No other data imputation will be performed.

Subjects with or without a diagnosis of co-morbid GAD (as defined by the MINI) are eligible for enrollment. Because co-morbid GAD is potentially a prognostic factor for efficacy, the randomization will be stratified by co-morbid GAD, and the strata will be incorporated into the analyses where appropriate.

13.2.1 Primary efficacy analysis

The change from baseline to Week 3 in the MADRS total score will be compared between each AZD6765 dose and placebo, using LOCF in the mITT analysis set, using an analysis of covariance (ANCOVA) model in which treatment, randomization stratification (co-morbid GAD), and baseline score will be included as fixed effects, and center as a random effect. The primary analysis will use Dunnett's procedure to adjust for multiplicity.

13.2.2 Secondary efficacy analyses

The change from baseline in the MADRS total score to 3 days and at the other scheduled assessments will be compared between each AZD6765 dose and placebo, using LOCF in the mITT analysis set, using the same ANCOVA model as the primary analysis. Similar analyses for the change from baseline in the MADRS total score at each scheduled assessment will be performed with OC in the mITT analysis set.

As a sensitivity analysis, the change from baseline in the MADRS total score will be analyzed with OC in the mITT analysis set using a mixed model repeated measures (MMRM) model in which treatment, time (scheduled assessments at 3 days and end of Weeks 1, 2 and 3), treatment-by-time interaction, randomization stratification (co-morbid GAD), and baseline score will be included as fixed effects, and center as a random effect. An unstructured variance-covariance matrix will be used in the MMRM model. The difference between each AZD6765 dose and placebo will be estimated at each scheduled assessment.

Additional secondary efficacy endpoints include remission (Yes=MADRS total score ≤10), response (Yes=≥50% reduction from baseline in MADRS total score), CGI-I score (≤2 vs. >2), sustained response (Yes=maintenance of response at all times between Week 3 and Week 8), and change from baseline in VAS total score, BSS total score (at Week 3), CGI-S score, HAM-A and HAM-D total scores, and QIDS-SR-16 total score.

For the continuous efficacy endpoints, ANCOVA models similar to that used for the primary analysis will be used with LOCF in the mITT analysis set. For the binary efficacy endpoints, a logistic model in which treatment, randomization stratification (co-morbid GAD) and baseline score are included as fixed effects will be used with LOCF in mITT analysis set. Also, several variables will be analyzed using the completers analysis set, including change from baseline in the MADRS total score, CGI-I, change from baseline in CGI-S, and sustained response.

For the secondary efficacy variables, each AZD6765 dose will be compared to placebo, but without any adjustment for multiplicity.

Descriptive statistics will be used to summarize all efficacy endpoints, including individual item scores.

13.2.3 Safety analyses

Adverse events will be coded using MedDRA. For each study treatment, numbers of events and crude incidence rates will be tabulated by preferred term and system organ class. An event that occurred 1 or more times on the date of, or subsequent to, randomization will contribute 1 observation to the numerator of the crude incidence rate. The denominator of the rate will comprise all randomized subjects exposed to the study treatment. If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences.

SAEs, AEs leading to death, and AEs leading to withdrawal of subjects will be tabulated for each treatment group. Commonly occurring AEs, ie, those which occur in 5% or more of the subjects in either treatment group, will be summarized using descriptive statistics.

All laboratory test results, vital signs, ECG results, weight, and BMI will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline. The proportions of subjects who have a weight gain ≥7% compared to baseline will be tabulated.

Suicidality measures based on the BSS and the C-SSRS will be summarized for each treatment group using descriptive statistics at each assessment.

13.2.4 Quality of life

For the Q-LES-Q-SF total score, change from baseline to Week 3 will be analyzed using ANCOVA models similar to that used for the primary analyses with LOCF in the mITT analysis set for Week 3.

Descriptive statistics will be used to summarize the Q-LES-Q-SF total score and all of the individual item scores.

13.3 Determination of sample size

A sufficient number of male and female subjects with MDD and a history of poor response to antidepressants between the ages of 18-65 years old inclusive will be screened to ensure that approximately 150 subjects are randomized into the study to obtain 135-140 evaluable subjects.

Based on the assumption of a treatment difference of 6 between each AZD6765 dose and placebo in the change from baseline to 3 weeks in the MADRS total score, and a standard deviation of 9, 45 evaluable subjects per treatment group will provide approximately 80% power with a multiplicity adjustment (ie, using Dunnett's procedure) and testing at the overall 2-sided α=5% level.

An evaluable subject is defined as one who has a non-missing MADRS total score at both baseline and at the 72-hour assessment. If a 10% early withdrawal rate is assumed, then 50 subjects per treatment group, for a total of 150 subjects, need to be randomized.

13.4 Interim analyses

No interim analysis for efficacy is planned.

13.5 Data safety monitoring board-Not applicable

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Clinical Study Protocol Appendix B

Drug Substance	AZD6765
Study Code	D6702C00009
Edition Number	1.0
Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalization

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

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

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

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

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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

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

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C	
Drug Substance	AZD6765
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Appendix C
IATA 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Cat A pathogens are eg. Ebola, Lassa fever virus

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

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Cat B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance	AZD6765
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Date	[redacted]

Appendix D
DSM-IV-TR Diagnostic Criteria For Major Depressive Disorder

1. DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER, SINGLE EPISODE

For and individual to be diagnosed with this Depressive Disorder, they must have experienced at least one Major Depressive Episode, but no Manic, Hypomanic, or Mixed Episodes.

Diagnostic criteria for 296.2x, Major Depressive Disorder, Single Episode

(a) Presence of a single Major Depressive Episode.

(b) The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

(c) There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.
Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode):

- Severity/Psychotic/Remission Specifiers
- Chronic
- With Catatonic Features
- With Melancholic Features
- With Atypical Features
- With Postpartum Onset

2. DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER, RECURRENT

For and individual to be diagnosed with this Depressive Disorder, they must have experienced at least one Major Depressive Episode, but no Manic, Hypomanic, or Mixed Episodes.

Diagnostic criteria for 296.3x Major Depressive Disorder, Recurrent

(a) Presence of two or more Major Depressive Episodes.
Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

(b) The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

(c) There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. Note: This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a general medical condition.

Specify (for current or most recent episode):

- Severity/Psychotic/Remission Specifiers
- Chronic
- With Catatonic Features
- With Melancholic Features
- With Atypical Features
- With Postpartum Onset

Specify:

- Longitudinal Course Specifiers (With and Without Inter-episode Recovery)
- With Seasonal Pattern

Criteria for a major depressive episode DSM-IV-TR

Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) or (2).

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (eg, appears tearful). Note: In children and adolescents, can be irritable mood.

2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3. significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.

4. Insomnia or Hypersomnia nearly every day

5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

6. fatigue or loss of energy nearly every day

7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The symptoms do not meet criteria for a Mixed Episode.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).

The symptoms are not better accounted for by Bereavement, ie, after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Criteria for a hypomanic episode DSM-IV-TR

1. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non depressed mood.

2. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

   - inflated self-esteem or grandiosity
   - decreased need for sleep (eg, feels rested after only 3 hours of sleep)
   - more talkative than usual or pressure to keep talking
   - flight of ideas or subjective experience that thoughts are racing

- distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)

- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

- excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

3. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

4. The disturbance in mood and the change in functioning are observable by others.

5. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

6. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).

Criteria for a mixed episode DSM-IV-TR

1. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period.

2. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

3. The symptoms are not due to the direct physiological effects of a substance (eg, an illicit drug, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).

Criteria for a manic episode DSM-IV-TR

1. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

2. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

   - inflated self-esteem or grandiosity, potentially including grandiose delusions

- decreased need for sleep (eg, feels rested after only 3 hours of sleep) or persistent difficulty falling asleep
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

3. The symptoms do not meet criteria for a Mixed Episode.

4. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

5. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).

Clinical Study Protocol Amendment	
Amendment Number	4
Drug Substance	AZD6765
Study Code	D6702C00009
Date	[redacted]
Protocol Dated	[redacted]

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

All centers.

The protocol for the study will not be amended as follows:

This Clinical Study Protocol (CSP) Amendment 4 will serve as a stand-alone amendment summary to the final approved revised CSP 2 dated [redacted].

The following changes were added to the protocol:

- A urine pregnancy test was added to the procedures currently required in the protocol.
- The effect of AZD6765 on embryo-fetal development.

As there are no other changes to the study design or study assessments and procedures, a revised (or amended) CSP and its accompanying amendment summary will not be provided.

Section of protocol affected:

A urine pregnancy test will be conducted at all infusion visits for all women of child-bearing potential (Visit 2/single-blind infusion, Visit 3/randomization, and Visit 4 through Visit 11), before the start of infusion. The urine pregnancy tests are in addition to the serum pregnancy tests currently being conducted (at visits specified by the protocol).

Site personnel must document that the urine pregnancy test was completed (this must include sample date and time) as well as the test results. A source document template page will be provided to assist the sites in collecting and documenting this information, as well as the lot number and expiration date of the pregnancy test.

If the urine sample cannot be collected or the urine pregnancy test is positive, the infusion must not be administered.

Section of protocol affected:

Section 2.5, Benefit risk/ethical assessment, 1st paragraph, page 23

Added the following text at the end of the 1st paragraph:

- Fetal skeletal malformations have been observed in embryo-fetal development studies in rats and rabbits. Although the clinical significance of this finding is unclear, every effort should be made to avoid pregnancies in the clinical study.

Reason for Amendment 4:

- The United States Food and Drug Administration (FDA) has requested that all women of child-bearing potential participating in this major depressive disorder study (D6702C00009) must have a urine pregnancy test prior to the start of each infusion (same day). This is in addition to the serum pregnancy tests currently being conducted. This request is not based on emergent findings; it is an additional precaution requested by the FDA to AstraZeneca.

- The effect of AZD6765 on embryo-fetal development was added to the protocol. Fetal skeletal malformations were observed in nonclinical studies conducted with AZD6765.

Persons who initiated the Amendment:

AstraZeneca AB, 151 85 Södertälje, Sweden.

Clinical Study Protocol Amendment No 4
Appendix A

Drug Substance	AZD6765
Study Code	D6702C00009
Edition Number	2.0
Date	[redacted]
Protocol Dated	[redacted]

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

I agree to the terms of this amendment.

AstraZeneca Research and Development site representative

[redacted]

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

I agree to the terms of this amendment.

AstraZeneca Research and Development site representativ [redacted]

QUINTILES SIGNATURE(S)

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

I agree to the terms of this amendment.

[redacted] **representative** [redacted]

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR

A Phase IIb, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Efficacy and Safety Study of Adjunctive AZD6765 in Subjects with Major Depressive Disorder (MDD) with at least Moderate Symptomatology and a History of Poor Response to Antidepressants

I agree to the terms of this amendment.

Centre No.: [redacted]

Signature: