AstraZeneca

Revised Clinical Study Protocol

Drug Substance	AZD6765
Study Code	D6702C00031
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase IIb Efficacy and Safety Study of Adjunctive AZD6765 in Patients with Major Depressive Disorder (MDD) and a History of Inadequate Response to Antidepressants

Sponsor: [redacted]

AstraZeneca Research and Development site representative [redacted]

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2			

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AstraZeneca

PROTOCOL SYNOPSIS

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

Principal Investigator

[redacted]

Study centres and number of subjects planned

This will be a global, multicenter study conducted at approximately 60 sites in the United States (US) and in other countries. Approximately 282 patients will be randomized into the study, resulting in 252 fully evaluable patients at Week 6 assuming a 10% loss of information at Week 6.

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

Objectives

Primary objective:

To evaluate the efficacy of AZD6765iv (AZD6765 Solution for Infusion, 0.5 mg/mL, or 1.0 mg/mL) given intravenously in 50 mg or 100 mg/infusion as adjunct to current antidepressant medication versus antidepressant medication + placebo as assessed by the change from baseline to Week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in patients with Major Depressive Disorder (MDD) (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision [DSM-IV-TR] 296.2x or 296.3x) who exhibited an inadequate response to 3 or more different antidepressant treatments during the patient's lifetime by history. Inadequate response is defined as persistent

symptoms that, as judged by the investigator, continue to meet the diagnostic criteria for a Major Depressive Episode (MDE) according to the DSM-IV-TR.

Secondary objectives:

To evaluate the efficacy of AZD6765iv 50 mg and 100 mg as adjunct to current antidepressant medication versus antidepressant medication + placebo in patients with MDD who exhibited an inadequate response to 3 or more different antidepressant treatments by history, as defined by:

- Change from baseline to Week 12 in MADRS total score
- Percentage of patients with sustained response from Week 6 to 12
- Change from baseline in MADRS total score
- Percentage of patients who are responders (defined as a ≥50% reduction from baseline on the MADRS total score)
- Percentage of patients who are remitted (defined as a ≤8 on the MADRS total score)
- Change from baseline in functional impairment as measured by the Sheehan Disability Scale (SDS) total score
- Change from baseline in severity of depressive symptoms as measured by Clinical Global Impression-Severity of Illness (CGI-S) scale
- Improvement of depressive symptoms as measured by Clinical Global Impression-Improvement (CGI-I) scale
- Change from baseline in severity of depressive symptoms as measured by Quick Inventory of Depressive Symptomology Self-Report 16-item scale (QIDS-SR-16) total score

To characterize the pharmacokinetics (PK) of AZD6765iv at 50 mg and 100 mg doses in patients with MDD utilizing a population PK approach.

Safety objectives:

- To assess the safety and tolerability of AZD6765iv as adjunct to current antidepressant medication versus antidepressant medication + placebo in the treatment of patients with inadequate response to antidepressant treatments as assessed by adverse events (AEs), vital signs, electrocardiogram (ECG), laboratory measures, the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Clinician Administered Dissociative States Scale (CADSS) total scores

- To assess any changes from baseline in cognition via CogState testing

Exploratory objectives:

- To conduct an exploratory analysis of whether family history of alcohol abuse and the γ-aminobutyric acid (GABA) A receptor alpha 2 (GABRA2) genes are involved in the efficacy of AZD6765iv treatment

- To conduct an exploratory analysis of whether AZD6765iv, as adjunct to current antidepressant medication versus antidepressant medication + placebo:

  – improves anxiety as measured by Hamilton Depression Rating Scale for Anxiety (HAM-A) total score

  – reduces suicidal ideation as measured by Sheehan Suicidality Tracking Scale (S-STS)

Study design

This will be a global, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase IIb efficacy and safety study of 2 dose groups conducted at approximately 60 sites in male and female outpatients between the ages of 18 and 70 years old, inclusive, with MDD and a lifetime history of inadequate response to 3 or more antidepressant treatments, 1 of which must include a current antidepressant medication.

At screening, a patient must be taking at least 1 antidepressant medication for a minimum of 4 weeks, and meet minimum scores of Hamilton Rating Scale for Depression (HAM-D-17) ≥24, CGI-S ≥5, and QIDS-SR ≥19. The patient must also meet these minimum ratings on the day of randomization. Randomization cannot occur until the treatment with the current antidepressant medication has lasted a minimum of 6 weeks.

Previous **antidepressant treatments** are defined as any of the following:

Antidepressant medications

Electroconvulsive therapy (ECT)

Transcranial Magnetic Stimulation (TMS)

Vagal Nerve Stimulation (VNS)

Inadequate response is defined as treatment with one of the above listed treatment options sustained for adequate dose and duration, after which the patient continues to meet DSM-IV-TR criteria for a MDE. The 3 or more different protocol-required inadequate responses can have occurred anytime during the life of the patient as documented by the Modified Antidepressant Treatment History Form (ATHF).

Allowed current antidepressant treatment options as well as the specified adequate dose and duration required are listed in Table 2 (primary antidepressant treatments) and Table 3 (adjunctive antidepressant treatments). In addition, Table 1 lists primary antidepressant treatments and their target dose and duration that may count toward the history of 3 inadequate responses. Medications listed in Table 1, but not in Table 2, may not be used as adjunct in the current trial (e.g. monoamine oxidase inhibitors [MAOIs]). These medications are either no longer marketed, despite having had proven efficacy, or are not allowed for safety reasons.

The study will consist of a screening period of up to 42 days (or ≤6 weeks). Patients will then be randomized to a 12-week, double-blind, outpatient infusion treatment period of AZD6765iv 50 mg, 100 mg, or placebo, followed by a 14-day follow-up visit. During the treatment period, patients will receive investigational product (IP), AZD6765iv, or placebo, as an adjunct to their existing allowed antidepressant medications (as specified in Table 2 and Table 3). The dose of the antidepressant medication should be stable for at least 4 to 6 weeks depending on the type of medication, prior to study entry and will not be changed after randomization.

Target subject population

The study will enroll male and female patients (aged 18 to 70 years inclusive) currently meeting criteria for a MDE and meeting lifetime criteria of MDD (single episode or recurrent), as confirmed by the Mini-International Neuropsychiatric Interview (MINI). A HAM-D-17 total score ≥24, CGI-S score ≥5, and a QIDS-SR-16 score ≥19 are required at: (i) screening (Visit 1), and (ii) at the baseline assessment before randomization (Visit 2).

Investigational product, dosage and mode of administration

All treatments will be given over 60 minutes and given once per day on non-consecutive days. The AZD6765iv 50 mg infusion will be given at a final volume of 100 mL at an infusion rate of 1.67 mL/min (0.833 mg/min) and the AZD6765iv 100 mg infusion will be given at a final volume of 100 mL at an infusion rate of 1.67 mL/min (1.667 mg/min). Patients will receive multiple infusions of AZD6765iv or placebo during the treatment period. There will be 3 infusions administered per week during Weeks 1 through 3 (1 per day on non-consecutive days), 1 infusion per week during Weeks 4 through 6, and 1 infusion every other week during Weeks 7 through 12 (ie, infusion to occur during Week 8, Week 10, and Week 12). Patients will remain on the same dose of all of their background psychoactive medication during the study, including the 14-day follow-up period.

Comparator, dosage and mode of administration

The comparator in this study is placebo (0.9% saline), which will also be administered intravenously. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min over 60 minutes. Patients assigned to the placebo treatment group will receive multiple infusions of placebo during the treatment period according to the same schedule as the patients assigned to the AZ6765iv dose groups.

Duration of treatment

Eligible patients will have a screening period of up to 6 weeks. Following the screening period, patients will enter a 12-week double-blind treatment period and a 14-day follow-up period.

Outcome variables:

- **Efficacy**

Primary outcome variable:

- Change from baseline to Week 6 in the MADRS total score

Secondary outcome variables:

- Change from baseline to Week 12 in the MADRS total score
- Percentage of patients with sustained response, defined as a ≥50% reduction from baseline in the MADRS total score at Week 6 and which is maintained through Week 12
- Change from baseline in the MADRS total score at each scheduled assessment
- Percentage of responders at each scheduled assessment where responders are defined as patients with a ≥50% reduction from baseline in MADRS total score
- Percentage of patients who are remitted at each scheduled assessment where remission is defined as MADRS total score ≤8
- Change from baseline in functional impairment at each scheduled assessment, as measured by the change from baseline in the SDS total score
- Change in severity of depressive symptoms at each scheduled assessment as measured by change from baseline in the CGI-S score
- Change in severity of depressive symptoms at each scheduled assessment as measured by the CGI-I response. Response in CGI-I is based on whether or not the CGI-I score is ≤2 (very much improved or much improved).
- Change from baseline in self-rated severity of depressive symptoms at each scheduled assessment as measured by QIDS-SR-16 total score

- **Safety**

- Adverse events (AEs)/serious adverse events (SAEs), including their severity
- AEs leading to treatment discontinuation or study withdrawal

- Suicidality as measured by AEs of suicidality, suicidal ideation, suicide attempts, and suicide completion
- Other significant AEs (OAEs), other AEs of special interest
- Change from baseline in physical examination results, weight, body mass index (BMI), vital signs, clinical laboratory test results, and ECG results
- Suicidality, as assessed by the C-SSRS
- Change from baseline in cognition as measured by a composite test score comprised of the following CogState test battery tasks: Detection task (DET), Identification task (IDN), One-card Learning task (OCL), and One-back task (OBK)
- Change in severity of dissociative symptoms at each scheduled assessment, as measured by change from baseline in the CADSS total scores

- **Exploratory**
  - Change in anxiety at each scheduled assessment as measured by HAM-A total score
  - Effect of family history of alcohol abuse and GABRA2 on change in MADRS total score and percentage of patients who respond at each scheduled time point
  - Change from baseline in suicidal ideation at each scheduled assessment as measured by change from baseline in S-STS

- **Pharmacokinetics**
  - AZD6765 plasma concentration levels (for population pharmacokinetics [PK] analysis)

- **Pharmacogenetics**
  - Exploratory analysis of the genes involved in the PK, pharmacodynamics (PD), safety, and tolerability related to AZD6765iv treatment may be performed. The polymorphism of genes that may be correlated with the disposition and response to AZD6765iv may be analyzed.

- **Biomarker analysis**
  - Serum samples for optional exploratory biomarker analysis

Statistical methods

Efficacy analyses will be based on the modified intent-to-treat (mITT) analysis set that will include all randomized patients, who received at least 1 dose of IP and who have a baseline MADRS total score assessment and at least 1 post-baseline MADRS total score classified according to their randomized treatment.

Safety and tolerability assessments will be based on the safety analysis set, which will include all randomized patients who are given the IP, and for whom any post-dose data are available, classified according to the treatment actually received.

The primary efficacy variable, change from baseline to Week 6 in the MADRS total score, will be analyzed using a Mixed Model Repeated Measures (MMRM) analysis of all of the post-baseline MADRS total scores through the end of the study (Week 14). The model will include treatment, visit, treatment by visit interaction, and the baseline MADRS baseline total score as fixed effects, and site as a random effect. Restricted Maximum Likelihood (REML) with an unstructured variance-covariance matrix will be used for estimation in the MMRM analysis. Each AZD6765iv dose will be compared with placebo.

Change from baseline in the MADRS total score at Week 12 and at the other scheduled visits will be assessed using the MMRM analysis for the primary efficacy variable. The MMRM analysis of the MADRS total score will be repeated on the Per-protocol (PP) analysis set to assess the robustness of the results. This PP analysis set will include only those mITT patients who have no significant protocol deviations and who received the treatment to which they were randomized.

For the other continuous secondary efficacy variables (change from baseline in the CGI-S score, the SDS total score, the HAM-A total score, and the QIDS-SR-16 total score at each scheduled assessment), the same MMRM approach as for the primary efficacy variable will be used for the analyses.

For the binary secondary efficacy variable with only a single post-baseline assessment (sustained response), the analysis will be performed using logistic regression with independent variables of treatment and the baseline MADRS total score.

For the binary secondary efficacy variables with multiple post-baseline assessments (response, remission, and CGI-I response), the analysis will be performed using a generalized linear model of the repeated measures. A logit link function will be used and the statistical inferences will be based on Generalized Estimating Equations (GEE). Independent variables will be treatment and a baseline measurement related to the dependent analysis variable. For response and remission, the baseline MADRS total score will be used as the baseline measurement; for CGI-I response, the baseline CGI-S score will be used.

For demonstration of superiority for the primary efficacy variable (change from baseline to Week 6 in the MADRS total score) and the 2 key secondary efficacy variables (change from baseline to Week 12 in the MADRS total score and sustained response), a gate-keeping

procedure with recycling approach (Burman et al 2009) will be used to control the overall family-wise error rate for comparisons of the 2 AZD6765iv doses with placebo and over the 3 endpoints (the primary endpoint and the 2 key secondary endpoints). Superiority of AZD6765iv over placebo will be shown if, following the gate-keeping procedure, either the 50 mg or 100 mg dose group demonstrates significantly better efficacy than the placebo group for at least the primary efficacy variable. No multiplicity adjustments will be made for the other secondary efficacy variables.

The exploratory variables of continuous and binary types will be evaluated the same way as for the secondary efficacy variables.

Descriptive statistics will be used to present the safety outcomes including incidences and severity of AEs and SAEs; incidences of AEs leading to treatment discontinuation and study withdrawal, incidences of AEs associated with suicidality, and incidences of OAEs; changes from baseline in physical examination results, weight, BMI, vital signs, clinical laboratory test results, and ECG results; suicidality as assessed by C-SSRS; and changes from baseline in the CADSS total scores.

For exploratory purposes, the impact of family history of alcoholism and pharmacogenetic biomarkers such as the GABRA2 gene on the primary endpoint and sustained response will be evaluated.

The results of the PK and pharmacogenetic analyses will be presented in reports separate from the clinical study report.

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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 6.4.1)
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
AST	aspartate transaminase
ATHF	Antidepressant Treatment History Form
$AUC_{(0-24)}$	area under curve 0 hr to 24 hrs
AZDD	AstraZeneca Drug Dictionary
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
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
CLIA	Clinical Laboratory Improvements Amendment
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
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
CV	coefficient of variation
DAE	discontinuation due to adverse event
DET	Detection task (CogState Battery)
DM	data management

Abbreviation or special term	Explanation
DNA	deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
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
eCRF	electronic case report form
ECT	electroconvulsive therapy
eDC	electronic data capture
EDTA	ethylenediamine tetraacetic acid
[redacted]	[redacted]
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GABRA2	GABA A receptor alpha 2
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GMP	Good Manufacturing Practice
hr	hour
HAM-A	Hamilton Depression Rating Scale for Anxiety
HAM-D-17	Hamilton Rating Scale for Depression
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high density lipoprotein
$HgbA_{1c}$	glycosylated hemoglobin
HIV	human immunodeficiency virus
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICD-10	International Classification of Diseases and Related Health Problems (10^{th} edition)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDN	Identification task (CogState Battery)

Abbreviation or special term	Explanation
IEC	Institutional Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
iv	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K_i	inhibition constant
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LIMS	Laboratory Information Management System
LOCF	last observation carried forward
LSM	least squares mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MCAR	missing completely at random
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
min	minute
MINI	Mini-International Neuropsychiatric Interview
mITT	Modified intent-to-treat
MMRM	Mixed Model Repeated Measures
MNAR	missing not at random
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 patient from study treatment; see definition in Section 11.2.1)
OBK	One-back task (CogState Battery)

Abbreviation or special term	Explanation
OCL	One-card Learning task (CogState Battery)
PCP	phencyclidine
PD	pharmacodynamics
PGx	pharmacogenetics
PI	principal investigator
PK	pharmacokinetics
PP	Per-protocol
PRO	patient-reported outcome
QIDS-SR-16	Quick Inventory of Depressive Symptomatology Self-Report 16-item scale
REML	Restricted Maximum Likelihood
rTMS	repetitive transcranial magnetic stimulation
SAE	serious adverse event (see definition in Section 6.4.2)
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Sheehan Disability Scale
SDV	source data verification
SNRIs	serotonin and norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
S-STS	Sheehan Suicide Tracking Scale
S-β-hCG	serum beta human chorionic gonadotropin pregnancy test
T_0	time before start of infusion
T_1	at the end of infusion
T_2	at least 1 hour after the end of infusion
T_4	at least 3 hours after the end of infusion
TEAE	treatment-emergent adverse event
THC	tetrahydrocannibinol
TMS	Transcranial Magnetic Stimulation
TSH	thyroid-stimulating hormone
UDS	urine drug screen
ULN	upper limit of normal
US	United States
VNS	vagal nerve stimulation

Abbreviation or special term	Explanation
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

AZD6765 is an N-methyl-D-aspartate (NMDA) receptor open-channel blocker undergoing evaluation as therapy for Major Depressive Disorder (MDD). Unlike standard antidepressants that may work by altering levels of neuromodulators such as serotonin, norepinephrine, and dopamine, NMDA-receptor antagonists may achieve an antidepressant effect by directly altering excitatory neurotransmission within brain structures involved in goal-directed behavior and emotional arousal. Although the precise mechanisms linking changes in glutamatergic transmission to antidepressant efficacy are unknown, converging evidence supports an emerging hypothesis whereby low doses of NMDA antagonists preferentially inhibit NMDA receptors on γ-aminobutyric acid (GABA)-ergic interneurons resulting in a net increase in glutamate synaptic transmission in brain regions where activity is chronically suppressed in MDD.

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 emergent reactions, ie, psychological manifestations—typically of short-term duration—that vary from pleasant dream-like states to emergent delirium.

However, 2 studies with ketamine (Berman et al 2000, Zarate et al 2006) showed antidepressant effects in patients with treatment-resistant depression. An additional study (aan het Rot 2010) suggested the feasibility of multiple doses of intravenous (iv) ketamine for the acute treatment of treatment-resistant depression. These findings encouraged AstraZeneca to further develop AZD6765 for the treatment of MDD.

AZD6765 was originally developed as an iv treatment for stroke and sleep apnea because of neuroprotective and antiepileptic properties demonstrated in early nonclinical studies. Although this development did not expand beyond Phase IIa studies, the results of the 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 indications, including MDD.

The current formulation of AZD6765 in the study will be a ready-to-use Solution for Infusion at 0.5 mg/mL, 1.0 mg/mL in a 100 mL bottle, which corresponds to 50 mg or 100 mg of AZD6765 dihydrochloride.

1.1.1 Drug-drug interactions

1.1.1.1 Effect of concomitant medicines on systemic exposure of AZD6765

Multiple routes of clearance (renal and hepatic) and multiple enzymes are involved in the clearance of AZD6765 (CYP1A2, CYP2C19, CYP3A4/5, CYP2B6, and CYP2D6). Hence, the potential for AZD6765 to be subject to significant drug-drug interaction is low.

1.1.1.2 Effect of AZD6765 on systemic exposure of concomitant medicines

AZD6765 exhibited minimal inhibitory effect towards human CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2E1 at concentrations up to 14.9 μg/mL (75.1 μM). AZD6765 competitively inhibited CYP2D6 and CYP3A4/5 with inhibition constant (K_i) values of 12.7 μg/mL (64.0 μM) and 5.35 μg/mL (27.0 μM), respectively. Results from a completed clinical drug-drug interaction study (Study D6702C00008) showed that multiple daily iv infusion doses of AZD6765 at 150 mg had no effect on the PK of midazolam, a CYP3A4 substrate. Hence, AZD6765 at proposed iv doses of 50 mg and 100 mg in future studies is not likely to be a perpetrator of CYP-mediated drug-drug interaction. Population PK analysis of exposure in Phase IIb studies indicated that between patient variability in exposure was small (<25% coefficient of variation [CV]) and the PK parameters were influenced mostly by body weight indices.

Pharmacokinetic drug-drug interaction potential caused by adjunct administration of concomitant medicines and AZD6765 is low.

1.1.2 Preliminary human experience

1.1.2.1 Safety and adverse events

AZD6765 has been administered to >500 subjects and patients across 15 clinical studies: 10 Phase I studies (healthy subjects and subjects with renal impairment), 4 Phase IIa studies (patients with stroke, sleep apnea, or MDD), and 1 Phase IIb study (Study D6702C00009) adjunct treatment of MDD). Treatment included single iv infusions (dose range: 1 mg to 350 mg) and multiple iv infusions (loading doses between 120 mg and approximately 460 mg plus maintenance doses of up to 120 mg every 8 hours for 3 days; 100 mg or 150 mg 3 times weekly for 3 weeks).

The most common adverse events (AEs) are dizziness and increase in blood pressure (BP) (both transient), and occasional orthostatic hypotension around the time of the infusion. Dizziness was the single most commonly reported AE in Phase I studies, although it was not necessarily dose related in all studies. The AEs possibly related to dysequilibrium (eg, balance disorder, feeling drunk, blurred vision) were also reported in Phase I studies, although no clear increase in accidental injury or falls was noted. Single case reports of vertigo and hyperacusis were also observed in these studies. Other central nervous system (CNS)-type AEs from Phase I studies included headache, somnolence, asthenia, impaired concentration, and various dysesthesias. Nausea and vomiting were also reported. Safety parameters from Phase I studies in healthy elderly subjects and subjects with renal impairment were qualitatively similar to that seen in other Phase I studies.

Analysis of Phase I vital signs demonstrated increased BP associated with AZD6765 in several studies; although, this did not generally appear to result in clinically meaningful events. Of note, AEs related to orthostatic decreases in BP have also been observed with AZD6765 in Phase I studies, which in some cases were associated with AEs related to syncope or presyncope (all of which recovered with conservative treatment).

AZD6765 up to a dose of 150 mg was well tolerated in patients with MDD. Again, the most common AEs were dizziness and increased BP, both transient. There were few AEs related to dissociative effects or euphoria.

AZD6765 has not been associated with clinically significant changes in clinical chemistry or hematology laboratory values or electrocardiogram (ECG) parameters.

1.1.2.2 Pharmacokinetics and product metabolism in humans

Following a constant iv infusion of up to 1 h, AZD6765 maximum plasma concentration level is reached at the end of infusion. Thereafter, the plasma concentration levels initially decrease rapidly followed by a slower decrease; hence, the disposition of AZD6765 can be characterized as multiphasic with an initial distribution phase and a later elimination phase. AZD6765 is slowly cleared from the body with a total clearance of about 9.2 L/h (0.13 L/h/kg) and a terminal elimination half-life that range from 11 hr to 14 hr. The PK of AZD6765 is linear in the dose range studied (1 mg to 160 mg) and is similar between elderly subjects and healthy adult males as well as between Japanese and Caucasian subjects. Since renal clearance is one of the major routes of elimination (accounting for approximately one quarter of total clearance), mild-to-moderate renal impairment had some effects on the PK of AZD6765.

Consistent with being a low clearance compound, AZD6765 showed a low degree of metabolism in humans. The unchanged parent compound accounted for >65% of the area under curve 0 hr to 24 hrs ($AUC_{(0-24)}$) of the total plasma radioactivity. The major metabolites in the plasma were glucuronic acid conjugates of carbamic acid, para-hydroxy and para-hydroxycarbamic acid metabolites.

1.1.2.3 Clinical efficacy

In the first MDD study (D6702C00001), 34 patients with a history of inadequate response to an adequate course of at least 2 antidepressants were randomly assigned to single 1-hour infusions of AZD6765iv 100 mg (n=16) or placebo (n=18). AZD6765 did not meet the primary endpoint of statistical significance at 24 hours as measured by change from baseline in total Montgomery-Åsberg Depression Rating Scale (MADRS) score. However, at 72 hours, AZD6765 showed a statistically significant superiority (p=0.089) over placebo in change from baseline in total MADRS score.

Study D6702C00009 was a Phase IIb, multicenter, double-blind, randomized, placebo-controlled, parallel group, outpatient study conducted in the United States to determine the effect of AZD6765 on symptom improvement in patients with MDD who had a history of poor response to antidepressants. The study consisted of a 3-week outpatient treatment

period, and a 5-week outpatient follow-up period. Male or female patients (18 to 65 years of age, inclusive) diagnosed with MDD, single episode or recurrent, were randomly assigned to receive AZD6765 at doses of 100 mg or 150 mg, or placebo 3 times per week on non-consecutive days for 3 weeks. Patients treated with AZD6765 (100 mg or 150 mg per infusion) exhibited a significantly greater antidepressant effect than the placebo-treated patients, as assessed by the primary efficacy variable change from baseline to Week 3 in the MADRS total score. Efficacy was numerically better for 100 mg than 150 mg at all visits, as measured by difference from placebo in change from baseline in total MADRS score. Onset of efficacy was seen at 2 weeks for 100 mg (least squares mean [LSM] difference from placebo=4.2, 95% confidence interval [CI] -7.50, -0.99, 2-sided p=0.011). Persistence of efficacy after stopping infusions was sustained for at least 2 weeks particularly for the 100 mg dose. For instance, 2 weeks after stopping infusions for 100 mg, the MADRS difference against placebo was substantial (LSM difference=-4.9, 95% CI -8.64, -1.24, 2-sided p=0.009 at 2-sided 20% significance level).

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

1.2 Research hypothesis

The primary goal of this study is to test the hypothesis that adjunctive AZD6765iv will demonstrate superiority over adjunctive placebo in decreasing depression symptoms as measured by change from baseline to Week 6 in the MADRS total score.

A secondary goal of the study is to determine whether continued administration of AZD6765iv every other week sustains efficacy to Week 12.

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

1.3 Rationale for conducting this study

The overall rationale for this study is to assess the acute and sustained antidepressant effect of adjunctive AZD6765iv in patients with MDD who have a history of inadequate response to currently available antidepressants. Inadequate response is defined as persistent symptoms that, as judged by the investigator, continue to meet the diagnostic criteria for a Major Depressive Episode according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR).

A previous study (Study D6702C00009) demonstrated an acute antidepressant effect of AZD6765 when administered 3 times per week for 3 weeks. However, the effect was not sustained beyond 2 weeks after the last infusion. Therefore in the current study, following the initial 3 infusions per week for 3 weeks dosing regimen, the dose administration will be tapered to once-weekly infusions during Weeks 4 to 6 and once every other weekly infusions during Weeks 8 to12 (Week 7 has no infusion scheduled) in an effort to sustain the antidepressant effects of AZD6765.

In an attempt to expand the 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 50 mg and 100 mg given in the treatment of MDD.

1.4 Benefit/risk and ethical assessment

Despite the various pharmacological interventions approved for the treatment of MDD, many patients have an inadequate response to either first-line treatment or to subsequent switching and augmentation treatment strategies across different classes of antidepressant medications. It is estimated that approximately 20% of patients with MDD have an inadequate response to 2 sequential antidepressant studies (Rush et al 2003) and in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, after unsuccessful treatment with a selective serotonin reuptake inhibitor (SSRI), approximately 70% of patients had an inadequate response to achieve remission despite augmentation with a second agent (Trivedi et al 2006). It is clear that even after multiple treatment cycles, existing therapies fail to achieve remission in a substantial number of patients.

For patients who have had an inadequate response to multiple courses of different classes and combinations of pharmacological treatments, there are few treatment options remaining. These patients may find themselves on many different pharmacological treatments including an SSRI, lithium, and a benzodiazepine. Current clinical practice and treatment guidelines generally support this group of patients being offered electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or vagal nerve stimulation (VNS) as final treatment options (NICE 2010, American Psychiatric Association 2010).

Ketamine, a high affinity non-selective NMDA antagonist, has been evaluated in the treatment of MDD in several independent randomized placebo controlled studies. Studies by Berman and colleagues (Berman et al 2000) and Zarate (Zarate et al 2006) demonstrated that a single sub-anesthetic dose of iv ketamine (0.5 mg/kg infused over 40 minutes) in unipolar depression could produce rapid, albeit short-lived antidepressant efficacy. However, both of these studies also demonstrated ketamine's propensity to cause euphoric and psychotomimetic side effects within 2 to 4 hours following iv administration.

Building upon the results of the positive NMDA clinical studies in MDD, AstraZeneca began its clinical investigation of AZD6765, a moderate affinity non-selective NMDA antagonist in treatment refractory MDD patients. The results of the single dose, proof-of-principle (Phase IIa) study, conducted as a monotherapy agent in patients with a history of inadequate response to antidepressants, showed comparable efficacy as those observed in previous studies with ketamine and CP-101,606, a NR2b antagonist, without the psychotomimetic effects. Following the results of the Phase IIa study, AstraZeneca conducted the Phase IIb study in severely depressed, highly refractory patients who had failed multiple medications in the past. The study was conducted in the adjunct setting, and utilized repeat dosing of AZD6765. Similar to the NMDA studies described above, the Phase IIb study demonstrated robust efficacy. Many of the patients in this study had an inadequate response to 3 or more

antidepressants in the past and were not deriving sufficient benefit from their current regimen of antidepressants. A similar population will be studied in this clinical study.

AZD6765 risk is based on previous clinical experience and non-clinical safety and toxicology studies. The spectrum of potential risks could include mild, transient elevations in BP, transient dizziness, and less frequent episodes of orthostatic hypotension. The clinical relevance of embryofetal developmental toxicity seen in rats and rabbits and neuronal vacuolation and degeneration seen at high doses (125 mg/kg) in rats is unknown. However, to mitigate any potential risks or embryofetal toxicity, all women of childbearing potential (WOCBP) will be required to use approved birth control measures and test negative on a urine pregnancy test prior to each infusion of AZD6765. To date, there has been no evidence of long-lasting neurological sequelae or cognitive impairment in the ≥500 subjects and patients who have received AZD6765. In order to further document the safety of AZD6765 in this regard, we plan to conduct cognitive testing in this study.

The frequency and intensity of behavioral and cognitive effects were much lower than that seen with other NMDA antagonists such as ketamine or phencyclidine (PCP). (This was confirmed in small head-to-head EEG and functional magnetic resonance imaging studies of ketamine and AZD6765.) 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 observed during or after a 100-mg infusion in 16 patients with MDD in the single-dose study. In the 3-week study in patients with MDD, a small number of patients had psychosis-related AEs; most of these cases were related to limitations of the classification system. In addition, while there were 3 cases of euphoria, there were no cases of truly diagnosed mania or hypomania upon AZD6765 exposure. Nevertheless, until more is known, it will be important to exclude patients with a history of bipolar disorder or psychosis. There were no treatment-group differences in suicidal ideation and suicidal behavior according to the Columbia-Suicide Severity Rating Scale. In fact, AZD6765 tended to reduce suicidal ideation according to the Beck Scale for Suicide Ideation after 3 weeks of treatment.

In clinical studies, AZD6765 has shown efficacy in patients with MDD who have had an inadequate response to multiple treatments by history. There was a signal for reduction in depressive symptoms seen at 72 hours after infusion of 100 mg AZD6765 in the Phase IIa single-dose study in patients with MDD. AZD6765 showed statistical superiority over placebo in change from baseline in total MADRS score at 72 hours and in depressive symptom response defined as a reduction of at least 50% from baseline in MADRS total score. The Phase IIb study with a 3-week treatment period in patients with MDD treated with AZD6765 adjunctively with their current antidepressant treatment also showed statistical superiority for both AZD6765 100 mg and 150 mg (2-sided $p<0.05$) for MADRS change from baseline versus placebo at Week 3 in the primary statistical analysis.

The potential to achieve antidepressant effects in patients refractory to standard antidepressant treatment at a well-tolerated dose supports a positive benefit-to-risk ratio. The full benefit-to-risk assessment will depend on clinical efficacy and safety data from future studies in patients with depression.

Please refer to the IB for additional information regarding risks.

2. STUDY OBJECTIVES

2.1 Primary objective

To evaluate the efficacy of AZD6765iv (50 mg or 100 mg/infusion) as adjunct to current antidepressant medication versus antidepressant medication + placebo as assessed by the change from baseline to Week 6 in the MADRS total score in patients with MDD (DSM-IV-TR 296.2x or 296.3x) who exhibited an inadequate response to 3 or more different antidepressant treatments by history. Inadequate response is defined as persistent symptoms that, as judged by the investigator, continue to meet the diagnostic criteria for a Major Depressive Episode (MDE) according to the DSM-IV-TR.

2.2 Secondary objectives

To evaluate the efficacy of AZD6765iv 50 mg and 100 mg as adjunct to current antidepressant medication versus antidepressant medication + placebo in patients with MDD who exhibited an inadequate response to 3 or more different antidepressant treatments by history, as defined by:

- Change from baseline to Week 12 in MADRS total score
- Percentage of patients with sustained response from Week 6 to 12
- Change from baseline in MADRS total score
- Percentage of patients who are responders (defined as a ≥50% reduction from baseline on the MADRS total score)
- Percentage of patients who are remitted (defined as a ≤8 on the MADRS total score)
- Change from baseline in functional impairment as measured by the Sheehan Disability Scale (SDS) total score
- Change from baseline in severity of depressive symptoms as measured by Clinical Global Impression-Severity of Illness (CGI-S) scale
- Improvement of depressive symptoms as measured by Clinical Global Impression-Improvement (CGI-I) scale
- Change from baseline in severity of depressive symptoms as measured by Quick Inventory of Depressive Symptomology Self-Report 16-item scale (QIDS-SR-16) total score

To characterize the PK of AZD6765iv at 50 mg and 100 mg doses in patients with MDD utilizing a population PK approach.

2.3 Safety objectives

- To assess the safety and tolerability of AZD6765iv as adjunct to current antidepressant medication versus antidepressant medication + placebo in the treatment of patients with inadequate response to antidepressant treatments as assessed by AEs, vital signs, ECG, laboratory measures, the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Clinician Administered Dissociative States Scale (CADSS) total scores

- To assess any changes from baseline in cognition via CogState testing

2.4 Exploratory objectives

- To conduct an exploratory analysis of whether family history of alcohol abuse and the GABA A receptor alpha 2 (GABRA2) genes are involved in the efficacy of AZD6765iv treatment

- To conduct an exploratory analysis of whether AZD6765iv, as adjunct to current antidepressant medication versus antidepressant medication + placebo:

  – improves anxiety as measured by Hamilton Depression Rating Scale for Anxiety (HAM-A) total score

  – reduces suicidal ideation as measured by Sheehan Suicidality Tracking Scale (S-STS)

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This will be a global, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase IIb efficacy and safety study of 2 dose groups conducted at approximately 60 sites in male and female outpatients between the ages of 18 and 70 years old, inclusive, with MDD and a lifetime history of inadequate response to 3 or more antidepressant treatments, 1 of which must include a current antidepressant medication.

At screening, a patient must be taking at least 1 antidepressant medication for a minimum of 4 weeks, and meet minimum scores of Hamilton Rating Scale for Depression (HAM-D-17) ≥24, CGI-S ≥5, and QIDS-SR ≥19. The patient must also meet these minimum ratings on the

day of randomization. Randomization cannot occur until the treatment with the current antidepressant medication has lasted a minimum of 6 weeks.

Previous **antidepressant treatments** are defined as any of the following:

Antidepressant medications

ECT

Transcranial Magnetic Stimulation (TMS)

Vagal Nerve Stimulation (VNS)

Inadequate response is defined as treatment with one of the above listed treatment options sustained for adequate dose and duration, after which the patient continues to meet DSM-IV-TR criteria for a MDE. The 3 or more different protocol-required inadequate responses can have occurred anytime during the life of the patient as documented by the Modified Antidepressant Treatment History Form (ATHF).

Allowed current antidepressant treatment options as well as the specified adequate dose and duration required are listed in Table 2 (primary antidepressant treatments) and Table 3 (adjunctive antidepressant treatments). In addition, Table 1 lists primary antidepressant treatments and their target dose and duration that may count toward the history of 3 inadequate responses. Medications listed in Table 1, but not in Table 2, may not be used as adjunct in the current trial (e.g. monoamine oxidase inhibitors [MAOIs]). These medications are either no longer marketed, despite having had proven efficacy, or are not allowed for safety reasons.

The following guidelines of prior treatments given at doses listed in Table 1 and Table 3 or higher apply to fulfill inadequate response criteria:

1. Treatment with primary antidepressant medications must be 6 weeks in duration.

– Example: Sertraline 100 mg for 6 weeks qualifies as 1 antidepressant treatment

2. Adjunctive medication added after 6 weeks of adequate treatment with a primary antidepressant medication, must be given for a minimum of 4 or 6 weeks (depending on adjunctive agent).

– Example A: Sertraline 100 mg for 6 weeks. Bupropion 150 mg added to sertraline for an additional 6 weeks fulfills criteria for 2 adequate antidepressant treatments.

– Example B: Sertraline 100 mg for 6 weeks. Aripiprazole 10 mg added to sertraline for an additional 6 weeks. This fulfills criteria for 2 adequate antidepressant treatments.

- Example C: Sertraline 100 mg for 6 weeks. Lithium 300 mg added to sertraline for an additional 4 weeks. This fulfills criteria for 2 adequate antidepressant treatments.

3. Two medications given together (ie, started at the same time point) must be given for 6 weeks.

- Example A: Sertraline 100 mg and bupropion 150 mg started together, given for 6 weeks, qualifies as 2 antidepressant treatments.

- Example B: Sertraline 100 mg and lithium 300 mg started together, given for 6 weeks, qualifies as 2 antidepressant treatments.

During the screening visit, arrangements should be made with the patient to obtain the necessary documentation from previous inadequate responses. (e.g. contact information of previous treating physicians and signed releases that may be necessary to obtain written medical records). Acceptable evidence of previous inadequate responses may include verbal or written communication with the treating physician (documented in the source document) or copies of medical or pharmacy records.

Table 1 Adequate dose and duration of prior antidepressant treatments

Treatment	Minimum adequate dose	Minimum adequate duration
Tricyclic/tetracyclics		
amitriptyline	100 mg	6 weeks
clomipramine	100 mg	6 weeks
desipramine	100 mg	6 weeks
doxepin	100 mg	6 weeks
imipramine	100 mg	6 weeks
maprotiline	100 mg	6 weeks
nomifensine	50 mg	6 weeks
nortriptyline	50 mg	6 weeks
protriptyline	30 mg	6 weeks
trimipramine	100 mg	6 weeks
SSRIs		
citalopram	20 mg	6 weeks
escitalopram	10 mg	6 weeks
fluoxetine[a]	20 mg	6 weeks
fluvoxamine	100 mg	6 weeks
paroxetine[b]	20 mg	6 weeks
sertraline	50 mg	6 weeks
vilazodone	40 mg	6 weeks
SNRIs		
desvenlafaxine	50 mg	6 weeks
duloxetine	40 mg	6 weeks
venlafaxine	75 mg	6 weeks
Other		
agomelatine	25 mg	6 weeks
amoxapine	200 mg	6 weeks
bupropion[c]	150 mg	6 weeks
fluoxetine /olanzapine (Symbyax™)	6/25 mg	6 weeks
mirtazapine	15 mg	6 weeks
nefazodone	150 mg	6 weeks
trazodone	200 mg	6 weeks

Table 1 Adequate dose and duration of prior antidepressant treatments

Treatment	Minimum adequate dose	Minimum adequate duration
MAOIs		
isocarboxazid	30 mg	6 weeks
moclobemide	300 mg	6 weeks
phenelzine	30 mg	6 weeks
selegiline transdermal	6 mg/24 h	6 weeks
tranycypromine	30 mg	6 weeks
Brain stimulation therapies		
VNS	Any stimulation schedule	12 months
ECT	Bilateral or unilateral	8 treatments
TMS	Left dorsolateral: 5 hz, 100% motor threshold, 1600 pulses per session	8 treatments

ECT electroconvulsive therapy; MAOI monoamine oxidase inhibitor; SNRIs serotonin and norepinephrine reuptake inhibitors; SSRI selective serotonin reuptake inhibitors; TMS Transcranial Magnetic Stimulation; VNS vagal nerve stimulation

[a] Fluoxetine – all formulations are acceptable that are generally equivalent to fluoxetine 20 mg daily.

[b] Paroxetine – all formulations are acceptable that are generally equivalent to paroxetine 20 mg daily.

[c] Bupropion – all formulations are acceptable that are generally equivalent to bupropion 150 mg HCl daily.

Note: This list is not exhaustive, and treatment situations that do not correspond to this table may be present. Please contact AstraZeneca or AstraZeneca's representative for approval if other primary antidepressant treatments require consideration.

Note: These primary antidepressants can also be used as adjunct antidepressants when added to other primary antidepressants.

Table 2 Adequate dose and duration of allowed current primary antidepressant treatments

Treatment	Minimum adequate dose	Minimum adequate duration
Tricyclic/tetracyclics		
amitriptyline	100 mg	6 weeks
clomipramine	100 mg	6 weeks
desipramine	100 mg	6 weeks
doxepin	100 mg	6 weeks
imipramine	100 mg	6 weeks
maprotiline	100 mg	6 weeks
nortriptyline	50 mg	6 weeks
protriptyline	30 mg	6 weeks
trimipramine	100 mg	6 weeks
SSRIs		
citalopram	20 mg	6 weeks
escitalopram	10 mg	6 weeks
fluoxetine[a]	20 mg	6 weeks
fluvoxamine	100 mg	6 weeks
paroxetine[b]	20 mg	6 weeks
sertraline	50 mg	6 weeks
vilazodone	40 mg	6 weeks
SNRIs		
desvenlafaxine	50 mg	6 weeks
duloxetine	40 mg	6 weeks
venlafaxine	75 mg	6 weeks
Other		
agomelatine	25 mg	6 weeks
amoxapine	200 mg	6 weeks
bupropion[c]	150 mg	6 weeks
fluoxetine /olanzapine (Symbyax™)	6/25 mg	6 weeks
mirtazapine	15 mg	6 weeks
nefazodone	150 mg	6 weeks
trazodone	200 mg	6 weeks

[redacted]

[a] Fluoxetine – all formulations are acceptable that are generally equivalent to fluoxetine 20 mg daily.
[b] Paroxetine – all formulations are acceptable that are generally equivalent to paroxetine 20 mg daily.
[c] Bupropion – all formulations are acceptable that are generally equivalent to bupropion 150 mg HCl daily.

Note: This list is not exhaustive, and treatment situations that do not correspond to this table may be present. Please contact AstraZeneca or AstraZeneca's representative for approval if other primary antidepressant therapies require consideration.

Note: These primary antidepressants can also be used as adjunct antidepressants when added to other primary antidepressants.

Table 3 Adequate dose and duration of allowed prior or current adjunctive antidepressant treatments

Treatment	Minimum adequate dose	Minimum adequate duration
Atypical antipsychotics		
aripiprazole	2 mg	6 weeks
olanzapine	5 mg	6 weeks
quetiapine	150 mg	6 weeks
risperidone	2 mg	6 weeks
Other		
buspirone	15 mg	4 weeks
lithium	300 mg	4 weeks
stimulants	any dose	4 weeks
thyroid supplements (triiodothyronine [T_3] only)	any dose	4 weeks

Note: This list is not exhaustive, and limited existing research on adjunctive therapies may not adequately address all treatment situations. Please contact AstraZeneca or AstraZeneca's representative for approval if other adjunctive therapies require consideration.

A sufficient number of male and female outpatients will be screened to ensure that approximately 282 patients are randomized into the study to obtain approximately 252 required evaluable patients at Week 6. Approximately 60 sites will participate in the study.

The study will consist of a screening period of up to 42 days (or ≤6 weeks). Patients will then be randomized to a 12-week, double-blind, placebo-controlled, outpatient infusion treatment period of AZD6765iv 50 mg, 100 mg, or placebo, followed by a 14-day follow-up visit. During the treatment period, patients will receive the investigational product (IP), AZD6765iv or placebo as an adjunct to their existing allowed antidepressant medications, as specified in Table 2 and Table 3. The dose of the antidepressant medication should be stable for at least 4 to 6 weeks depending on the type of medication, prior to study entry and will not be changed after randomization including the 14-day follow-up period.

At Visit 1 and again before randomization at Visit 2, assessments will be conducted to ensure that the HAM-D-17 is ≥24, CGI-S is ≥5, and QIDS-SR-16 is ≥19. The HAM-D-17 and a review of the patient's prior antidepressant therapy will also be conducted prior to randomization and after medical clearance. If the patient does not meet the study entry criteria at Visit 2, the patient will be considered a screen failure and will not be randomized to the study. Patients who qualify will receive baseline clinical assessments of MADRS, HAM-A, S-STS, and CogState, and be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms:

- **Treatment A:** AZD6765iv 50 mg (AZD6765 Solution for Infusion, 0.5 mg/mL) by iv infusion
- **Treatment B:** AZD6765iv 100 mg (AZD6765 Solution for Infusion, 1.0 mg/mL) by iv infusion
- **Treatment C:** Placebo (0.9% sodium chloride [normal saline] solution for injection) by iv infusion

Patients will receive multiple infusions of AZD6765iv 50 mg or 100 mg, or placebo saline during the 12-week study treatment period and must be treated as outpatients during the entire course of the study. Patients will undergo the study procedures and assessments at designated visits per the study assessments (Table 4). Patients will be encouraged to eat and drink within 4 hours prior to infusion to reduce the risk of orthostatic hypotension.

The patient's depression and suicidality (suicide risk) will be assessed by the following instruments: Mini-International Neuropsychiatric Interview (MINI) (at screening), QIDS-SR-16, HAM-D-17 (screening and randomization only), MADRS, Columbia-Suicide Severity Rating Scale (C-SSRS), HAM-A, S-STS, CGI-S, and CGI-I. Dissociative symptoms will be assessed by Clinician Administered Dissociative States Scale (CADSS). The patient's quality of life will be assessed by the self-reported SDS. Cognitive functioning will be assessed using a battery of 4 tests of CogState ClinicalTrials (CogState, Ltd., New Haven, CT). A HAM-D-17 and a review of the patient's prior antidepressant treatment will be conducted after medical clearance and prior to randomization. After randomization, clinical measures to be conducted prior to infusion include QIDS, MADRS, HAM-A, S-STS, SDS, CGI-S, CGI-I and CogState. Measures to be collected after infusion include C-SSRS and CADSS.

There will be 3 visits per week on non-consecutive days during Weeks 1, 2, and 3. All patients will receive a single infusion of AZD6765iv or placebo per visit for a total of 3 infusions per week (Figure 1). During Weeks 4, 5, and 6, patients will receive a total of 1 infusion per week (Visits 11, 12, and 13), and during Weeks 7 through 12, patients will receive 1 infusion every other week (infusion to occur during Weeks 8, 10, and 12).

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 IP (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).

Prior to each dose, all WOCBP must have a negative urine pregnancy test and confirmed use (by the investigator) of a highly effective form of birth control plus the use of a condom by the male sexual partner. The highly effective form of birth control includes: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective intrauterine device (IUD)/intrauterine system (IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch™ or Nuvaring™. Women should be on a stable method of birth control for a minimum of 3 months prior to randomization as judged by the investigator.

3.1.1 Screening/enrollment period (Visit 1, Days -42 to -1)

The screening and enrollment period will be up to 42 days (Days -42 to -1) prior to Day 1 (randomization) of the treatment period. Note, the assessments to be performed during the screening visit can be completed over 2 days if agreed upon with medical advisor.

Eligible patients (aged 18 to 70 years inclusive), will meet a DSM-IV-TR (American Psychiatric Association 2000) criteria for a diagnosis of MDD, single episode (296.2x) or MDD, recurrent (296.3x) as confirmed by the MINI. At the screening visit, patients meeting preliminary eligible criteria will undergo all study procedures and assessments, including safety evaluations, listed in Table 4 in the manner and sequence specified in Section 6.2.1.1. Assessments will be conducted to ensure that the patient's HAM-D-17 is ≥24, CGI-S is ≥5, and QIDS-SR-16 is ≥19. Psychiatric history and a brief screening for family psychiatric history will be administered as well. If the screening and randomization visits are <7 days apart, a repeat serum pregnancy test is not required; however, negative urine pregnancy tests are required prior to each dose of IP.

If the patient qualifies for enrollment based on the inclusion/exclusion criteria (including HAM-D-17 ≥24, CGI-S ≥5, and QIDS-SR-16 ≥19), the patient will return to the study site for reconfirmation of inclusion criteria, and if still eligible, randomization and after baseline MADRS, HAM-A, S-STS and CogState, the first infusion (Visit 2). If the patient does not meet these criteria, the patient will be considered a screen failure and will not be enrolled.

Patients will continue on their existing antidepressant medication during the study. The list of permitted antidepressants and dual-therapy combinations during the study is given in Table 2 and Table 3. Other treatments that are prohibited, allowed with restrictions, or permitted, are listed in Table 6. The screening period (from Visit 1 to Visit 2) may take up to 42 days to allow the investigator time to obtain treatment history reports in support of the ATHF and also to review the results of laboratory assessments (which may confound the results of the study and to ensure the safety of patients).

3.1.2 Randomization/double-blind treatment period (Weeks 1 to 12)

Patients will undergo all procedures and assessments at the designated visits per the study assessments (Table 4); visits are as follows:

Week 1: Visits 2, 3, and 4 (Days 1 to 7, Infusions 1 to 3)

Only qualified patients will be randomized (Visit 2, Day 1).

Patients will undergo the study procedures and assessments described for Day 1 (Visit 2) before randomization (Table 4). Assessments conducted before randomization will be considered baseline assessments. Qualified patients who meet the entry criteria including HAM-D-17 score ≥24, CGI-S score ≥5, and QIDS-SR-16 score ≥19 will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms:

- **Treatment A:** Patients will receive AZD6765iv 50 mg (total dose) intravenously once per dosing day at the study site. The infusion will be a

final volume of 100 mL given at an infusion rate of 1.67 mL/min (0.833 mg/min) over 60 minutes.

- **Treatment B:** Patients will receive AZD6765iv 100 mg (total dose) intravenously once per dosing day at the study site. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min (1.667 mg/min) over 60 minutes.

- **Treatment C:** Patients will receive placebo (0.9% saline) intravenously once per dosing day at the study site. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min over 60 minutes.

During Week 1, all patients will receive 3 infusions on non-consecutive days. After Infusion 1 (Visit 2), patients will remain on site for at least 3 hrs after the end of infusion. Starting from Infusion 2 (Visit 3), patients will remain on site for at least 1 hr after the end of infusion. Prior to release from the site during every visit, patients must demonstrate stable vital signs and will be questioned about any AEs being experienced. To ensure safety, all patients must refrain from driving and operating heavy machinery for the remainder of the day after infusions 1, 2, and 3 (Week 1). Patients who are unaccompanied by a driver will be provided transportation to their home.

Patients should be semi-recumbent in a bed or reclining chair such that their feet are at the same level as their torso during the iv infusion. Patients will receive multiple infusions of AZD6765 (50 mg or 100 mg) or placebo during the treatment period. For visits with a scheduled infusion and MADRS assessment, the MADRS assessment should be given prior to the infusion.

Blood samples will be collected for PK analysis at specified visits during Weeks 1, 3, 6, and 12 (see Table 9 for blood sampling schedule for all patients during the study).

This study includes the option for randomized patients to participate in optional exploratory genetic research and optional biomarker analysis, where permitted. A 9 mL sample of blood will be collected from qualified patients who have also provided consent for optional exploratory genetic research. The blood sample for genetic research will be collected anytime after a patient has qualified for the study, but it is preferred that collection be done at the baseline/randomization visit (Visit 2, Day 1). The serum sample for biomarker analysis will be collected at baseline/randomization visit (Visit 2, Day 1) and at Visit 13.

Weeks 2 and 3: Visits 5 to 10 (Days 8 to 21, Infusions 4 to 9)

During Weeks 2 through 3, all patients will receive 3 infusions per each week on non-consecutive days (Table 4). Each infusion will be given over 60 minutes.

At designated visits when the QIDS-SR-16 is administered, it must always be done prior to any other procedure in a quiet room without staff input as specified. After medical clearance and confirming negative urine pregnancy test, urine drug screen, and confirmation that the

patient is taking no prohibited concomitant medications, MADRS, CGI-S, CGI-I, HAM-A, S-STS and CogState will be administered prior to infusion during the visits specified on Table 4. The CADSS and C-SSRS will be administered after the infusion. The S-STS self report version must be reviewed by the investigator during the C-SSRS interview and signed by the investigator.

During Weeks 2 and 3, patients will remain on site for at least 1 hour from the end of infusion (ie, up to T_2).

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

Weeks 4, 5, and 6: Visits 11 to 13 (Days 22 to 42, Infusions 10 to 12)

During Weeks 4 through 6, all patients will receive 1 infusion per week (Visit 11 [Infusion 10], Visit 12 [Infusion 11], and Visit 13 [Infusion 12]) (Table 4). Visit 11 (Infusion 10) must occur 7 days (±2 days) after Visit 10 (Infusion 9). All efforts should be made to complete the infusions on the same day of the week allowing for a 7-day interval between infusions; however, if this is not possible, a visit window of ±2 days is permitted (minimum interval of 5 days and maximum interval of 9 days). The QIDS-SR-16, MADRS, CGI-S, CGI-I, HAM-A, S-STS and CogState will be administered prior to infusion during the visits specified in Table 4. The CADSS and C-SSRS will be administered after the infusion. The S-STS self report version must be reviewed by the investigator during the C-SSRS interview and signed by the investigator.

During Weeks 4 through 6, patients will remain on site for at least 1 hour from the end of infusion (T_2).

At Week 6, a 2 mL serum sample will be collected from qualified patients who have also provided consent for optional exploratory biomarker research. The serum sample will be collected prior to the start of infusion.

Weeks 7 through 12: Visits 14 to 16 (Infusions 13 to 15)

During Weeks 7 through 12, all patients will receive 1 infusion every other week beginning on Week 8. This corresponds to Visit 14 (Infusion 13), Visit 15 (Infusion 14), and Visit 16 (Infusion 15) (Table 4). All efforts should be made to complete the infusions at 14-day intervals during this period. However, a minimum interval between infusions of 10 days and a maximum of 18 days must be observed.

The QIDS-SR-16, MADRS, CGI-S, CGI-I, S-STS, and CogState will be administered prior to infusion during the visits specified on Table 4. The CADSS and C-SSRS will be administered after the infusion. The S-STS self report version must be reviewed by the investigator during the C-SSRS interview and signed by the investigator.

During the infusion days in Weeks 8 through 10, patients will remain on site for at least 1 hour after the end of infusion (T_2); at Week 12 (Visit 16), patients will remain on site for at least 3 hours after the end of infusion (T_4).

3.1.3 Follow-up Visit

As implemented by Amendment 2, patients will be scheduled for a 14 (± 4 days)-day follow-up visit (Week 14) from last dosing to collect laboratory measurements and other assessments as detailed in Table 4, including CogState.

Patients who have completed the infusions prior to implementation of Amendment 2, but are still within the 14 (± 4 days)-day window from last dosing, will have a 14 (± 4 days)-follow-up visit (Week 14), regardless of whether they have completed assessments scheduled for Week 13 (Visit 17) under the previous protocol amendment. Patients who have completed assessments scheduled for Week 13 (Visit 17) under the previous protocol amendment do not need to repeat any laboratory assessments.

Patients who have completed the infusions and are outside the 14 (± 4 days)-day window from last dosing at the time of implementation of Amendment 2 will be considered complete. These patients may return to the site for an unscheduled follow-up visit at the discretion of the investigator.

Table 4 Study assessments through the treatment period

	Enroll-ment		Treatment Period														
	Screen/ Washout	R														EOT	Follow-up[b]
Visit	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Infusion		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Week	**-6 to -1**	**Week 1**			**Week 2**			**Week 3**			**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W14**
Day (±x days)	**-42 to -1**	**non-consecutive days**									**(±2)**	**(±2)**	**(±2)**	**(±4)**	**(±4)**	**(±4)**	**(±4)**
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Demography	X																
Psychiatric (including number of depressive episodes) and family history	X																
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical and surgical history	X																
Alcohol and drug history	X																
ATHF	X																
Employment status	X	X															X
Vital signs (supine)	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X
Orthostatic BP[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination		X															X

Table 4 Study assessments through the treatment period

	Enroll-ment		Treatment Period														
	Screen/ Washout	R														EOT	Follow-up[b]
Visit	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Infusion		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Week	**-6 to -1**	**Week 1**			**Week 2**			**Week 3**			**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W14**
Day (±x days)	**-42 to -1**	**non-consecutive days**									**(±2)**	**(±2)**	**(±2)**	**(±4)**	**(±4)**	**(±4)**	**(±4)**
Weight, height, BMI	X	X															X
Digital 12-lead ECG[d]	X	X		X						X			X			X	
Hematology	X	X											X				X
Clinical chemistry[e]	X[f]	X											X				X
Glucose	X	X															X
$HgbA_{1c}$	X																X
HIV, HBsAg, and HCV	X																
MINI	X																
HAM-D-17	X	X															
Serum pregnancy for all females[g]	X																X
Urine Pregnancy for WOCBP[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X											X				X
Urine drug screen	X																

Table 4 Study assessments through the treatment period

	Enroll-ment		Treatment Period														
	Screen/ Washout	R														EOT	Follow-up[b]
Visit	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Infusion		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Week	**-6 to -1**	**Week 1**			**Week 2**			**Week 3**			**W4**	**W5**	**W6**	**W8**	**W10**	**W12**	**W14**
Day (±x days)	**-42 to -1**	**non-consecutive days**									**(±2)**	**(±2)**	**(±2)**	**(±4)**	**(±4)**	**(±4)**	**(±4)**
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prohibited medication washout period (see Section 5.6.1)	X																
PK sampling (AZD6765 levels)		X								X			X			X	
QIDS-SR-16[i]	X	X						X					X			X	X
S-STS[i]	X	X			X			X			X	X	X	X	X	X	X
MADRS[i]		X	X	X	X			X			X	X	X	X	X	X	X
HAM-A[i]		X											X			X	
SDS		X											X			X	X
CGI-S[i]	X	X			X			X			X	X	X	X	X	X	X
CGI-I[i]					X			X			X	X	X	X	X	X	X
CogState[i]	X[j]	X											X				X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Study assessments through the treatment period

	Enroll-ment		Treatment Period														
	Screen/ Washout	R														EOT	Follow-up[b]
Visit	1[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Infusion		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Week	-6 to -1	Week 1			Week 2			Week 3			W4	W5	W6	W8	W10	W12	W14
Day (±x days)	-42 to -1	non-consecutive days									(±2)	(±2)	(±2)	(±4)	(±4)	(±4)	(±4)
CADSS[k]		X											X				
Biomarker sampling (optional)		X											X				
PGx sampling (optional)		X															
IP infusion[l]		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	

AE adverse event; ATHF Antidepressant Treatment History Form; BMI body mass index; BP blood pressure; CADSS Clinician Administered Dissociative States Scale; CGI-I Clinical Global Impression-Improvement; CGI-S Global Impression-Severity of Illness; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; EOT end of treatment period; HAM-A Hamilton Depression Rating Scale for Anxiety; HAM-D-17 Hamilton Rating Scale for Depression; HBsAg hepatitis B surface antigen; HCV hepatitis C virus; HIV human immunodeficiency virus; IP investigational product; MADRS Montgomery-Åsberg Depression Rating Scale; MINI Mini-International Neuropsychiatric Interview; PK pharmacokinetic; PRO patient-reported outcomes; QIDS-SR-16 Quick Inventory of Depressive Symptomology Self-Report 16-item scale; R randomization; SDS Sheehan Disability Scale; S-STS Sheehan Suicide Tracking Scale; WOCBP women of childbearing potential.

[a] The screening visit can be completed over 2 days if agreed upon with medical advisor.

[b] Patients who have completed assessments scheduled for Week 13 (Visit 17) under the previous protocol amendment and are still within the 14 (± 4 days)-day window from last dosing, will have a follow-up visit (Week 14), but laboratory assessments will not need to be repeated.

[c] Vital signs will be measured at time 0 (T_0 before infusion, within 1 hour before infusion is acceptable), at the end of infusion (T_1), and either at least 1 hour (T_2) after the end of infusion (all indicated visits, except for Visits 2 and 16), or, at least 3 hours (T_4) after the end of infusion (applies to Visits 2 and 16).

[d] Orthostatic BP will be measured at T_0 (within 1 hour before infusion is acceptable) and either at least1 hour (T_2) after the end of infusion (all indicated visits except for Visits 2 and 16), or at least 3 hours (T_4) after the end of infusion (applies to Visits 2 and 16).

[e] ECGs will be measured at T_0 (before infusion, within 1 hour before infusion is acceptable) and T_1 (end of infusion) at Visit 2, and at T_1 only for Visits 4, 10, 13, and 16.

[f] Serum lithium concentrations for patients receiving lithium as adjunct therapy for the treatment of their MDD will be measured as part of the clinical chemistry assessment.

[g] Blood sampling for FSH for all post-menopausal women under 50 years of age.

[h] A negative urine pregnancy test result is required prior to each dose of IP. Pregnancy tests will be administered and processed at the study site.

[i] These measures will always be administered **prior to** any IP infusion.

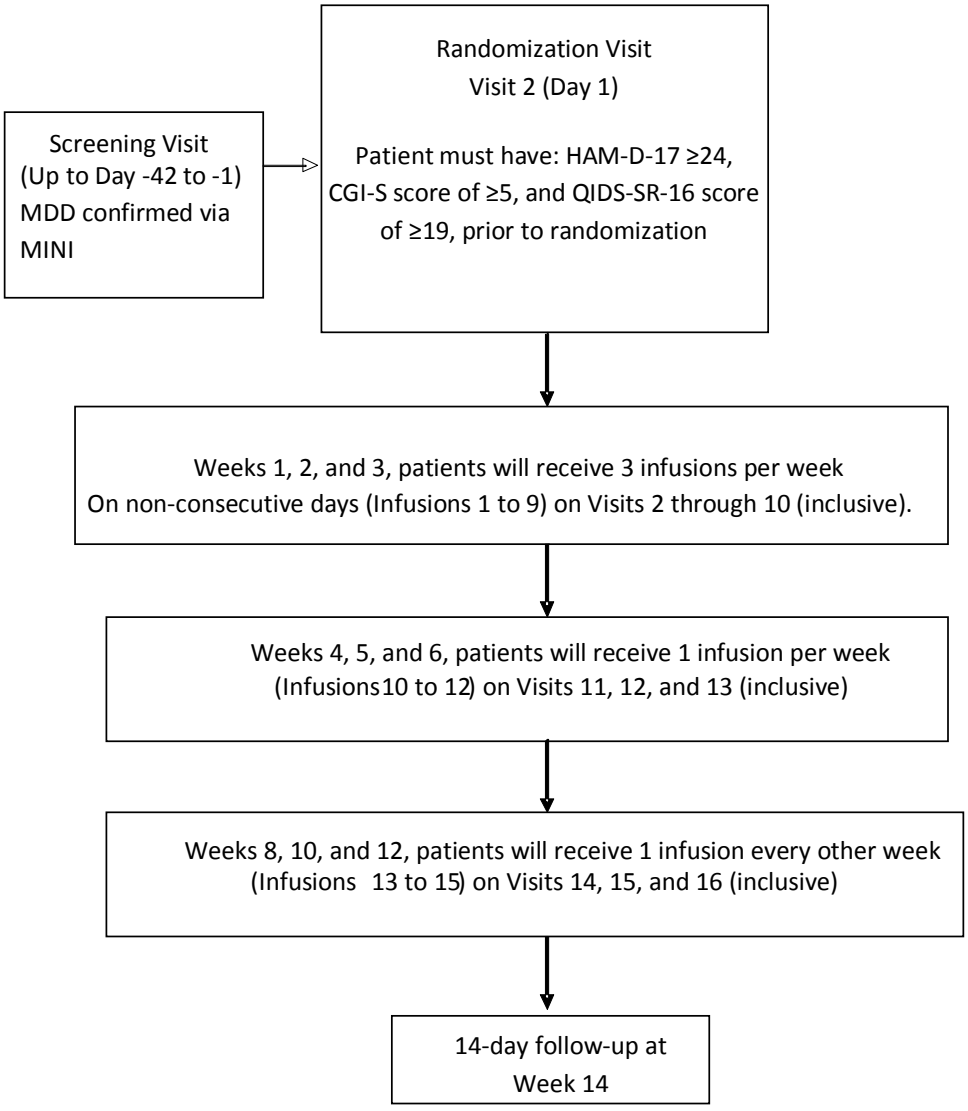
[j] At the screening visit, practice CogState is administered for training. The tests should be given twice (or more frequently if required to assure complete understanding of the requirements of each task).

[k] CADSS will be administered at designated visits **after** infusion.

[l] Patients must remain on site at randomization and the last infusion visit for at least 3 hours after the end of the infusion and at least 1 hour after the end of infusion at other scheduled infusions. Patients should be queried about any AEs and assessed for ability to leave the clinic, including their ability to drive or access to alternative transportation (see Section 5.1), prior to dismissal from the clinic at each infusion.

[m] Weeks 1 through 3 post randomization-dose administration 3 times a week; Weeks 4 through 6 – dose administration once weekly; Weeks 8, 10, and 12 – dose administration once weekly. No drug administration will take place on Week 7, Week 9, and Week 11.

Figure 1Dosing flow chart



3.2 Rationale for study design, doses and control groups

The primary objective of the study is to evaluate the efficacy of multiple infusions of AZD6765iv 50 mg or 100 mg versus placebo when given adjunctively with selected allowed antidepressants (Table 2 and Table 3) for patients with MDD (DSM-IV-TR 296.2x or 296.3x) who exhibited an inadequate response to 3 or more different antidepressant treatments by history. Inadequate response is defined as persistent symptoms that, as judged by the investigator, continue to meet the diagnostic criteria for a MDE according to DSM-IV-TR.

The dose and study design chosen for this study are based on information gained from previous AstraZeneca clinical studies with AZD6765 in MDD, as well as toxicological, pharmacological, and PK studies in different animal species and in vitro human data.

Please see the IB for further information.

An enrollment period of up to 42 days is required to allow the investigator to review the results of laboratory assessments and treatment history reports in support of the ATHF.

4. SUBJECT SELECTION CRITERIA

The patient population should be selected without bias.

Investigator(s) must keep a record of patients who entered pre-study screening, but were never enrolled, eg, patient screening log. Each patient 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. The sponsor reserves the right to utilize external representatives to oversee severity of illness determination, diagnosis, and other factors to identify appropriate patient population.

4.1 Inclusion criteria

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

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

2. Patients must provide acceptable proof of identity documentation to confirm initials and date of birth

3. Male and female patients aged 18 to 70 years, inclusive. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 12 weeks after their last dose. All females must have a negative serum pregnancy test. Women of childbearing potential (WOCBP, see below) must use (confirmed by the investigator) a highly effective form of birth control plus the use of a condom by the male sexual partner. The highly effective form of birth control includes: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any

effective IUD/IUS, Depo-Provera™ injections, oral contraceptive, and Evra Patch™ or Nuvaring™. Women should be on a stable method of birth control for a minimum of 3 months as judged by the investigator, prior to randomization and 3 months after the last dose of IP.

Women of non-childbearing potential. Women of non-childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they are amenorrheic for 12 months prior to randomization without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

- Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

4. Documented clinical diagnosis meeting criteria from the DSM-IV-TR confirmed via the MINI of Major Depressive Disorder: 296.2x MDD, Single Episode or 296.3x MDD, Recurrent.

5. Currently taking an allowed antidepressant treatment for at least 4 weeks prior to screening. The dose of the antidepressant medications should be as specified in Table 2 and Table 3. All primary and secondary antidepressant treatments must remain at a stable dose and frequency, without clinically significant adjustment. Randomization cannot take place until a minimum adequate duration of stable treatment, as specified in Table 2 and Table 3, has been achieved.

6. HAM-D-17 score ≥24, CGI-S ≥5, and QIDS-SR-16 ≥19 at screening, and Visit 2/randomization

7. Lifetime history of inadequate response, as described in Section 3.1, to at least 3 trials of antidepressant treatment of adequate dose and duration as specified in Table 1, Table 2, and Table 3. One of these trials must be the current treatment trial.

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

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

10. Capable of returning for study-related assessments, as judged by the investigator

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

1. Provision of informed consent for genetic research

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

4.2 Exclusion criteria

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

1. Involvement in the planning/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrollment in the present study

3. Patients who are currently participating in another clinical study in which the patient is exposed to an investigational or non-investigational drug or device, or have done so within the last 30 days prior to screening for studies unrelated to MDD, or 6 months for studies related to MDD.

4. Patients who have no regular contact with an adult who could come to the patient's aid should an urgent need arise. This excludes patients who are undomiciled or who do not have at least one adult with whom there is regular contact.

5. Patients with a history of DSM-IV-TR diagnosis of bipolar disorder or schizophrenia or schizoaffective disorder or currently exhibiting psychotic features associated with their depression; dementia or suspicion thereof, is also exclusionary. Other DSM-IV-TR Axis I disorders are permitted as long as they are not considered primary disorders.

6. Patients who during the past two years have met DSM-IV-TR diagnostic criteria for post-traumatic stress disorder.

7. Currently being treated with MAOIs, depakote, carbamazepine, lamotrigine, topiramate, opiates, memantine, barbiturates, or bupropion >300 mg per day (see Table 6 for details and additional prohibited medications)

8. ECT, VNS, or TMS, or previous treatment with ketamine infusion within the 6 months prior to randomization, or any history of deep brain stimulation

9. Substance abuse or dependence within the 6 months prior to screening. Patients with a positive urine drug screen (UDS) for methamphetamines benzodiazepines, cocaine and/or metabolites, amphetamines, tetrahydrocannibinol (THC), opiates, PCP, ethanol, methaqualone (South Africa only), and barbiturates will be excluded

except for patients testing positive for prescribed medications **that are otherwise permitted and there is no evidence of misuse, abuse, or dependence**. Patients can be re-tested only if either the initial THC, opiate, or barbiturate result is positive and they have a prescription, but the patient should be excluded if the result is still positive for THC, opiate, or barbiturate, respectively, at the second test. Patients with positive UDS for a drug(s) legally available by prescription must provide evidence of prescription for the drug(s).

10. Patients with a DSM-IV-TR Axis II disorder, which in the opinion of the investigator, has a major impact on the patient's current psychiatric status

11. Systolic BP <85 or >160 mmHg or diastolic BP >95 mmHg or heart rate <50 or >105 beats per minute at screening or randomization. Exclusionary values may be repeated once.

12. QTcF (Fridericia-corrected) ≥450 msec at screening (Visit 1) or randomization

13. Patients who have had a suicide attempt within the last 6 months. Patients who, in the investigator's judgment, pose a significant suicide risk. Evidence of significant suicide risk may include any history of suicidal behavior and/or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 6 months at screening or randomization.

14. Patients who are pregnant or lactating

15. Patients with unstable or inadequately controlled medical conditions (eg, unstable angina) or 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 patient is on a stable treatment regimen for a minimum of 6 months. Combination of abnormal thyroid-stimulating hormone (TSH) test results and abnormal free thyroxine levels require discussion with Sponsor or Sponsor's representative.

16. Patients with diabetes mellitus fulfilling any of the following criteria:

    - Unstable diabetes mellitus defined as glycosylated hemoglobin (HbA_{1c}) >8.5% at screening

    - Admitted to hospital for treatment of diabetes mellitus or diabetes mellitus-related illness in the past 12 weeks

    - Not under physician care for diabetes mellitus

- Has not been on the same dose of oral hypoglycaemic drug(s) and/or diet for the 4 weeks prior to screening. For thiazolidinediones (glitazones) this period should not be less than 8 weeks.

17. Patients whose depression is secondary to an organic or medical cause or first presented after the age of 60 years

18. Patients with any history of seizure disorder (except for febrile seizures in childhood)

19. Clinically significant laboratory value that signifies a major medical illness that is inadequately controlled in the judgment of the investigator: Patients with laboratory values outside normal limits, but not judged to be clinically significant may be randomized. However, such laboratory parameters should be followed. Examples of clinically significant laboratory values that would require exclusion include: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3.0 times the upper limit of normal (ULN) or total bilirubin ≥1.2 times the ULN (unless documented Gilbert's syndrome).

20. Previous exposure to AZD6765

21. Currently hospitalized at screening

22. Current diagnosis of sleep apnea

23. Body mass index (BMI) ≥45 kg/m^2

For the patient to be qualified for the optional genetic research, the patient must not have had:

1. Previous allogeneic bone marrow transplant

2. Non-leukocyte depleted whole blood transfusion within 120 days prior to the date of genetic sample collection

If either of these 2 exclusion criteria is present, the patient cannot participate in the optional genetic research.

5. STUDY CONDUCT

5.1 Restrictions during the study

When applicable, WOCBP as defined in Section 4.1, must agree to use adequate contraception (adequate contraception can include abstinence if the investigator deems it appropriate) and must have a negative urine pregnancy test prior to the administration of the IP. A positive urine pregnancy test during the study, including at the final visit, will be followed by a serum pregnancy test for confirmation.

Use of concomitant medications is restricted as detailed in Section 5.6, Table 6.

To ensure safety, all patients must refrain from driving and operating heavy machinery for the remainder of the day after infusions 1, 2, and 3 (Week 1). Patients who are unaccompanied by a driver will be provided transportation to their home. After Week 1, the investigator will determine the patient's ability to drive prior to leaving the site at every infusion visit. The investigator may restrict driving at any time should there be a safety concern, and provide alternative transportation for the patient.

5.2 Subject enrolment and randomisation

The principal investigator (PI) will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

2. Assign potential patient a unique enrollment number, beginning with "E#" (for example, E-1100-001).

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Assign via Interactive Voice Response System (IVRS) an eligible patient unique randomization code (patient number), beginning with "#".

As patients 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 site number (4-digits) and the patient number within that particular site (3-digits) (for example, E-1100-001).

5.2.1 Procedures for randomisation

Eligible patients will be randomized in balanced blocks to receive AZD6765iv 50 mg or 100 mg, or placebo saline infusion in a 1:1:1 ratio. The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the IVRS database. If a patient is discontinued from the study, his/her randomization or enrollment number will not be reused, and the patient will not be allowed to re-enter the study. Patients 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 patient will continue with the allocated number and study material. AstraZeneca or representative should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated randomization number in the original numbering sequence.

5.3 Procedures for handling subjects incorrectly enrolled or randomised

Patients 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 patients must be followed. These procedures must take into consideration ethical and safety factors and how these patients will be treated in the analyses.

When an incorrectly enrolled patient 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 patient in the study. The AstraZeneca Study Team Physician or representative will ensure all such decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The investigator, patient, and study staff will be blinded. Both AZD6765iv doses and placebo (normal saline) will be prepared as pre-mixed solutions in glass vials that must be refrigerated and should be available to the study staff on the morning of the dosing. Packaging and labeling of the IPs will be performed in a way to ensure blinding throughout the study.

No member of the study team in AstraZeneca, at study sites, 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 Product Services and Patient Safety.

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

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS/ Interactive Web Response System (IWRS). Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca or representative, without revealing the treatment given to the patient to the AstraZeneca or representative's staff.

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP 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 patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product

AstraZeneca or representative will supply AZD6765iv as either AZD6765 Solution for Infusion, 0.5 mg/mL (for the 50 mg dose) or AZD6765 Solution for Infusion, 1.0 mg/mL (for the 100 mg dose) as a ready to use iv solution in infusion bottles containing 100 mL (Table 5). Also, matching placebo infusion bottles of 100 mL will be supplied.

Handling instructions will be provided to the site regarding administration.

AZD6765iv or placebo must be infused using an infusion pump.

Table 5 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
AZD6765 Solution for Infusion (AZD6765iv)	0.5 mg/mL solution for infusion 100 mL	[redacted]
AZD6765 Solution for Infusion (AZD6765iv)	1.0 mg/mL solution for infusion 100 mL	[redacted]
Placebo (0.9% saline)	100 mL solution for infusion	[redacted]

The batch numbers will be recorded in the Study Master File and identified in the clinical study report.

5.5.2 Doses and treatment regimens

Patients will be randomized to receive 1 of the following treatments: Treatment A (AZD6765iv 50 mg), Treatment B (AZD6765iv 100 mg), or Treatment C (placebo saline) by iv infusion in a 1:1:1 ratio. Patients should be semi-recumbent in a bed or reclining chair such that their feet are at the same level as their torso during the iv infusion.

- **Treatment A:** Patients will receive AZD6765iv 50 mg (total dose) intravenously once per dosing day at the study site. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min (0.833 mg/min) over 60 minutes.
- **Treatment B:** Patients will receive AZD6765iv 100 mg (total dose) intravenously once per dosing day at the study site. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min (1.667 mg/min) over 60 minutes.
- **Treatment C:** Patients will receive placebo (0.9% saline) intravenously once per dosing day at the study site. The infusion will be a final volume of 100 mL given at an infusion rate of 1.67 mL/min over 60 minutes.

Patients will receive multiple infusions of AZD6765iv (50 mg or 100 mg) or placebo during the treatment period. The AZD6765iv dose assigned will be used for all infusions for any given patient.

5.5.3 Additional study drug

No additional study medication will be supplied by AstraZeneca or representative for this study.

5.5.4 Labeling

AstraZeneca or representative will provide the IP to the study sites. Labeling of the IPs will be performed in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language. Investigational products will be provided in labeled vials.

All clinical study material will 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 dispense the IP according to the IVRS.

5.5.5 Storage

All IPs must be kept in a secure place under appropriate storage conditions. The IP label on the vial specifies the appropriate storage.

5.6 Concomitant and post-study treatments

5.6.1 Concomitant medications

Medications prohibited or permitted with restrictions are specified in Table 6.

Antidepressant medications must follow the guidelines provided in Section 3.1.

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

Serum lithium concentration

Serum lithium concentrations for patients receiving lithium as adjunct therapy for the treatment of their MDD will be measured as part of the clinical chemistry assessment at time points specified in Table 4. Additional assessments may be performed as needed. In addition to serum lithium concentration levels, sampling dates and 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 patient's memory/or 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.

All prior treatments for depression will be collected on the ATHF. Medications used for other indications up to 60 days prior to screening will be recorded in the appropriate sections of the source documentation and eCRF.

Table 6 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
Prohibited	MAOIs	A 4-week washout prior to screening is required.
	VNS, ECT, TMS, deep brain stimulation	VNS ECT, or TMS within 6 months at randomization is exclusionary; however, VNS, ECT, or TMS history >6 months would qualify as prior therapy and is acceptable for the purposes of the ATHF.
	lamotrigine	A 2-week washout prior to randomization is required.
	valproate	A 2-week washout prior to randomization is required.
	topiramate	A 2-week washout prior to randomization is required.
	opiates	A 2-week washout prior to randomization is required.
	carbamazepine	A 4-week washout prior to randomization is required.
	memantine	A 4-week washout prior to randomization is required.
	ketamine	Prohibited within the last 6 months at randomization.
	barbiturates	A 2-week washout prior to randomization is required.
	bupropion >300 mg	All formulations at this dose are prohibited after randomization. Dose adjustment to non-exclusionary levels must be done prior to randomization.

Table 6 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 patient has been taking a stable regimen and dose at least 4 weeks prior to randomization. The dosage in the past 4 weeks 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.
	Hypnotics	One of the following medications can be used for insomnia at the restricted and maximum allowable dose of: • Zolpidem tartrate 10 mg • Ambien CR 12.5 mg • eszopiclone 3 mg • zopliclone 7.5 mg • chloral hydrate 1 gram • zaleplon 20 mg, or • ramelteon 8 mg (in the evening) up to the specified dosage per night if treatment has been ongoing on a regular basis since 4 weeks prior to randomization.
Permitted		
	Stable psychotherapy	Ongoing for at least 3 months at randomization.
	Nonpsychoactive medications, including over-the-counter medications	

Table 6 Concomitant medications that are prohibited, allowed with restrictions, or permitted

Use category	Type of medication	Details
	Nonpsychopharmacologic medications with psychotropic properties	May be used upon discussion with Sponsor or Sponsor's representative with appropriate washout prior to randomization.
	Medications required to treat illnesses or complaints that occur during the study	May be used at the discretion of the investigator.
	Medications that are considered necessary for the patient's safety and well-being	May be given at the discretion of the investigator. Includes medication and devices for contraception.
	Other permitted drugs and treatments not counted toward 3 inadequate responses	Includes other psychoactive drugs indicated for attention deficit hyperactivity disorder (eg, atomoxetine, etc) or anxiety (diphenhydramine, etc).

5.7 Treatment compliance

The administration of all IPs (AZD6765iv and placebo) should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by supervised administration of the IPs by the investigator or his/her designee. The investigator will query the patient to assess antidepressant therapy treatment compliance.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel and the [redacted] monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, on-site destruction or return to Fisher, should be signed by the investigator or designee.

5.8 Discontinuation of investigational product

If the patient is discontinued from IP, the scheduled study visits, data collection, and procedures should continue according to the study protocol until study closure. Alternatively, if the patient does not agree to this option, a modified follow-up through regular telephone contacts or a contact at study closure should be arranged, if agreed to by the patient and in

compliance with local data privacy laws/practices. The approach taken should be registered in the eCRF.

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe non-compliance to study protocol

5.8.1 Procedures for discontinuation of a subject from investigational product

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4).

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4).

Patient-specific reasons for discontinuing a patient are:

- Voluntary discontinuation by the patient who is at any time free to discontinue the patient's participation in the study, without prejudice to further treatment
- Severe non-compliance to protocol
- Incorrectly enrolled patients
- Patient is lost to follow-up
- The patient 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 patient
- Safety reasons as judged by the investigator, particularly if patient becomes pregnant
- The condition under investigation worsened

- The patient is unable to comply with the restrictions on the use of concomitant medications as detailed in Section 5.6.1

- The patient is unable to tolerate the assigned dose of IP

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

- Withdrawal of consent for genetic research. A patient 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 patient will not prejudice further treatment.

If a patient discontinues from the study before randomization, then no further follow-up will be expected. However, if the patient discontinues after randomization, but before receiving any study treatment, the patient will be asked to return for the scheduled follow-up visits though Week 10 (inclusive) for AEs and concomitant medication assessments.

If a patient discontinues from the study before completion and has received at least 1 dose of IP, the patient will be asked to return for scheduled study-related visits for the remainder of the study. If they discontinued during Weeks 1 to 3 when there are 3 scheduled visits per week, they will only be asked to return to the site once a week. The following assessments will be obtained at each visit: MADRS, CGI-S, CGI-I, C-SSRS, AEs, and concomitant medications according to the schedule displayed in Table 4 whenever possible. Every effort should be made to follow up with patients who discontinue from the study prior to Week 12. If patients refuse to return to the clinic for the study-related assessments, a modified follow-up through, for example, regular telephone contact or a contact at study closure should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. If the patient refuses follow-up, the reason for the refusal and last contact date should be documented in the eCRF and source documents.

The investigator must notify AstraZeneca or representative of any hospitalization. Hospitalization is an SAE and should be reported as described in Sections 6.4.2 and 6.4.4. If a patient is hospitalized, the AstraZeneca/[redacted] safety review group will decide if the patient is to be discontinued from the study. Should the patient need to be discontinued from the study, all assessments and procedures required at Week 14 in Table 4 will be conducted.

Patients who discontinue from the study will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The electronic data capture (eDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA) or locally defined contract. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Confirmation of clinical inclusion criteria

Any patient considered for enrollment into the study must provide written informed consent (signed and dated) prior to conducting any study-specific procedure.

6.2.1.1 Screening visit (Visit 1)

This section describes the preferred order of assessments; however, this order is not mandatory, except that QIDS-SR-16 and S-STS must be done first. Note, that the assessments to be performed during the screening visit can be completed over 2 days if agreed upon with medical advisor.

During the screening visit, the QIDS-SR-16 and S-STS (self report) will be administered first.

Prior to conducting any further procedures, the QIDS-SR-16 should be independently scored (without review by the investigator) and if the inclusion criterion score of ≥19 is not met, no further study procedures are to be conducted and the patient will not be randomized. At no time may the patient be informed of the inclusion criterion score on the QIDS-SR-16. If the QIDS-SR-16 criterion is met, the HAM-D-17 interview will be conducted and the CGI-S will be completed to determine whether the patient meets the inclusion criteria of a HAM-D-17 total score ≥24 and CGI-S ≥5. If these criteria are not met, no further procedures are to be conducted and the patient will not be randomized. If these criteria are met, the MINI interview will be conducted.

While completing Module B of the MINI (suicidality), the investigator will review the S-STS self report responses and inquire further into any suicidal ideation that was reported. During this portion of the interview, the investigator will also complete the C-SSRS baseline version. If the patient is judged by the investigator to pose a significant suicide risk, the patient will not be enrolled and the investigator will take appropriate steps to assure the patient's safety. Evidence of significant suicide risk may include any history of suicidal attempt or behavior and/or any suicidal ideation of type 4 or 5 on the C-SSRS in the last 6 months.

If the patient is judged not to pose a significant suicide risk, the MINI interview is completed to confirm that the patient meets diagnostic inclusion criteria for the study (DSM-IV-TR 296.2 or 296.3), and to confirm the absence of lifetime history of previous manic or hypomanic episodes (Module C), the absence of current alcohol abuse or dependence (Module I), the absence of current substance dependence/abuse (Module J) and the absence of current mood disorder with psychotic features (Module K). Note that history of alcohol or substance abuse or dependence for the past 6 months is also exclusionary and that determination should be made at this point.

If the patient still meets inclusion criteria for the study, the ATHF should be completed with the patient. If based upon the patient's self report and the investigator's best judgment the patient is deemed reasonably likely to meet the inclusion criterion of at least 2 previous (in addition to the current) antidepressant treatment regimens of adequate dose and duration (as specified in Table 1 and Table 3), all remaining clinical and laboratory assessments listed in Table 4 should be completed and arrangements should be made with the patient to obtain the necessary documentation from previous inadequate responses (e.g. contact information of previous treating physicians and signed releases that may be necessary to obtain written medical records). Acceptable evidence of previous inadequate responses may include verbal or written communication with the treating physician (recorded in the source document), or copies of medical or pharmacy records.

6.2.1.2 Randomization visit (Visit 2)

Prior to the randomization visit, adequate documentation must be in place to confirm that the patient meets modified ATHF inclusion criteria of inadequate response to at least 2 previous antidepressant treatments of adequate dose and duration. In addition, results from all laboratory assessments conducted at the screening visit should be available and confirm that the patient continues to meet clinical and safety criteria for inclusion.

At the randomization visit, the QIDS-SR-16 will be administered first. Prior to conducting any further procedures, the QIDS-SR-16 should be scored (without review by the investigator) and if the inclusion criterion score of ≥19 is not met, no further study procedures are to be conducted and the patient will not be randomized. At no time may the patient be informed of the inclusion criterion score on the QIDS-SR-16. If the QIDS-SR-16 criterion is met, the HAM-D-17 interview will be conducted and the CGI-S will be completed to determine whether the patient meets the inclusion criteria of a HAM-D-17 total score ≥24 and CGI-S ≥5. If these criteria are not met, no further procedures are to be conducted and the patient will not be randomized. If these criteria are met, the patient is randomized and the remaining clinical and laboratory assessments are conducted in accordance with Table 4.

The MADRS, CGI-S, S-STS, HAM-A, SDS, and Cogstate are conducted prior to the first infusion. After the first (and last) infusion, the patient must remain in the clinic for at least 3 hours after the infusion (T_4) during which time AEs are collected, and CADSS and C-SSRS are administered. Vital signs and orthostatic BP are measured at every infusion at multiple time points: T_0, T_1(vital signs only), and either at least 1 hour (T_2) after the end of infusion (all indicated visits, except for Visits 2 and 16), or, at least 3 hours (T_4) after the end of infusion (applies to Visits 2 and 16, which corresponds to first and last infusions).

6.2.2 Follow-up procedures

Description of clinical rating instruments used for diagnosis and entry criteria

The following instruments are administered during the screening and randomization visits (Visits 1 and 2, respectively) to evaluate the presence and severity of MDD and to establish inclusion and exclusion criteria. Several of these measures are also administered at follow-up visits to monitor study outcome, severity of clinical symptoms and safety. The timing of all instruments is specified in Table 4.

All clinician ratings must be conducted by raters who are trained and certified to conduct the required clinical interviews and to make the required ratings. During the clinical interviews, the trained rater will record clinical observation on each scale, which will be used as the source documents. If at all possible, the same individual should perform each 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 ratings.

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

The QIDS-SR-16 is a 16-question self-report inventory (patient-reported outcome [PRO]) that includes the 9 DSM-IV-TR criteria symptom domains: sad mood, concentration, self-outlook, suicidal ideation, involvement, energy/fatigability, sleep disturbance (4 items: initial, middle, late insomnia, and hypersomnia), appetite/weight increased or decrease (4 items), and psychomotor agitation/retardation (2 items) (Rush et al 2003, Trivedi et al 2006). At designated visits, the QIDS-SR-16 should be completed as soon as possible after the patient arrives at the clinic, prior to the infusion and before there has been significant clinical contact. It should be completed by the patient alone in a quiet, private space without influence from clinic staff or any person accompanying the patient, including family.

6.2.2.2 Sheehan Suicide Tracking Scale (S-STS) Self report form

The S-STS is a prospective, patient self-report or clinician-administered rating scale that tracks suicidal ideation and behaviors and has been shown to be sensitive to clinical change with treatment (Coric et al 2009, Khan et al 2011).

Only the self-report portion of the scale will be used in this study, which must be reviewed and signed by the investigator prior to conducting the C-SSRS interview. The S-STS will be administered at designated visits prior to the infusion. Note that the C-SSRS should be administered after the infusion.

6.2.2.3 Hamilton Rating Scale for Depression (HAM-D-17)

The HAM-D-17 is a 17-item observer-rated scale that assesses depressive symptoms (Hamilton 1960) each of which is rated from 0 to 2 to 0 to 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, 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. The HAM-D-17 will be performed during the screening (Visit 1) and randomization visits (Visit 2) to determine whether the patient meets the severity inclusion criterion of a total score of ≥24.

6.2.2.4 Clinical Global Impression of Severity (CGI-S)

The CGI scale is a 3-part, clinician-administered scale that assesses global illness severity and change (Guy 1976). For inclusion criteria and to examine the effects of the IP, the first part, Severity of Illness (CGI-S) will be used. This is a single score, rated on a scale from 1 to 7, to reflect the patient's current clinical state.

A CGI-S score of 1 indicates that a patient is "Normal, not ill" and a score of 7 indicates that a patient is "Among the most extremely ill patients." The CGI-S should be administered at designated visits prior to the infusion.

6.2.2.5 The Mini-International Neuropsychiatric Interview (MINI)

The Mini-International Neuropsychiatric Interview (Sheehan et al 1998) is a short, structured diagnostic interview developed jointly by psychiatrists and clinicians in the United States and Europe for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and International Classification of Diseases and Related Health Problems (10th edition) (ICD-10) psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short and accurate structured psychiatric interview for multicenter clinical studies and epidemiology studies. The MINI Version 6.0.0 will be used in this study.

6.2.2.6 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 must be administered after each infusion and prior to discharging the patient from the clinic.

6.2.2.7 Psychiatric and family history

For psychiatric and family history, information is collected on previous psychiatric episodes of the patient and also includes a brief family history of psychiatric disorder and alcohol abuse/ dependence. This form is completed once at the screening visit. If additional information about family history is obtained during the course of the study, this form may be updated to reflect the most accurate family history information known to the investigator.

6.2.3 Recording of data

All clinical ratings and other data collected for this study will be recorded on specifically designed eCRFs.

6.3 Efficacy

6.3.1 Sequence of clinical rating assessments

Table 4 lists all clinical and laboratory assessments to be conducted at the screening visit and all subsequent visits. The following "priority order" among clinical ratings will be in effect for all visits after the screening visit.

Pre-infusion

- QIDS-SR-16
- S-STS (self report)
- MADRS
- HAM-A
- SDS
- CGI-S
- CGI-I
- CogState

Post-infusion

- C-SSRS (conducted by the investigator after reviewing and signing S-STS during visits when both instruments are used)
- CADSS

6.3.2 Instruments

The following is a description of all clinical rating instruments used to measure efficacy not described above in Section 6.2.2. All ratings will be made by the investigator or delegate, according to the schedule of events in Table 4. Patient-reported outcome scales include: QIDS-SR-16, SDS (efficacy), and S-STS, CADSS (safety).

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, 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, CGI, and C-SSRS scale administration (prior to rating these scales for this 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 an SAE or are the reason for discontinuation from treatment with the IP. Please see Table 4 for the timing of evaluations.

6.3.2.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item scale for the evaluation of depressive symptoms (Montgomery SA, Åsberg M 1979). The MADRS will be administered by a physician, PhD, RN, or other healthcare professional skilled and experienced in the care of this patient 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 patient will be classified as in remission if their MADRS total score is ≤8. The MADRS must be administered at designated visits prior to infusion. The MADRS administered at Visits 3, 4, and 5 (prior to infusions 2, 3, and 4) will evaluate depressive symptoms since last infusion; at all other time points MADRS will evaluate depressive symptoms during the past week regardless of the interval between doses/visits.

6.3.2.2 Sheehan Disability Scale (SDS)

The SDS total score will be calculated as the sum of the score for the 3 inter-correlated domains (school/work, social life, and family life/home responsibilities) and can range from 0 to 30 (Sheehan KH, Sheehan DV 2008). It is designed for patients to self-rate their level of functional impairment over the last week. The SDS also includes an assessment of lost productivity due to symptoms of illness through 2 items evaluating lost days and under productive days. Each of these 3 items is scored on an 11-point scale, where a score of 0 is "not at all impaired," 5 is "moderately impaired", and 10 is "very severely impaired." A total SDS score will measure total impairment (range (0 to 30). To calculate the total score, the 3 items within the SDS are summed into a single dimensional measure of functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). Subscale scores for work, social, and family domains are calculated separately. The subscale numerical ratings range is 0 to 10. Total scores, ranging from 0 to 30, are calculated only for patients who rate all 3 items. The SDS must be administered at designated visits prior to infusion.

6.3.2.3 Clinical Global Impressions: (CGI-S and CGI-I)

The 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 2 parts of the scale will be used.

The first part, Severity of Illness (CGI-S), was described above and constitutes 1 of the study inclusion criteria. The second part, Global Improvement (CGI-I), is scored to rate the patient's change post-treatment.

Each CGI item is scored on a scale from 1 to 7. A CGI-I score of 1 indicates that a patient is "Very much improved" and a score of 7 indicates that a patient is "Very much worse." The CGI-I is administered at various times during the course of the study to assess patient progress. CGI-I scores greater than 4 indicate worsening, while scores less than 4 indicate improvement.

The CGI-I will be evaluated at designated visits prior to infusion. In addition to examining rating scores, scores will be dichotomized into "Much or Very much improved" (a CGI-I rating ≤2), or "Not much improved" (a CGI-I >2).

6.3.2.4 The Hamilton Scale for Anxiety (HAM-A)

The HAM-A (Hamilton 1959) is a widely used interview scale that measures the severity of a patient'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). At baseline and randomization, this scale provides an indication as to the patient's level of anxiety, a frequent comorbidity with depression. At subsequent visits, change in level of anxiety will be monitored. The HAM-A must be administered at designated visits prior to infusion.

6.3.3 Procedures for collecting patient reported outcomes (PRO)

Appropriate procedures for minimizing bias and enhancing compliance will be followed throughout the study. To ensure this, a study coordinator at each study site will be responsible for the PRO evaluation and a standardized procedure for the administration of the PRO questionnaires will be applied. The patient will complete the questionnaires independently, so that the responses reflect the patient's perception and views rather that those of family, friends, staff, or others.

Each study site will have a designated quiet space in the clinic for the patients to complete the questionnaires at each visit. The questionnaires should be completed prior to other examinations, before there are substantial professional encounters with transmission of information, such as disease status. Such information may influence the answers that the patients provide on questionnaires. Training will be provided to study personnel to ensure the data quality through the standardized administration of the PRO questionnaires.

The QIDS-SR-16 and S-STS must both be administered prior to the infusion at designated visits.

The PROs of QIDS-SR-16 and SDS are discussed in Sections 6.2.2.1 and 6.3.2.2, respectively.

6.4 Safety

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

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (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 even if no study treatment has been administered.

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

6.4.2 Definitions of serious adverse events

An SAE is an AE occurring during any study phase (ie, enrollment, treatment, washout, follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient 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, MDD, it will be reported as an SAE. The psychiatric assessments will reflect the worsening of the patient's condition and the need for hospitalization. These hospitalizations will be reported in the eCRF. Further guidance on the reporting of deterioration of the patient's condition with respect to MDD is contained in the following Section 6.4.3. If a patient is hospitalized, the AstraZeneca/[redacted] safety review group will decide if the patient is to be discontinued from

the study. Should the patient need to be discontinued from the study, all assessments and procedures required at Week 14 in Table 4 will be conducted.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events and SAEs will be collected from the time of signature of informed consent throughout the treatment period and follow-up period. In patients who discontinue prior to final visit, unsolicited SAEs will be collected for 30 days post last study treatment.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient'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 or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to IP
- Causality assessment in relation to other medication
- Description of AE

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

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 6.4.4. Misuse of IP is an AE, but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose of IP occur, it must be reported in accordance with the procedures described in Section 13.2. An overdose associated with symptoms must be reported as an AE, while an overdose without associated symptoms, must be reported only on the separate AstraZeneca Clinical Study Overdose Report Form.

Suicidality

Any patient who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued from the study (see Section 5.8 and Section 5.9). All efforts should be taken to minimize the risk of suicide and the investigator should carefully monitor the

patient. If during the course of the study, a patient shows evidence of serious suicidality (for example warranted by a scoring of 4 or 5 on the C-SSRS), the patient should be referred to their attending psychiatrist, a local emergency room etc. for further evaluation to see if they are safe to continue in the study. The site should have the ability to direct any patient that requires emergency hospitalization to an emergency room or inpatient psychiatric unit that is within a 50 mile radius of the site. In addition, the patient should be able to contact someone at the site 24 hours per day should they have serious worsening of their condition.

Suicide and attempted suicide, irrespective of the method, but occurring in connection with the use of IP, 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 6.4.4. Strong 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 6.4.4 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 patient 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.

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 Sapphire and coded using MedDRA.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 13.3, Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

Causality collection

The investigator will assess the causal relationship (ie, the relationship to study treatment) between the IP 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.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient 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 eCRF. 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.

Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

NB. Cases where a patient shows an AST **or** ALT ≥3x ULN **or** total bilirubin ≥2xULN may need to be reported as SAEs, please refer to Appendix E "Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law" for further instructions.

Disease progression or worsening depression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of worsening depression should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug AZD6765.

6.4.5 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 4).

The clinical laboratory tests that will be assessed are listed in Table 7. The date and time of each collection will be recorded on the appropriate source documentation and eCRF.

Table 7 Laboratory assessments

Hematology	Clinical chemistry	Urinalysis
B-Hemoglobin	S-Creatinine	Specific gravity
B-Leukocyte (white blood cell) differential count	S-Uric acid	pH
B-Platelet count	S-Total bilirubin (direct and indirect)	Glucose

Table 7 Laboratory assessments

Hematology	**Clinical chemistry**	**Urinalysis**
B-Hematocrit	S-Albumin	Protein
B-Red blood cells	S-Alkaline phosphatase	Ketones
	S-ALT	Blood/hemoglobin
Other	S-AST	Leukocytes
HIV[a]	S-Potassium, S-Calcium, S-Sodium	Nitrates
HBsAg[a]	S-Chloride	Bilirubin
HCV[a]	S-Bicarbonate	Urobilinogen
$HgbA_{1c}$	S-Glucose	Urine osmolality
	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[b]**
	Lithium	Cocaine
	FSH[a]	Cannabinoids
		PCP
	S-Thyroid function tests	Amphetamines class, including methamphetamine
	Free triiodothyronine	Benzodiazepines class
	Free thyroxine	Barbiturates class
	TSH	Opiates class
		Propoxyphene
	S-β-hCG pregnancy test	Methaqualone[c]
		Methadone
		Ethanol
		Urine for β-hCG pregnancy test

ALT alanine transaminase; AST aspartate transaminase; β-hCG beta human chorionic gonadotropin; BUN blood urea nitrogen; HBsAg hepatitis B surface antigen; HCV hepatitis C virus; HDL high density lipoprotein; $HgbA_{1c}$ glycosylated hemoglobin; HIV human immunodeficiency virus; LDH lactate dehydrogenase; LDL low density lipoprotein; PCP phencyclidine.

[a] Blood sampling for FSH will be conducted for all post-menopausal women under 50 years of age at screening only.

[b] HIV, HBsAg, HCV, and urine drug screen will be conducted at the screening visit only.

[c] Methaqualone testing will be conducted in South Africa only via a local laboratory.

Prefix: B for blood and S for serum.

For UDS, patients can be re-tested only if either the initial THC, opiate, or barbiturate result is positive and they have a prescription, but the patient should be excluded if the result is still positive at the second test. The retest of opiates should occur after a 2-week washout. Patients with positive UDS for a drug(s) legally available by prescription must provide evidence of prescription for the drug(s).

Samples should be taken by adequately trained study personnel and handled in accordance with given instructions. Volumes of blood samples are described in Section 7.1. The central laboratory (see Section 13.1) will perform all clinical laboratory determinations as listed in Table 7. Up-to-date reference lists will be provided during the study and laboratory results will be compared with 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. If the laboratory value is outside the normal range and clinically meaningful, it should be followed until resolution or until the investigator considers no further follow-up necessary. The paper copy should be signed and archived in the eCRF and is the source data for laboratory variables at the site.

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

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN, please refer to Appendix E "Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law", for further instructions.

6.4.6 Physical examination

A complete physical examination should be completed by a physician or any qualified licensed staff at the randomization visit (Week 1, Visit 2), and Week 14 (follow-up visit), 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: height, weight, and calculated BMI, 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 in centimeters (cm) and weight will be measured in kilograms (kg) with the patient wearing light clothing and without shoes.

6.4.7 ECG

6.4.7.1 Resting digital 12-lead ECG

Digital ECGs for all patients at all sites will be conducted at the sites using a machine provided by the central ECG laboratory [redacted] and will be transmitted to [redacted] (Section 13.1). Digital ECG will be performed at specified study visits at screening, prior to start of infusion (T_0), and at the end of the infusions (T_1). Table 8 displays a summary of the timing of study-related ECG assessments.

The ECG at T_0 of Visit 2 (Day 1) will be considered the baseline value.

Table 8 Schedule of ECG assessments after enrollment

			ECG assessments	
Week	**Visit**	**Infusion number**	**Predose (T_0)**	**Post dose (T_1)**
1	2	1	x	x
1	4	3		x
3	10	9		x
6	13	12		x
12	16	15		x

Digital ECGs will be obtained after the patient has been resting in a semi-recumbent position for at least 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 patient demographics will be conducted by a central laboratory operator at [redacted]. 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 site.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine BP and pulse rate will be measured at the screening visit, randomization (Day 1), and at each scheduled weekly visit, ending at Week 14 (Table 4).

An appropriately sized cuff will be used to obtain systolic and diastolic BP. Orthostatic BP should be assessed at baseline and at least 1 hour or 3 hours after the end of the infusion. The assessment will be done first with the patient in the supine position for 3 minutes and again within 3 minutes of the patient attaining a standing position. Standing and supine BP and pulse rate should be measured with the right arm at heart level.

6.4.8.2 Body temperature

Oral body temperature will be measured in degrees centigrade (°C) using an automated thermometer and will be taken at the screening visit, randomization (Day 1), and at each scheduled weekly visit (Table 4).

6.4.9 Other safety assessments

6.4.9.1 Medical, surgical, and medication history

A detailed medical surgical history including medication history will be recorded for each patient during the screening visit (Visit 1). Significant medical conditions that have occurred within the past 12 months (1 year) or conditions that are ongoing (ie, headache, backache, indigestion) will be recorded in the eCRF (Table 4).

The medication history must identify any known drug allergies, presence or history of drug abuse, and use of chronic medications.

6.4.9.2 Pregnancy test

A serum pregnancy test will be performed on all females at the screening visit (Visit 1). A negative urine pregnancy test is required each visit prior to the administration of IP for all WOCBP. If a pregnancy test is found to be positive at any time, the patient will not be able to continue participation in the study (see Table 4 for the timing of pregnancy testing and Section 13.3 for procedures in case of pregnancy).

6.4.9.3 Urine drug screen

A urine sample will be evaluated only during the screening visit. Additional evaluations may be performed at the discretion of the investigator. These additional assessments can be performed using a dipstick method such as a Clinical Laboratory Improvements Amendment (CLIA)-Waved dipstick, but if positive, the test should be confirmed by a full urine drug screen.

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 7).

Patients who have a positive UDS for a drug(s) legally available by prescription must provide evidence of the prescription for the drug(s). Patient can in some cases be re-tested and may be eligible to continue in the study, see exclusion criterion 9 for details.

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

6.4.9.4 Serology testing

Serology testing for HIV antibody, HBsAg, and HCV antibody will be performed on all patients during the screening visit only (Table 4). If a test is positive, the patient 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 patient's file, the results will not be collected on eCRFs and will therefore not be recorded in the study database.

6.4.9.5 CogState (cognitive functioning measurement)

The CogState battery selected for this study is a collection of 4 highly sensitive computerized neurocognitive tests assembled to meet the objectives of this study for brevity (12 to 15 minutes), sensitivity to areas previously reported to be affected by ketamine, another NMDA antagonist (psychomotor speed, attention, working memory, and short-term memory) and is appropriate for a depressed population. The tasks used (Detection task [DET], Identification task [IDN], One-card Learning task [OCL] and One-back task [OBK]) are all language free with the exception of test instructions, which are provided in the local language. Patients practice each test twice, during the screening visit, (or more frequently if required to assure complete understanding of the requirements of each task). If both practice tests could not be completed at the screening visit or if task understanding is not achieved at the screening visit, it is acceptable to administer one or more practice tests at the randomization visit. The patient must demonstrate complete understanding of each task prior to baseline testing. No sedatives, hypnotics, benzodiazepines, or sedating antihistamines are permitted within 12 hours of cognitive testing.

The CogState battery is presented on a laptop computer, with 2 external response buttons attached. At the beginning of each battery, a training task, called the "Fixed Response Mapping Task" is conducted. The purpose of this task is to train the patient on which is the "Yes" button and which is the "No" button. In the unlikely event that a patient has difficulty learning this, it is acceptable for study staff to place a small card or post-it note with the words No and Yes near the left and right buttons respectively.

On each trial of each cognitive task, a single playing card stimulus is presented in the center of the computer screen. The value, color, and suit of each playing card are determined according to the requirements of each cognitive task. At the presentation of each playing card stimulus patients are required to respond either "Yes" or "No" by pressing the designated button. At the beginning of each task, the rules are presented on the computer screen. They are also read out by the administrator to the participant. This is followed by a short practice of the task.

Once the practice are complete, the actual task begins. On each assessment, the 4 tasks are presented in the same order (ie, that given above). At the beginning of each task, participants are instructed to "respond as quickly and as accurately as possible." The CogState tests must be administered at designated visits prior to infusion.

6.4.9.6 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 C-SSRS must be administered at designated visits after the infusion.

6.4.9.7 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 CADSS must be administered at designated visits after the infusion.

6.5 Patient reported outcomes

The patient-reported outcomes of QIDS-SR-16 and SDS are discussed in Sections 6.2.2.1 and 6.3.2.2, respectively.

6.6 Pharmacokinetics

For timing of individual samples, refer to Table 9. The actual date and time of dosing and sample collection must be recorded on the appropriate eCRF page.

6.6.1 Collection of samples

Samples for determination of AZD6765 concentration in plasma will be analyzed by [redacted] 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 only be used to

confirm the reproducibility of the method and will be reported in a separate table in the bioanalytical study contribution report.

Venous blood samples (6 mL) will be taken at the times presented below. Pharmacokinetic sample collection during or after dosing should not occur on the same arm used for drug administration, except samples taken prior to drug administration (ie, trough samples). Individual venipunctures for each time point 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.

Six milliliter (6 mL) samples of whole blood will be collected into potassium ethylenediamine tetraacetic acid (K_2-EDTA) spray-dried tubes for the determination of AZD6765 in human plasma as follows:

Week 1: Infusion 1 at Visit 2 has 5 samples (0 hr, and 50 min, 2 hr, 3 hr, and 4 hr post dose)

Week 3: Infusion 9 at Visit 10 has 3 samples (0 hr, 70 min to 1.5 hr, 1.5 to 2 hr)

Week 6: Infusion 12 at Visit 13 has 3 samples (0.5 hr, 1.25 hr, 2 hr)

Week 12: Infusion 15 at Visit 16 has 3 samples (~1 hr, 70 mins to 1.5 hr, 2 to 4 hr)

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 (USA Nunc 1.8-mL polypropylene round-bottom [free-standing] tubes with screw cap, 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 or representative will instruct the site when to ship the retention sample.

Samples will be drawn at random according to the PK sample schedule in Table 9. All PK times given are based upon the time beginning at the start of the infusion, not relative to the end of the infusion. A maximum of 14 blood samples (approximately 84 mL) will be collected from each patient for PK assessments.

It is important that the actual date and time of the PK sample collection as well as the time and date and time of the administration of IP are recorded in the eCRF.

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

Table 9 Timing of PK sampling

	Visit	Infusion	1st sample[a]	Subsequent samples[a]	Number of samples
Week 1	**2**	Infusion 1	0 hr (T_0)	50 min, 2 hr, 3 hr and 4 hr	5
Week 3	**10**	Infusion 9	0 hr (T_0)	70 min to 1.5 hr, 1.5 to 2 hr	3
Week 6	**13**	Infusion 12: ≥7 days from Infusion 11 in Week 5	0.5 hr	1.25 hr, 2 hr	3
Week 12	**16**	Infusion 15: ≥14 days from Infusion 14 in Week 10	~1 hr	70 min to 1.5 hr, 2 to 4 hr	3
				Totals	14

[a] T_0 samples should be drawn before infusion is started.
Samples should be collected at random within the specified sample collection except where no window is given.
It is paramount that samples must be drawn in the arm opposite to the infusion arm, except samples taken prior to drug administration (ie, trough samples).
Samples scheduled to be drawn during the infusion period should be drawn while the infusion pump is still infusing.
Actual sample collection date and time as well as dosing date and time must be recorded in the eCRF.

6.6.1.1 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: D6702C00031
E-code:
Accession No.:
Visit No.:
Protocol Sampling Time:

Analyte: AZD6765

6.6.1.2 Shipment of AZD6765 plasma samples

All AZD6765 plasma samples accompanied by the sample shipment logs will be shipped via an agreed upon courier to the local [redacted] site. 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 monitoring scientist at AstraZeneca or representative 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 2 days prior to a legal holiday.

6.7 Pharmacodynamics

6.7.1 Collection and processing of serum samples for the determination of biomarkers

Venous blood samples (2 mL) (Table 10) for determination of biomarkers will be collected at the times presented in Table 4. Blood 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 time point 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 samples 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 or representative. 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.

Please see Section 7.5 for withdrawal of informed consent for donated biological samples.

6.7.2 Labeling of serum samples for determination of biomarkers

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

Study Number: D6702C00031
Patient Number:
Site Number:
Sample Number: (Tube and Set Number)

Week:
Visit:
Protocol Sampling Time:

Dose Number:
Analyte: AZD6765
Matrix: Serum

6.7.3 Shipment of serum samples to Rules Based Medicine Laboratories

All serum samples accompanied by the specimen shipment logs will be shipped via an agreed upon overnight courier to the local [redacted] site. 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.

The primary monitoring scientist at AstraZeneca or representative must be notified by email and fax at 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 2 days prior to a legal holiday.

6.8 Pharmacogenetics

6.8.1 Collection of samples

The blood sample for genetic research will be obtained from the patients at Visit 2 prior to randomization. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

AstraZeneca intends to perform genetic research on AZD6765 to explore how genetic variations may affect the clinical parameters associated with AZD6765. Collection of DNA samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets.

Refer to Appendix D for collection of PGx samples for the optional genetic research.

For blood volume, see Section 7.1.

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including glucose, serum pregnancy, and lithium)	**3**	**5**	**15**
	Hematology (without $HgbA_{1c}$)	**2**	**2**	**4**
	Hematology (including $HgbA_{1c}$)	**3**	**2**	**6**
Thyroid function tests		**2**	**1**	**2**
FSH		**1**	**1**	**1**
HIV, HBsAg, HCV		**6**	**1**	**6**
Pharmacokinetics (AZD6765 levels)		**6**	**14**	**84**
Pharmacodynamics (optional biomarker analysis)		**2**	**2**	**4**
Pharmacogenetics (optional)		**9**	**1**	**9**
Total[a]			**32**	**131**

[a] The total volume given is the upper limit of volume of blood to be drawn for scheduled assessments. The FSH sample will only be collected from women <50 years old who could be considered postmenopausal and the pharmacogenetic and biomarker samples are optional.

For patients who participate in optional genetic sampling, a 9 mL blood sample will be collected after randomization.

For patients who participate in optional serum biomarker analysis, a 2 mL blood sample will be collected at randomization and at Week 6.

7.2 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 including processing, handling, storage, and shipment of laboratory samples before the study start. The samples should be properly obtained, processed, labeled, stored, and shipped in accordance with the instructions provided by the laboratory. Samples should be shipped to the laboratory by courier unless otherwise agreed.

7.2.1 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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 person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient 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 when the patient has requested disposal/destruction of collected samples not yet analyzed.

Refer to Appendix D for collection and storage of PGx samples.

7.3 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 Appendix C "International Airline Transportation Association (IATA) 6.2 Guidance Document").

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

It is the responsibility of the PI to ensure that staff packing the samples for shipment are IATA certified.

7.4 Chain of custody of biological samples

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

The PI at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

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

The CRO is responsible for keeping oversight of the samples during the study.

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

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed/destroyed, if not already analyzed and the action documented. If samples are already analyzed, AstraZeneca or representative is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is conveyed immediately to AstraZeneca or its representative.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, and the action documented and the signed document returned to the study site.
- Ensures the patient and AstraZeneca or its representative are informed about the sample disposal.

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

7.5.1 Procedures for discontinuation from optional genetic aspects of the study

Patients 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 patient:

- 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 or representative 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 patient 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 patient 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 along with copies of the relevant documentation detailing study code and patient enrollment code. AstraZeneca or representative and the PI will receive written confirmation from the Clinical Genotyping Group that the genetic sample has been destroyed.

If the withdrawal of consent for donated biological samples is limited only to the pharmacogenetic samples, the patient need not necessarily be withdrawn from further study participation.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 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.

8.2 Subject data protection

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

AstraZeneca or representative will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An IRB/Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF and assent form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/EC, and to the study site staff.

The opinion of the IRB/EC should be given in writing. The investigator should submit the written approval to AstraZeneca or representative before enrollment of any patient into the study.

The IRB/EC should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative should approve any modifications to the ICF and Assent Forms that are needed to meet local requirements.

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

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

AstraZeneca or its representative will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or its representative will provide regulatory authorities, IRBs/ECs, and PIs with safety updates/reports according to local requirements including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each PI is responsible for providing the IRB/EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca or its representative will provide this information to the PI so that he/she can meet these reporting requirements.

8.4 Informed consent

The PI at each site will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study.
- Ensure that each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICFs are stored in the investigator's study file.
- Ensure a copy of the signed ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an IRB/EC.

8.5 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 CSP, then these changes will be documented in a study protocol amendment and in a new version of the CSP (Revised CSP).

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to the IRB/EC, see Section 8.3.

If a protocol amendment requires a change to a site's ICFs, AstraZeneca and the site's IRB/EC are to approve the revised ICFs before the revised form is used.

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

8.6 Audits and inspections

Authorized representatives of AstraZeneca, the regulatory authority, or the IRB/EC may perform audits or inspections at the site, 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 CSP, 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 site.

9. STUDY MANAGEMENT BY ASTRAZENECA

Study management will be performed by the designated CRO.

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of the CRO to discuss with and/or visit the site to:

- Determine the adequacy of the facilities.
- Determine availability of appropriate patients for the study.
- Discuss with the investigator (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the CRO. This will be documented in a CSA between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, a representative of the CRO will review and discuss the requirements of the CSP and related documents with the site staff and also train them in any study-specific procedures and systems 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).

9.3 Monitoring of the study

During the monitoring visits, a representative of the CRO will have regular contacts with the study site including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the site staff is adhering to the CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that IP accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent/assent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The CRO representative will be available between visits if the investigator(s) or other staff at the site needs information and advice about the study conduct.

9.3.1 Source data

Source data are any data generated as a result of the patients' inclusion in the study (including run-in and/or follow-up related to the study) and includes all related medical examinations and other records. Original data recorded on the eCRFs are regarded as source data.

Refer to the CSA for location of source data.

9.4 Study agreements

The PI at each site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

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

- Signed CSA between AstraZeneca and the PI/study site
- Signed CSP and other agreements between AstraZeneca and the PI/study site
- Written approval of the study by the IRB/EC
- Signed and dated Financial Disclosure forms

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." The end of study definition is for the entire study.

The study is expected to start in the [redacted] and to be completed by [redacted]

The study may be terminated at individual sites 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.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management (DM) will be performed by the CRO. The data collected through third party sources will be obtained and reconciled against study data.

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 patient'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 patients at their own sites. Data management and other co-ordinator teams will have access to data at all sites.

AstraZeneca or its representative will supply the eCRFs. All eCRFs are to be completed by an authorized member of the site 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 site 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 patient's eCRF correspond to the entries on the patient's medical records.

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

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

Dataflow

The data will be validated as defined in the DM Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

After data are entered into the eCRF by site, autoqueries that are generated by the eDC system should be addressed by site. Data queries will be raised for inconsistent, impossible, or missing data. At the monitoring visit, the Study Monitor must perform the source data verification (SDV) of the required fields on completed forms and if there are no open queries, freeze the form. Data management 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 are 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. Any treatment revealing data may thereafter be added and the final database will be locked. All entries to the study database will be available in an audit trail.

Database lock

Once all patient 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 classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the AstraZeneca 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 site. 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.

PGx reporting

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variables

11.1.1 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.

The following definitions will apply to the efficacy analyses:

- Response is defined as a ≥50% reduction from baseline in the MADRS total score
- Remission is defined as MADRS total score ≤8
- Sustained response is defined as a ≥50% reduction from baseline in the MADRS total score at Week 6 and which is maintained through Week 12

11.1.2 QIDS-SR-16

The QIDS-SR-16 total score is derived from 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.

The QIDS-SR-16 total scores range from 0 to 27. The total score is obtained by adding the scores for each of the 9 symptom domains of the DSM-IV-TR MDD criteria: depressed mood, loss of interest or pleasure, concentration/decision making, self-outlook, suicidal ideation, energy/fatigability, sleep, weight/appetite change, and psychomotor changes (Rush et al. 2003). Sixteen items are used to rate the 9 criterion domains of major depression: 4 items are used to rate sleep disturbance (early, middle, and late insomnia plus hypersomnia); 2 items are used to rate psychomotor disturbance (agitation and retardation); 4 items are used to rate appetite/weight disturbance (appetite increase or decrease and weight increase or decrease). Only 1 item is used to rate the remaining 6 domains (depressed mood, decreased interest, decreased energy, worthlessness/guilt, concentration/decision making, and suicidal ideation). Each item is rated 0 to 3. For symptom domains that require more than 1 item, the highest score of the item relevant for each domain is taken. For example, if early insomnia is 0, middle insomnia is 1, late insomnia is 3, and hypersomnia is 0, the sleep disturbance domain is rated 3. The total score ranges from 0 to 2.

The total score is calculated as follows from the following 9 scores.

The maximum score of the 4 sleep items (item 1 to item 4)

The score for item 5

The maximum score of the 4 appetite/weight items (item 6 to item 9)

The scores for item 10 to item 14

The maximum score of the 2 psychomotor items (item 15 and item 16)

Total scores range from 0 to 27.

11.1.3 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.

For CGI-I, the score will be evaluated at each assessment following randomization. Also, a binary variable, CGI-I response, will be calculated as ≤ 2 (very much or much improved) or >2.

11.1.4 HAM-D-17 and HAM-A

The HAM-D-17 total score will be calculated as the sum of the first 17 individual item scores on the HAM-D-17 GRID score sheet; the total score can range from 0 to 52. Items 18 to 21 will be regarded as single items. It is used solely as an entry criterion.

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.

Change from baseline to each assessment will be calculated as the visit score minus the baseline score.

11.1.5 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.

11.2 Calculation or derivation of safety variables

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

11.2.1 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 discontinuations due to adverse events (DAEs). Based on the expert's judgment, 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. A similar review of laboratory, vital signs, and ECG data will be performed for identification of OAEs.

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

11.2.2 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.

11.2.3 Weight and BMI

A screening and baseline BMI will be calculated. Change from baseline to Week 14 will be calculated as the Week 14 value minus the baseline value. Also, the proportions of patients who have a weight gain ≥7% compared with baseline will be tabulated.

11.2.4 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 calculated QTcF interval.

11.2.5 Vital signs

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

11.2.6 Other safety assessments

11.2.6.1 C-SSRS

Occurrence of suicidal behavior after baseline up to Week 3 will be defined as having answered "yes" to at least 1 of the 4 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 1 of the 5 suicidal ideation subcategories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [no 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.

11.2.6.2 CADSS

The CADSS is a 23 item self-report scale (Bremner et al 1998). It is a reliable, valid self-report instrument. The severity of each dissociative symptom range from 0 (not present) to 4 (extreme). The change from baseline at each scheduled assessment in CADSS total score will be calculated.

11.2.6.3 CogState

Outcome measures of CogState Battery

For each cognitive task, a single primary outcome measure was selected from each test in the battery to minimize experiment-wise error rates. Each primary outcome measure was selected because it has been shown to be optimal for the detection of change because:

- it is drawn from a data distribution that contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values.

- it is drawn from a distribution that is distributed normally or which can be corrected to normal through the use of appropriate mathematical transformation (e.g., logarithmic base 10, or arcsine).

Table 11 summarizes the primary outcome measures for each task in CogState battery the operational definition and the variable code.

Table 11 CogState outcome measures and the cognitive tasks

Task name	Major cognitive domain	Unit of measurement	Description
Detection Task*	Psychomotor speed	Log10 milliseconds	Speed of performance; mean of the log10 transformed reaction times for correct responses (lower score = better performance)
Identification Task*	Attention/ vigilance	Log10 milliseconds	Speed of performance; mean of the log10 transformed reaction times for correct responses (lower score = better performance)
One-card Learning*	Visual learning	Arcsine proportion correct	Accuracy of performance; arcsine transformation of the proportion of correct responses (higher score = better performance)
One-back	Working memory	Arcsine proportion correct	Accuracy of performance; arcsine transformation of the proportion of correct responses (higher score = better performance)

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 SDS

The SDS total score will be calculated as the sum of the scores for the 3 inter-correlated domains (school/work, social life, and family life/home responsibilities). Each domain score can range from 0 to 10 and the total score can range from 0 to 30. The total score will be calculated only for patients who rate all 3 domains. Change from randomization will be calculated for the total score and for each domain score.

11.4 Calculation or derivation of pharmacokinetics variables

The population PK analysis will be performed by AstraZeneca Research and Development. 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 modeling, 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.

11.4.1 Pharmacokinetics analysis method

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

11.5 Calculation or derivation of pharmacodynamic variables

See Section 11.1 for details.

The biomarker panel will be analyzed by Rules Based Medicine. The data will be analyzed separately and the results may be included in the CSR.

11.6 Calculation or derivation of pharmacogenetic variables

Results from the optional exploratory genetic research performed will be reported separately from the CSR.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

12.1.1 Efficacy analysis sets

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

The mITT analysis set will include all randomized patients, who took IP and who have a baseline MADRS total score assessment and at least 1 post-baseline MADRS total score classified according to their randomized treatment. The mITT analysis set will be used for the efficacy analyses.

12.1.1.2 Per-protocol (PP) analysis set

The PP analysis set will include only those mITT patients who have no significant protocol deviation, and who received the treatment to which they were randomized. The Statistical Analysis Plan (SAP) will provide the exact criteria for defining the PP analysis set. The analysis of the primary efficacy variable will be repeated on the PP analysis set, and additional analyses of efficacy variables may be performed using the PP analysis set to assess the robustness of the treatment effects.

12.1.2 Safety analysis set

The safety analysis set will include all randomized patients who were given at least 1 dose of IP, and for whom any post-dose data are available and are classified according to the treatment actually received. That is, erroneously treated patients (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.

12.2 Methods of statistical analyses

Details of the statistical analysis methods will be provided in a comprehensive SAP that will be prepared and finalized prior to unblinding.

In general, all efficacy, safety, and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean standard deviation (SD), median, minimum and maximum). For PK variables, the geometric mean and CV will be used instead of the arithmetic mean and SD, if appropriate. Categorical variables will be summarized in frequency tables (n, frequencies, and percentages). Individual patient data will be presented in listings.

All statistical tests will be conducted at a 2-sided significance level of 5% unless otherwise specified. In general, each of the AZD6765iv dose groups (50 mg and 100 mg) will be compared with the placebo group. Where appropriate, model-based point estimates, together with their 95% Cis, will be presented along with the 2-sided p-value for the test.

12.2.1 Primary efficacy analysis

The primary efficacy variable, change from baseline to Week 6 in the MADRS total score, will be analyzed using a Mixed Model Repeated Measures (MMRM) analysis of all of the post-baseline MADRS total scores through the end of the study (Week 14). The MMRM model will include treatment, visit, treatment by visit interaction, and the baseline MADRS total score as fixed effects, and site as a random effect. Restricted Maximum Likelihood (REML) with an unstructured variance-covariance matrix will be used for estimation in the MMRM analysis. If the model with unstructured covariance does not converge, the model with the non-iterative minimum variance quadratic unbiased estimation will be tried first. If it still fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. Each AZD6765iv dose will be compared with placebo; model-based point estimates for the treatment effects, 95% CIs, and p-values will be calculated.

Subgroup analyses may be performed by age, gender, race, and background antidepressant.

The MMRM analysis of the MADRS total score will be repeated on the PP analysis set to assess the robustness of the results.

For exploratory purposes, the impact of family history of alcoholism and pharmacogenetic biomarkers such as the GABRA2 gene on the primary endpoint and sustained response will be evaluated.

12.2.2 Secondary efficacy analyses

Change from baseline in the MADRS total score at Week 12 and at the other scheduled visits will be assessed using the MMRM analysis used for the primary efficacy variable. At each visit, each AZD6765iv dose will be compared with placebo and model-based point estimates for the treatment effects, 95% CIs, and p-values will be calculated. The MMRM analysis of

the MADRS total score will be repeated on the PP analysis set to assess the robustness of the results.

For the other continuous secondary efficacy variables (change from baseline in the CGI-S score, the SDS total score, the HAM-A total score, and the QIDS-SR-16 total score at each scheduled assessment), the same MMRM approach as for the primary efficacy variable will be used for the analysis.

For the binary secondary efficacy variable with only a single post-baseline assessment (sustained response), the analysis will be performed using logistic regression with independent variables of treatment and the baseline MADRS total score.

For the binary secondary efficacy variables with multiple post-baseline assessments (response, remission, and CGI-I response), the analysis will be performed using a generalized linear model of the repeated measures. A logit link function will be used and the statistical inferences will be based on Generalized Estimating Equations (GEE). Independent variables will be treatment and a baseline measurement related to the dependent analysis variable. For response and remission, the baseline MADRS total score will be used as the baseline measurement; for CGI-I response, the baseline CGI-S score will be used.

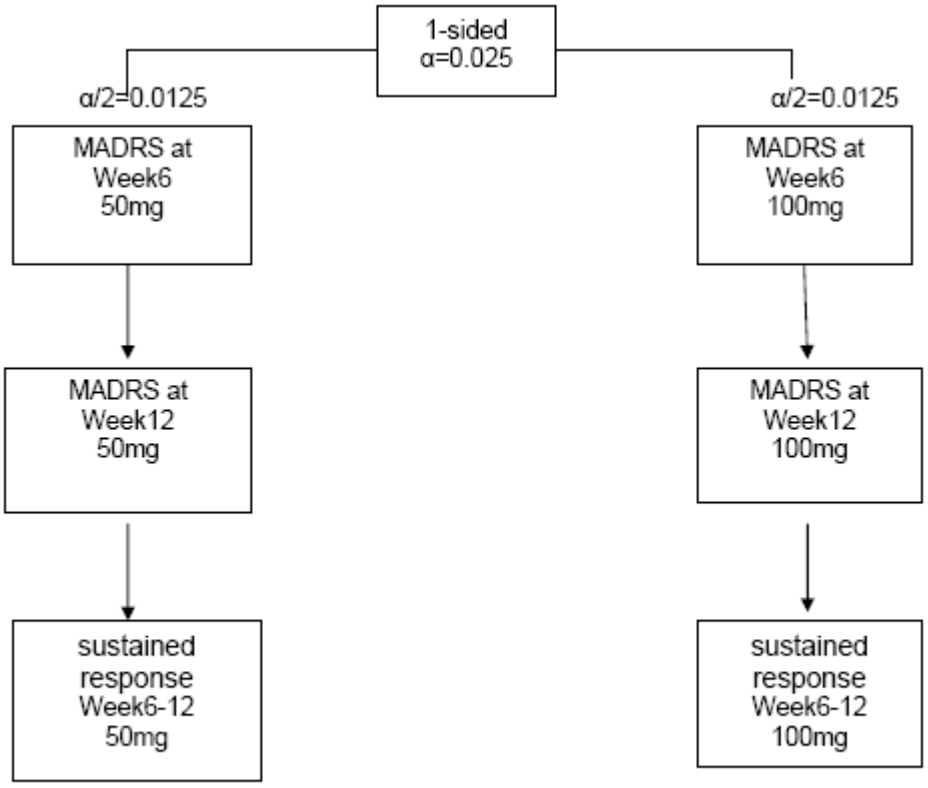
The exploratory variables of continuous and binary types will be evaluated the same way as for the secondary efficacy variables

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

12.2.3 Multiplicity adjustments for the primary and key secondary variables

The proposed basic testing strategy will be in the order as follows: 1) primary endpoint of MADRS change from baseline at Week 6; 2) key secondary endpoint of MADRS change from baseline at Week 12; 3) key secondary endpoint of sustained response from Week 6 to Week 12. The overall, family-wise type-I error rate at α=0.05 (α=0.025 one-sided) will be equally split in half (α=0.0125 one-sided) for each of the 2 doses (50 mg and 100 mg) versus placebo. For each dose versus placebo, if the primary endpoint of MADRS change from baseline at Week 6 is significant, then its test mass is recycled to test the first key secondary endpoint of MADRS change from baseline at Week 12. If the first key secondary endpoint is significant, then its test mass is recycled to test the second key secondary endpoint of sustained response from Week 6 to Week 12. The testing strategy is displayed graphically in Figure 2. This approach controls the overall family-wise type-I error rate at α=0.05 (α=0.025 one-sided) in the strong sense.

Figure 2 Multiplicity adjustment strategy



12.2.4 Safety analyses

Adverse events will be coded using the 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 patients 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.

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

Descriptive statistics will be used to present the safety outcomes including incidences and severity of AEs and SAEs; incidences of AEs leading to treatment discontinuation and study withdrawal, incidences of AEs associated with suicidality, and incidences of OAEs; changes from baseline in physical examination results, weight, BMI, vital signs, clinical laboratory test

results, and ECG results; suicidality as assessed by C-SSRS; and changes from baseline in CADSS total scores.

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 patients who have a weight gain ≥7% compared with baseline will be tabulated.

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

The results of the PK and pharmacogenetic analyses will be presented in reports separate from the CSR.

12.2.5 Interim analyses

No interim analysis for efficacy is planned.

12.2.6 Handling of missing data

Despite efforts to minimize missing data in the design and conduct of this study, the problem of missing data is unavoidable in any MDD study due to patient dropout. Based on the previous Phase II study of D6702C00009 data, estimates for dropouts in the current study are approximately 14% by Week 6 and an additional 10% dropout by Week 12. These missing data will have some impact on the efficacy. The degree of the impact on the efficacy analysis will depend on the analysis method used, dropout reasons, amount and pattern of missing data, and the magnitude of expected treatment effect.

To mitigate the effect of dropouts on the efficacy analysis, the proposed analysis plan includes multiple layers to capture as complete a dataset as possible. First, patients will be asked to return to the clinic to collect primary and key secondary endpoint measures for the intended study period of 12 weeks even after the patient discontinues the study in order to provide the most complete dataset possible of all randomized patients. This retrieved dropout information will be included in the main efficacy analysis. Second, the reasons, proportions, and timing of patient withdrawal from the study for each treatment group will be carefully collected and adequately described and presented to help evaluate the scale of the missing data. Third, a MMRM analysis is proposed for the primary analysis. The MMRM is considered as a method of handling missing data, which does not employ explicit imputation. The MMRM methods provide a valid approach in the case that data are missing at random (MAR). The MAR is a less restricted assumption than the most restricted missing completely at random (MCAR) assumption upon which last observation carried forward (LOCF) and complete case analysis are based.

Nevertheless, missing not at random (MNAR) can never be ruled out. As indicated in regulatory guidelines and published literature that all methods require untestable assumptions because the “missingness” mechanism involves assumptions about the relationships among variables with missing values and results often vary depending on the assumptions made about

these relationships. Furthermore, the validity of these assumptions cannot generally be determined from the collected data. Therefore, there is no single correct method for handling missing data and specific sensitivity analyses under MNAR will be proposed to assess the robustness of the primary MMRM results. These MNAR sensitivity analyses, along with their justifications, including some type of Pattern-Mixture approach, will be detailed in the SAP.

In general, unless otherwise indicated, no data imputation will be done for the missing values.

12.3 Determination of sample size

The sample size calculation in this study was done to ensure a 90% power to show that at least 1 of the 2 AZD6765 doses will be better than placebo with regard to the primary outcome variable, change in MADRS total score from baseline to Week 6. The sample size was calculated by assuming an anticipated difference of 5.5 units from placebo and a standard deviation of 10 for the change in MADRS total score from baseline to Week 6. Based on the Bonferroni multiplicity adjustment, the one-sided significance level is planned at 1.25%, which yielded a planned sample size of 84 patients per arm required at Week 6 for the primary analysis. Assuming approximately 10% of information will be lost at Week 6 due to dropout, it is estimated that 282 patients (94 patients per arm) will need to be randomized.

The assumptions for the sample size estimation were based on the results of the targeted subgroup (HAM-D-17 ≥24, CGI-S ≥5, QIDS-SR-16 ≥19) from previous a Phase II study of D6702C00009. The average treatment difference observed for AZD6765 100 mg and 150 mg versus placebo at Week 3 in this targeted subgroup was about 5.5. With the continuous once-a-week iv treatment, we expect the same treatment effect can be maintained to the primary time point at Week 6. The observed SD in this targeted subgroup was about 10 across the 3 treatment groups from this study. The dropout rates for D6702C00009 study was about 6% at Week 3 and about 19% at Week 8, so we expect about 14% dropout rate by Week 6 and an additional 10% dropout by Week 12. The MMRM approach on the primary variable uses the correlation between visits that allows us to recover some lost information. The correlations among these visits were between 0.4 and 0.7 in Study D6702C00009, so it seems to be reasonable to assume this correlation to be about 0.5. With this assumption, we expect to recover about 30% of the lost information by the MMRM approach (Lu et al 2008).

The sample size for this study was selected to be consistent with the research hypothesis.

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP will be prepared where appropriate.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and contacts

The PI is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

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

Name	**Role in the study**	**Telephone number**
[redacted]	Global Medical Advisor 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]

13.2 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. For the AZD6765iv program, any overdoses of AZD6765iv, placebo, or antidepressant therapy in the interval from Visit 2 to the end of follow-up should be recorded. Overdose is defined as a dose ingested (or taken via any other route), confirmed by the patient (if possible), in excess of the total daily dose specified for the patient in their treatment group of the protocol (including prospective antidepressant therapy).

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 AEs, the patient 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 IP in doses in excess of that specified in the protocol should not be recorded in the 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 IP 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 patients is collected by AstraZeneca or representative and forwarded to AstraZeneca's clinical patient safety data entry sites. Should a patient experience an overdose during the course of the study (whether accidental or deliberate), the investigator or qualified designee must contact AstraZeneca or representative **within 1 business day,** ie, immediately, but no later than **the end of the next business day** of when the investigator or qualified designee first becoming aware of the overdose.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca patient safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

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

13.3.1 Maternal exposure

Requirements for contraception in WOCBP are specified in inclusion criterion #2 (Section 4.1).

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within 1 day** ie, immediately, but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 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 patients must refrain from fathering a child during the study and **3 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 patient'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.

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Clinical Study Protocol Appendix B

Drug Substance	AZ6765
Study Code	D6702C00031
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Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the subject 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 subject'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).

Hospitalisation

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

Important medical event or medical intervention

Medical and scientific 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, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical 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 anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- 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 subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

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

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

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

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? 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 recognised 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	AZ6765
Study Code	D6702C00031
Edition Number	1.0
Date	[redacted]

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are 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. Category 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 Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation 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
Study Code	D6702C00031
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix D
Pharmacogenetics Research

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the AZD6765 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD6765. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD6765 but also susceptibility to Major Depressive Disorder for which AZD6765 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

2. GENETIC RESEARCH OBJECTIVES

To the Author:

- Use the default paragraph below.
- Where the project/study team has agreed that an objective with a "narrow" scope of research is appropriate, the above paragraph should be edited to provide the specific details– eg, research only on drug response, or only on named genes etc.
- Consult the local or therapeutic area pharmacogenetics advisor/ project for advice.

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD6765.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2 prior to randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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 person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be coded. The link between the subject enrolment/randomisation 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.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

To the Author:

- Delete this duplicate text from the CLINICAL STUDY PROTOCOL and reference the PGx Appendix.
- Indicate whether data will be reported in the CSR for the main study or will be reported separately.
- Where genetic data will be merged with the clinical database use the standard text given in option 1 below.
- Where genetic data will not be merged with the clinical database use standard text given in option 2 below.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

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.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES (NOT APPLICABLE)

AstraZeneca

Clinical Study Protocol Appendix E	
Drug Substance	AZD6765
Study Code	D6702C00031
Edition Number	1.0
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Appendix E

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

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

When a subject has an AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit, the central laboratory will immediately send an alert to the Investigator (also sent to the AstraZeneca representative)

If a subject is found to meet PHL criteria from a local laboratory sample:

- Repeat test with the central laboratory
- Complete the appropriate laboratory CRF modules with the original local laboratory test result.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP

- Completes the Liver CRF Modules.

- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP,

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

- As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

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

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

Clinical Study Protocol Appendix F

Drug Substance	AZD6765
Study Code	D6702C00031
Edition Number	1.0
Date	[redacted]

Appendix F
DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder

1. DSM-IV-TR DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER

Criteria for Major Depressive Episode

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

Note: Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(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 (e.g., 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 (e.g., 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

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

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

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

E. The symptoms are not better accounted for by Bereavement, i.e., 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.

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.

Clinical Study Protocol Administrative Change Number 1

Drug Substance	AZD6765
Study Code	D6702C00031
Date	[redacted]
Protocol Dated	[redacted]

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

[redacted]

Sponsor:

[redacted]

Centres affected by the Administrative Change:

All

The protocol for the study is to be changed as follows:

Section of protocol affected:

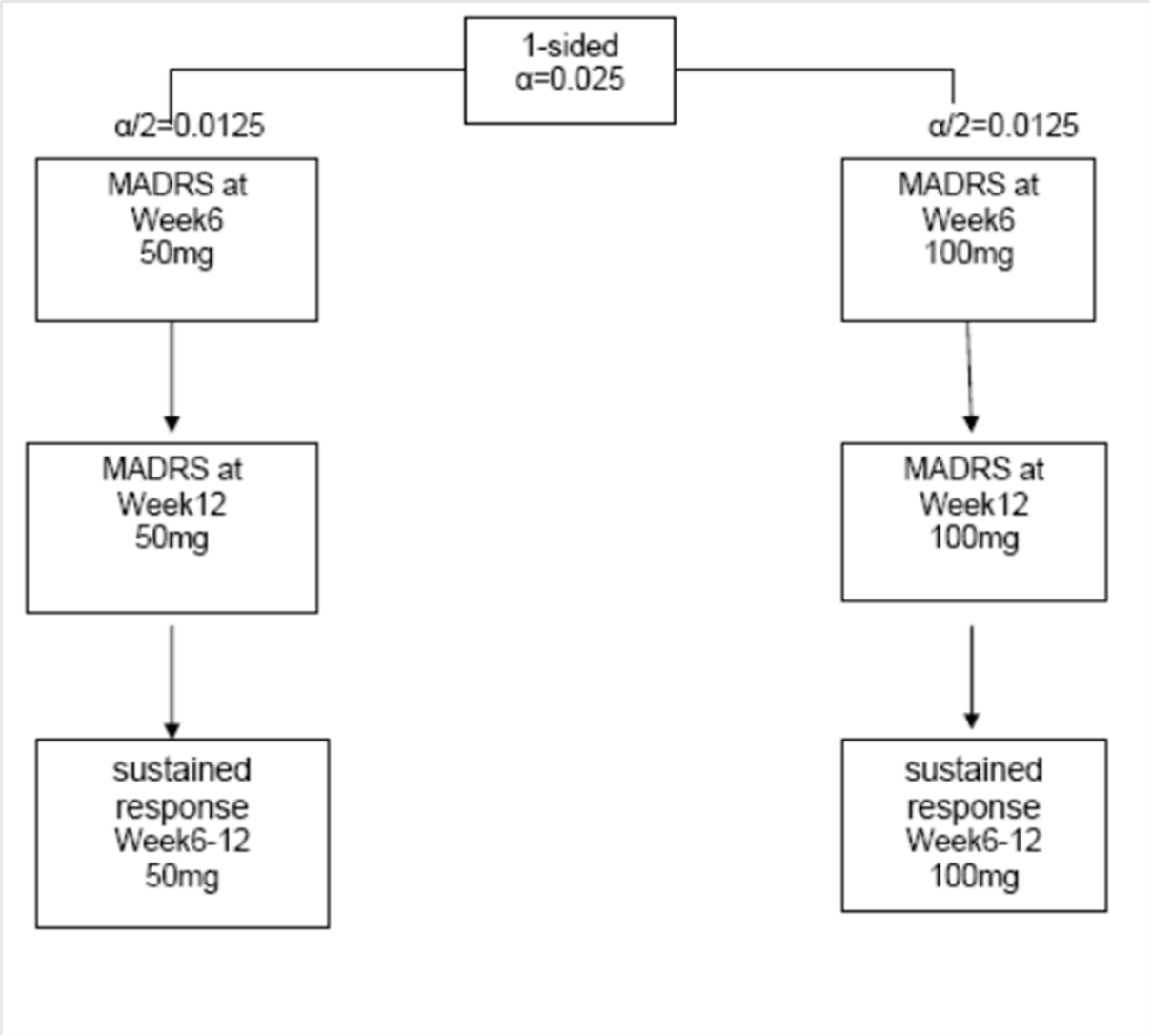
12.2.3 Multiplicity adjustment for the primary and key secondary variables

Previous text:

The proposed basic testing strategy will be in the order as follows: 1) primary endpoint of MADRS change from baseline at Week 6; 2) key secondary endpoint of MADRS change from baseline at Week 12; 3) key secondary endpoint of sustained response from Week 6 to Week 12. The overall, family-wise type-I error rate at α=0.05 (α=0.025 one-sided) will be equally split in half (α=0.0125 one-sided) for each of the 2 doses (50mg and 100mg) versus placebo. For each dose versus placebo, if the primary endpoint of MADRS change from baseline at Week 6 is significant, then its test mass is recycled to test the first key secondary endpoint of MADRS change from baseline at Week 12. If the first key secondary endpoint is significant, then its test mass is recycled to test the second key secondary endpoint of sustained response from Week 6 to Week 12. The testing strategy is displayed graphically in

Figure 2. This approach controls the overall family-wise type-I error rate at α=0.05 (α=0.025 one-sided) in the strong sense.

Figure 1 Multiplicity adjustment strategy



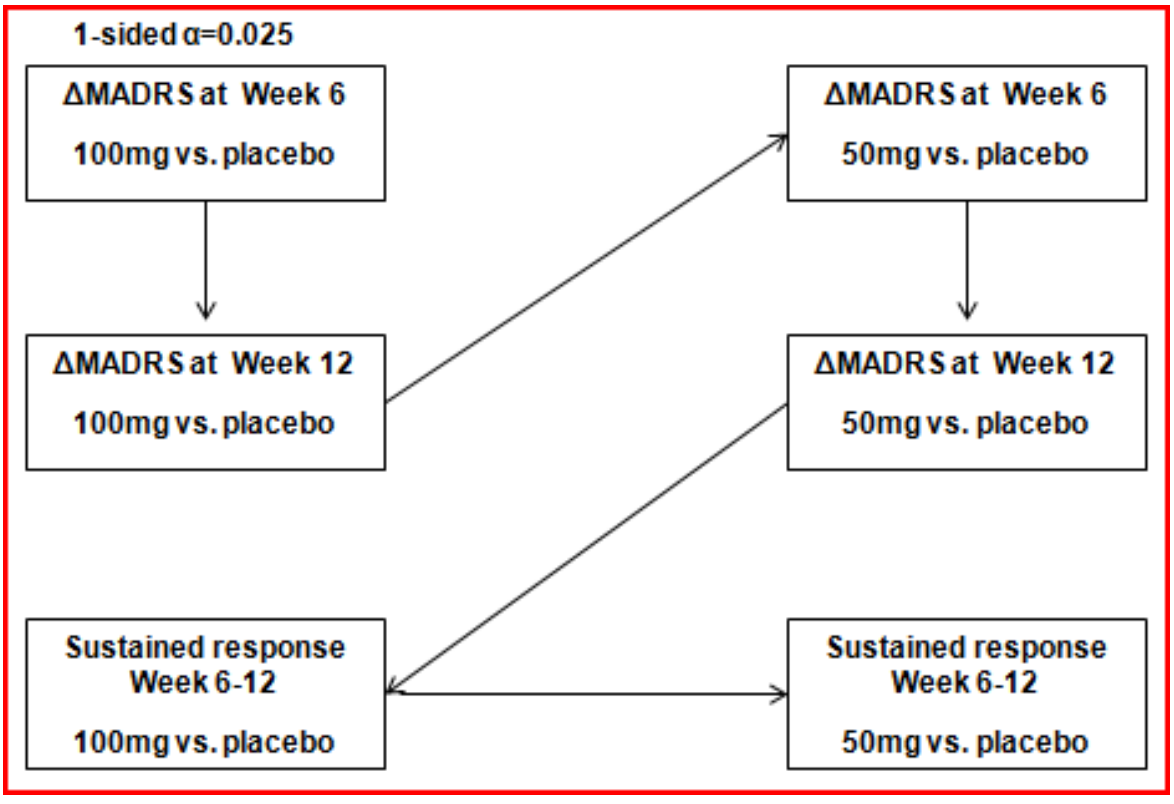
Revised text:

The proposed testing strategy will be a fixed sequence testing procedure in the strict order as follows: 1) primary endpoint of MADRS change from baseline at Week 6 for AZD6765 100mg versus placebo; 2) key secondary endpoint of MADRS change from baseline at Week 12 for AZD6765 100mg versus placebo; 3) primary endpoint of MADRS change from baseline at Week 6 for AZD6765 50mg versus placebo; 4) key secondary endpoint of MADRS change from baseline at Week 12 for AZD6765 50mg versus placebo; 5) key secondary endpoint of sustained response from Week 6 to Week 12 for AZD6765 100mg

versus placebo; 6) key secondary endpoint of sustained response from Week 6 to Week 12 for AZD6765 50mg versus placebo. This fixed sequence testing procedure controls the overall family-wise type-I error rate at two-sided α=0.05 (one-sided α=0.025). The fixed sequence procedure starts by testing the first pre-specified hypothesis. If it is significant at two-sided α=0.05, then its test mass is recycled to test the second hypothesis. If the second hypothesis test is significant, then its test mass is recycled to test the next hypothesis. This process continues until either an insignificant p-value (two-sided $p>0.05$) is obtained or all 6 hypothesis tests are completed. In the case when an insignificant p-value is obtained, all subsequent tests will be considered as non-significant. The adjusted p-values for this fixed sequence testing procedure will be reported. The adjusted p-value for the first test is its raw unadjusted p-value. The adjusted p-value of each step starting from the second step is the maximum of the p-values of all the steps up to the step to be adjusted. Superiority of AZD6765iv compared with placebo is established if the results favour AZD6765 with adjusted two-sided p-value ≤ 0.05.

This fixed sequence testing procedure is displayed graphically in Figure 2.

Figure 2 Multiplicity adjustment strategy



Reason for Administrative Change:

The sample size calculation in this study was based on the observed 5.5 difference of primary endpoint for AZD6765 100 mg versus placebo at Week 3 from previous Phase II study (D6702C00009). However, we later realized that this assumption may be too optimistic as the collection of the primary efficacy data in this study is one week after the most recent infusion which is different than the collection of primary efficacy data at 2 hours after the start of most recent infusion in study D6702C00009. A more conservative estimate of the treatment effect would be from Week 4 and 5 (1 & 2 weeks after the last infusion) data of the previous study D6702C00009. The estimates of the treatment effect from Week 4 and 5 for AZD6765 100 mg versus placebo were 4.4 and 4.9 (LSM difference), respectively. Therefore, an estimate of 4.5 is a more likely estimate of the treatment effect we will see in the current study at Week 6. To compensate for the loss of power due to the more conservative effect size, we propose to modify our multiplicity adjustment procedure for the primary and key secondary variables as indicated in the previous section. The order of proposed testing sequence is based on the confidence we have on the dose and likelihood of success on these hypotheses. Without any modification to the multiplicity adjustment procedure, the power will reduce from 90% to about 74% for the first hypothesis test of AZD6765 100 mg versus placebo at Week 6 assuming the current sample size, and the more conservative effect size. With the proposed modified multiplicity adjustment procedure, the power will improve to about 82% for the same first hypothesis test.

Persons who initiated the Administrative Change:

[redacted]

Signed agreement to the Administrative Change:

I hereby approve the Administrative Change to the Clinical Study Protocol.

Study Code: D6702C00031

.....	.....
Date	AstraZeneca Study Leader
(Day Month, Year)	[redacted]