Clinical Pharmacology Study Protocol

Drug Substance	AZD6765
Study Code	D6702C0001
Date	[redacted]

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Parallel-Group Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

Sponsor:

AstraZeneca Pharmaceuticals LP 1800 Concord Pike, Wilmington, DE 19850

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**
Administrative Change No.	**Date of Administrative Change**

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE, PREGNANCY, SUICIDE ATTEMPT OR SUICIDE

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address and Telephone number
Study Delivery Team Leader	[redacted]	[redacted]
Study Delivery Leader	[redacted]	[redacted]
Study Delivery Team Physician	[redacted]	[redacted]

For further clarifications regarding:

- Procedures in case of medical emergency see Section 8.2
- Procedures in case of overdose see Section 8.3.
- Procedures in case of pregnancy see Section 8.4
- Procedures in case of suicide attempt or suicide see 8.5

PROTOCOL SYNOPSIS

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Parallel-Group Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

Investigator

This will be a multi- center study conducted in the US.

Study center(s), type and number of subjects planned

This will be a multi-center study. A sufficient number of male and female patients with treatment resistant major depressive disorder between the ages of 21-65 years old inclusive will be screened to ensure that approximately 50 patients are randomized into the study to obtain 40 evaluable patients.

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

Objectives

Primary objective:

The primary objective of the study is to determine whether a rapid antidepressant effect can be achieved with intravenous (IV) doses of up to 100 mg of AZD6765, in patients with Treatment Resistant Depression (TRD) determined by a change from baseline to 24 hours in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Secondary objectives:

1. To assess the safety and tolerability of IV doses of up to 100 mg of AZD6765 at the designed infusion rate as assessed by vital signs, physical examination, clinical laboratory evaluations, electrocardiograms (ECG's) and the incidence of adverse events.

2. To investigate the effects of IV doses of up to 100 mg of AZD6765 on subject mood, anxiety, perception and cognitive function using a battery of: Montgomery-Åsberg Depression Rating Scale (MADRS), Visual Analogue Scale (VAS), Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Beck Depression Inventory (BDI), Clinical Global Impression (CGI) and CogState.

3. To explore the potential Pharmacokinetic/Pharmacodynamic (PK/PD) relationship of IV doses of up to 100 mg of AZD6765 exposure calculated by C_{max} and AUC and/or cognitive function or MADRS.

4. To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of AZD6765.

Study design

This will be a multi-center, randomized, double-blind, placebo controlled, parallel-group study conducted in male and female patients who are between the ages of 21 and 65 years old inclusive with TRD. This study will consist of a screening period of up to 30 days, 1 inpatient treatment period and 1 follow-up visit.

Investigational product, dosage and mode of administration

Patients will be randomized to either AZD6765 (Treatment A) or placebo (Treatment B) on a 1:1 randomization ratio. Treatments will be determined by the randomization schedule (generated by Global Randomization (GRand)).

Treatment A: Treatment A will consist of 1 dose of 100 mg of AZD6765 given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute (1.67 mg/minute) over 60 minutes. (The dose may be reduced based on emerging safety data).

Treatment B: Treatment B will consist of 1 dose of 0.9% saline (placebo) given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute over 60 minutes.

Duration of treatment

The duration of participation will be up to 45 days including:

- **Screening Period** (**Visit 1**) of up to 30 days prior to Day 1 of the Treatment Period. After signing informed consent all patients will undergo a health examination including a review of medical/surgical history, medication history, a physical examination, an ECG, assessment of vital signs, review of depression history and severity of depression and clinical laboratory evaluations. All female patients will be required to provide a blood sample for a pregnancy test. All patients will be required to stop current treatment for TRD 7 days prior to Day 1 of the Treatment Period (or 14 days prior to Day 1 of the Treatment Period for patients using MAO inhibitors or fluoxetine). Patients may be admitted to the Clinical Research Center (CRC) during the washout period based on deterioration of depressive symptoms (at the discretion of the investigator).

- **Treatment Period (Visit 2)** will consist of a 5 day/4 night inpatient stay. On Day-1 of the Treatment Period, patients will be reassessed for inclusion/exclusion criteria. All female patients will be required to provide a blood sample for a pregnancy test. On Day 1 of the Treatment Period. Patients will be randomized to receive either AZD6765 (Treatment A) or placebo (Treatment B) based on the randomization schedule generated by GRand. Patients will remain in house until all study procedures are completed on Day 4. Patients will be allowed to resume their treatment for depression after discharge from the CRC on Day 4 of the Treatment Period. At the discretion of the investigator, patients may remain in the CRCfor resumption of treatment for depression.

- **Follow-up Visit (Visit 3)**: The Follow-up Visit will take place 7-10 days after discharge from the Treatment Period. During the follow-up visit, patients may be asked to voluntarily respond to questions regarding the impact of depression on their daily functioning.

Variables

- Pharmacokinetic

Maximum AZD6765 plasma concentration at the end of infusion (C_{max}), time of maximum plasma concentration at the end of infusion, (t_{max}), and area under the plasma concentration time curve from time zero to 24 hours [$AUC_{(0-24h)}$]. Other PK parameters, such as partial AUCs, clearance, half-life and volume of distribution may be calculated as appropriate.

The relationship between plasma levels of AZD6765 and change from baseline of the MADRS evaluation will be explored by pharmacokinetic/pharmacodynamic relationship if appropriate.

- **Pharmacodynamic**

  Pharmacodynamic (PD) will include the following scales and cognitive tests listed below to assess patient mood, anxiety, perception and cognitive function.

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Visual Analogue Scale (VAS)
- Clinician-Administered Dissociative Status Scale (CADSS)
- Brief Psychiatric Rating Scale (BPRS)
- Beck Depression Inventory (BDI)
- Clinical Global Impression (CGI)
- CogState

- **Safety**

Safety will be assessed by the nature and incidence of adverse events (AEs), vital signs, physical examinations, laboratory parameters and electrocardiograms (ECGs). In addition, safety will be assessed by 10th-item of the MADRS score $\geq$4 at any time after the first dose of study medication or a treatment-emergent adverse event of suicidality/suicidal ideation/suicide attempt/suicide completion. Incidences of suicidality will also be evaluated using a suicidality classification similar to the one established by Columbia University.

- **Genetics**

Genetic analysis of the genes involved in the PK, PD, safety and tolerability related to AZD6765 treatment may be performed.

The polymorphism in the genes that may influence the response to AZD6765 may be analyzed.

- **Statistical methods**

The change from baseline in MADRS total score will be compared between two treatment groups, at each scheduled assessment with Last Observation Carried Forward (LOCF) in the Intent-to-Treat (ITT) population, using analysis of covariance (ANCOVA) model with the baseline MADRS as the covariate and treatment as fixed effect in the model. The analysis of the change from baseline to the 24 hour assessment will be considered the primary efficacy analysis. Additionally, the MADRS response will be compared between two treatment groups, at each scheduled assessment with LOCF in the ITT population, using logistic regression with treatment and baseline MADRS in the model. The MADRS response is defined as a reduction of at least 50% from baseline in MADRS total score.

As sensitivity analyses, the above analyses will be repeated at each scheduled assessment using observed cases(OC) in the ITT population.

Descriptive statistics will be used to present secondary efficacy variables and safety variables. Additionally, ANCOVA model will be used for key secondary efficacy variables if appropriate.

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACTH	Adrencocorticotropic Hormone
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of co-variance
AST	Aspartate aminotransferase
ATHF	Anti-Depressant Treatment History Form
$AUC_{(0-t)}$	Area under the total plasma concentration-time curve from zero t the last sampling time t
$AUC_{(0-24h)}$	Area under the plasma concentration time curve from zero to 24 hours
AZSRC	AstraZeneca Safety Review Committee
BDI	Beck Depression Inventory
BDNF	Brain Derived Neurotrophic Factor
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociative States Scale
CGI	Clinical Global Impression
C_{max}	Maximum plasma drug concentration
CRC	Clinical Research Center
CRF	Case report form
DMPK	Drug Metabolism and Pharmacokinetics
DSM-IV	Diagnostic and Statistical Manual-4
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GRand	Global Randomization
HBV	Hepatitis B Virus
HAM-D	Hamilton Depression Rating Scale
HCV	Hepatitis C Virus

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IC-50	Inhibition concentration of 50%
IRB	Institutional Review Board
ITT	Intent- to-Treat
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I.	Mini-International Neuropsychiatric Interview
NMDA antagonist	N-methyl-D-aspartate antagonist
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 4.9.1.1).
OC	Observed Cases
PD	Pharmacodynamics
PK	Pharmacokinetics
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fredericia formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
TIA	Transient Ischemic Attack
t_{max}	Time to reach maximum plasma concentration
TRD	Treatment Resistant Depression
TSH	Thyroid Stimulating Hormone
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization

1. INTRODUCTION

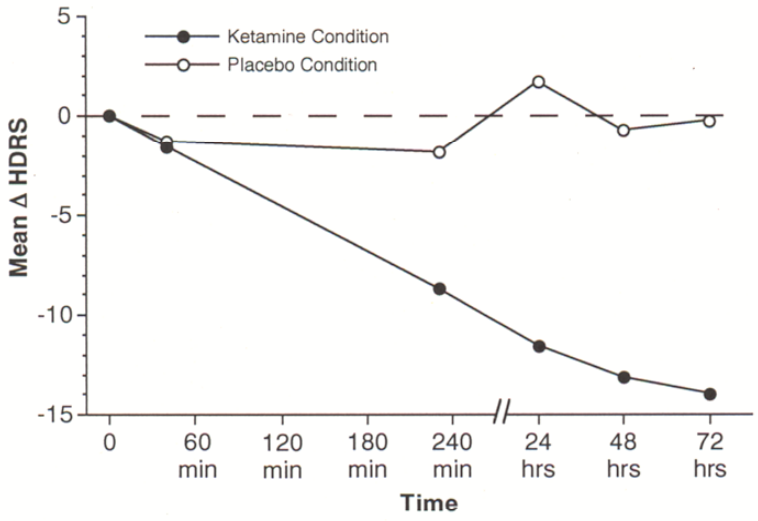
1.1 Background

Treatment-resistant depression (TRD) is a, severe, and often chronic illness that is associated with significant morbidity and mortality. Despite the availability of a wide range of antidepressant drugs, clinical trials indicate that 30% to 40% of patients with major depression fail to respond to first-line antidepressant treatment, despite adequate dosage, duration, and compliance. Moreover, there is a significant lag time in the onset of antidepressant action of these drugs. There is a clear need to develop novel and improved therapeutics for unipolar depression. A therapy for TRD with a quicker onset of action and an equal or better tolerability profile from existing therapies would have a huge impact on public health by providing physicians with a better alternative for the treatment of this disease which would potentially reduce the time patients suffered from symptoms and the risk of suicidal behavior.

Recently, two studies have demonstrated that ketamine appears to have very rapid antidepressant effects in patients with TRD (Berman et al 2000and Zarate et al 2006) The placebo-controlled pilot study completed at Yale demonstrated that the administration of a single dose of ketamine 0.5 mg/kg, intravenously, had antidepressant effects in depressed patients (Berman et al 2000). In these subjects ketamine infusion produced mild psychosis and euphoria that dissipated within 120 minutes, while the antidepressant effects of ketamine infusion emerged over the first 180 minutes and persisted over 72 hours (Berman et al 2000) see Figure 1. This finding has recently been replicated in a study by Zarate et al 2006 where a 72% response rate was reported within 24 hours following the administration of ketamine.

Figure 1 Flow Chart Ketamine Dosing Results

Figure 1



Ketamine is an FDA approved anesthetic that is used to induce surgical anesthesia due to its low incidence of significant respiratory depression and hypotension. Its anesthetic effects are considered directly related to non-competitive inhibition of N-methyl-D-Aspartate(NMDA) receptors. To date five NMDA receptor subunits have been cloned (NR1, NR2A, NR2B, NR2C, NR2D) that combine in pairs containing a voltage-dependent calcium channel that is activated by the binding of glutamate, allowing calcium to enter the neuron (Ishii et al 1993) see Section 9. Ketamine binds non-selectively to NMDA receptor subtypes at a site within the open channel (Yamakura et al 1993). Ketamine's utility in treating depression may be limited by its psychotomimetic effects including dissociation and depersonalization.

AZD6765 is a low-affinity glutamate antagonist that has been shown to be very well tolerated in 300 human volunteers and patients with little propensity for causing psychotomimetic effects. It has been shown to possess antidepressant-like properties in animal models such as forced swim and learned helplessness. AZD6765 has an IC_{50} of 350 nM at the NR1A/2A subtype of the NMDA receptor. One single intravenous dose of up to 100 mg of AZD6765 in approximately 20 treatment resistant depressed patients in a double-blind placebo-controlled parallel study is planned. At 100 mg given over 60 minutes, peak plasma concentration of AZD6765 is expected to be approximately 700 ng/ml (3.5 µM and 1.75 µM free, 50% protein bound). This will give information regarding a free concentration that is at least five times the IC_{50} at the targeted NMDA subtype.

Thus, a small proof of concept study will be carried out to investigate whether a dose of AZD6765, that has been shown to be well tolerated and devoid of psychotomimetic effects, will prove to have antidepressant efficacy within 24 hours in patients with treatment-resistant depression.

1.2 Preliminary Human Experience

AZD6765 had been in clinical development in Europe as an intravenous treatment for stroke and other indications between 1994 and 2001. To date 6, Phase I studies to investigate the safety and tolerability and pharmacokinetics (PK) of AZD6765 in healthy volunteers were completed. In addition, 2 Phase IIa studies were completed in stroke patients and another in sleep apnea. A total of 91 volunteers and 209 patients (total = 300) have been exposed to various doses of AZD6765.

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

AZD6765 loading doses of 160 mg in normal volunteers and 250-460 mg in stroke patients were shown in previous studies to be generally well tolerated up to a C_{max} of 3000 ng/mL (>12 uM). In the proposed study, as well as in future studies in depression, a C_{max} of 700 ng/mL (3.5 uM) or less will be targeted.

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

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

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

In human experience to date, with exposure in 300 subjects and patients, mild and transient CNS adverse events, especially at IV doses above 250 mg , have occurred. However, the frequency and intensity of behavioral and cognitive effects were much less than that seen with other NMDA antagonists such as ketamine, PCP, and MK-801. Notably, the behavioral profile of AZD6765 has more in common with that of other weak NR1/NR2A antagonists, such as memantine. For example, no hallucinations or dissociative episodes were reported in

any of the 91 healthy young and elderly volunteers who received AZD6765 at doses up to 160 mg. In the 2 stroke studies, about 6% of patients had hallucinations after doses of 250 to 460 mg of AZD6765. To avoid potential psychotomimetic effects with AZD6765 in the proposed study (evaluating effects in patients with treatment-resistant depression), a dose of 100 mg infused over a 60-minute period has been proposed for study. Should more than 2 patients have hallucinations or dissociation, the 100-mg dose will be lowered to avoid such adverse events in the remaining patients.

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

1.3 Rationale

The overall rationale for this study is to assess the antidepressant effect of AZD6765 in patients who have not responded to an adequate course of antidepressants with at least 2 different antidepressants.

In an attempt to expand the treatment options currently available for the treatment of TRD 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 up to100 mg in the treatment of TRD.

During the study blood samples will be collected (for research purposes only) for the purpose of measuring Brain Derived Neurotrophic Factor (BDNF). Experimental studies suggest that BDNF expression is induced by chronic antidepressant treatments, and that BDNF itself has antidepressant activity in animal models with depression. Studies suggest that low BDNF levels may play a pivotal role in the pathophysiology of major depression.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to determine whether a rapid antidepressant effect can be achieved with intravenous(IV) doses of up to 100 mg of AZD6765 in patients with Treatment Resistant Depression (TRD) determined by a change from baseline to 24 hours in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

2.2 Secondary objective(s)

The secondary objectives of the study are:

1. To assess the safety and tolerability of IV doses of up to 100 mg of AZD6765 at the designed infusion rate as assessed by vital signs, physical examination, clinical laboratory evaluations, electrocardiograms (ECG's) and the incidence of adverse events.

2. To investigate the effects of IV doses of up to 100 mg of AZD6765 on subject mood, anxiety, perception and cognitive function using a battery of: Montgomery-Åsberg Depression Rating Scale (MADRS), Visual Analogue Scale (VAS), Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Beck Depression Inventory (BDI), Global Clinical Impression (CGI) and CogState.

3. To explore the potential Pharmacokinetic/Pharmacodynamic (PK/PD) relationship of IV doses of up to 100 mg of AZD6765 exposure calculated by C_{max} and AUC and/or cognitive function or MADRS.

4. To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety and tolerability of AZD6765.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design

This will be a multi-center, randomized, double-blind, placebo-controlled parallel-group study conducted in male and female patients with TRD to determine whether a rapid antidepressant effect can be achieved with IV infusions of AZD6765 in patients with TRD. The study will consist of an up to 30 day screening period, 1 inpatient treatment period and 1 follow-up visit.

Patients will be randomized to receive either AZD6765 (Treatment A) or Placebo (Treatment B) on a 1:1 randomization ratio. Treatments will be determined by the randomization schedule (generated by GRand).

Treatment A: Treatment A will consist of 1 dose of 100 mg of AZD6765 given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute (1.67 mg/minute) over 60 minutes. (The dose may be reduced based on emerging safety data).

Treatment B: Treatment B will consist of 1 dose of 0.9% saline (placebo) given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute over 60 minutes.

A sufficient number of male and female patients with treatment resistant major depressive disorder between the ages of 21-65 years old inclusive will be screened to ensure that approximately 50 patients are randomized into the study to obtain 40 evaluable patients. Women of child bearing potential must have a negative serum pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control. The highly effective form of birth control includes but is not limited to: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, IUD/IUS (copper coils), Depo-Provera injections, low dose combined oral contraceptive only if used in TriCycle regime, and

Evra Patch or Nuvaring used in TriCycle regime. Women should be on a stable method of birth control for a minimum of 3 months prior to study entry.

3.1.1 The Screening Period (Visit 1)

The screening period will be up to 30 days prior to Day 1 of the Treatment Period. All patients will be required to stop current treatment for TRD 7 days prior to Day 1 (14 days prior to Day 1 for patients using MAO inhibitors or fluoxetine). Patients may be admitted to the CRC during the washout period based on deterioration of their depressive symptoms (at the discretion of the investigator).

3.1.2 Treatment Period (Visit 2)

After assessment for inclusion/exclusion criteria, patients will be admitted to the CRC on Day-1 for the Treatment Period .

On Day 1 of the Treatment Period, patients will be randomized to either Treatment A or Treatment B based on the randomization schedule:

> **Treatment A:** Treatment A will consist of 1 dose of 100 mg of AZD6765 given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute (1.67 mg/minute) over 60 minutes. (The dose may be reduced based on emerging safety data).
>
> **Treatment B:** Treatment B will consist of 1 single dose of 0.9% saline (placebo) given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute over 60 minutes.

Patients will remain in the CRC until all study procedures are completed on Day 4. Patients will be allowed to resume treatment for depression at the completion of the Treatment Period. At the discretion of the investigator, patients may remain in the CRC for resumption of their treatment for depression.

3.1.3 Follow-up Visit (Visit 3)

Patients will be asked to return for a Follow-Up Visit 7-10 days after discharge from the Treatment Period. During the follow-up visit, patients may be asked to voluntarily respond to questions regarding the impact of depression on their daily functioning.

3.1.4 Stopping criteria

Study sites will be required to contact AstraZeneca after dosing if 1 patient experiences:

- A seizure

The AstraZeneca Safety Review Committee (AZSRC) will review the safety information and recommend procedures to follow for stopping the study. The blind may be broken by the AZSRC if deemed necessary. AZSRC will consist of the study physician, the drug safety

physician, and the principal investigator. Additional ad hoc members will be added as necessary.

3.1.5 Criteria for Dose Reduction

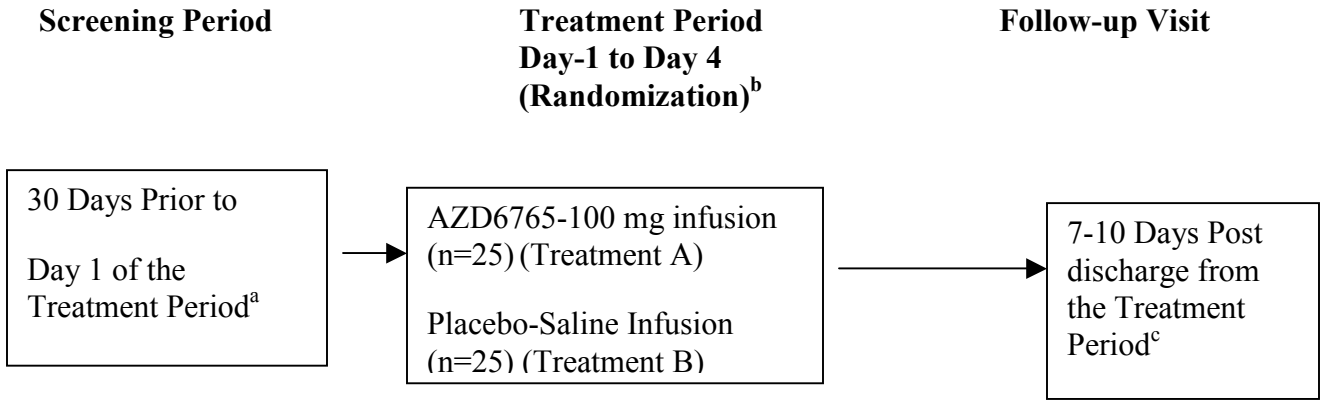
Study sites will be required to contact AstraZeneca after dosing to report any instances of significant intolerance to dose such as drug related adverse events, including: laboratory abnormalities, vital sign abnormalities, psychotic reactions or prolonged QTcF intervals. The blind may be broken by the AstraZeneca safety committee if deemed necessary. The need for dose reduction and determination of what the dose will be for the remaining patients not yet exposed to AZD6765, or termination of the study will be determined by the AstraZeneca safety committee.

Significant dose intolerance could be:

- Drug related, Severe Adverse Event's (SAE's) in 2 or more patients determined to have received AZD6765 (from 1 or more sites).
- Two or more patients who experience a psychotic reaction.
- Two or more patients who experience dysphoric mood.
- Two or more patients experience hallucinations or dissociation.
- Increase in serum AST or ALT >3 times the upper limit of normal.
- Increase in serum bilirubin >2 times the upper limit of normal.
- Decreases in White Blood Cell Count (WBC) to <2500 mm^3 and equal or less than 50% of the baseline values.
- Decrease in platelet count to <100,000 mm^3.
- Increase in serum creatinine to >1.5 times the upper limit of normal.
- QTcF >500 msec in 2 or more patients (confirmed by repeat measurement).
- Semi-reclining systolic blood pressure <80 or >180 mm Hg in 2 or more patients (confirmed by repeat measurement).
- Heart rate <40 or >120 beats per minute in 2 or more patients (confirmed by repeat measurement).

If it has been decided by the AZSRC that the dose should be lowered, the dose will be lowered for the next patient scheduled to be randomized.

Figure 2 Study Flow Chart



[a] The washout period for fluoxetine and MAO inhibitors begins on Day-14 and on Day-7 for all other antidepressants. The washout can take place in-house due to worsening symptoms of depression (at the discretion of the investigator).

[b] Approximately 50 patients will be randomized to obtain 40 evaluable patients. Patients will be randomized to either Treatment A or Treatment B based on the randomization schedule. Randomization will take place on Day 1 of the Treatment Period.

[c] Patients may remain in-house after the Treatment Period for resumption of treatment for depression (at the discretion of the investigator).

Table 1 Table of assessments

Study Procedures	**Screen[a] (Visit 1)**	**Washout Period Day-7(Day-14 for fluoxetine or MAOI's)[b]**	**Treatment Period[c] (Visit 2)**					**Follow-Up Visit (Visit 3)**
Study Day			**-1**	**1**	**2**	**3**	**4**	**7-10 days post DC the Treatment Period**
Informed Consent	X							
Med/Surg/ Medication History	X		X					
Inclusion/Exclusion	X		X					
Demographics	X							
Height and Weight[d]	X							X
Physical Examination	X		X				X	X
12-lead ECG	X							X
Digital ECG's				X				
Semi-reclining blood pressure and pulse[e]	X		X	X	X	X	X	X
Orthostatic blood pressure and pulse			X[f]	X				
Oral Body Temperature[g]	X			X				
Clincal Chem/Hematology/Urine	X		X		X			X
Thyroid Function Panel	X							
HIV/Hepatitis Screening	X							
Pregnancy test	X		X					X
Alcohol Screen/ urine drug screen	X		X					

Study Procedures	**Screen[a] (Visit 1)**	**Washout Period Day-7(Day-14 for fluoxetine or MAOI's)[b]**	**Treatment Period[c] (Visit 2)**					**Follow-Up Visit (Visit 3)**
Study Day			**-1**	**1**	**2**	**3**	**4**	
Randomization[h]				X				
Study drug administration per randomization schedule				X				
PK blood sampling[i]				X	X			
BDNF blood sampling[j]				X	X			
Optional Genetic Blood Sample Collection[k]				X				
Assessment of Depression (MADRS, VAS, BDI,)[l]			X	X	X[m]	X[m]	X[m]	X
CGI	X		X	X	X[m]	X[m]	X[m]	
HAM-D	X							
Assessment of Psychotic Reaction (CADSS, BPRS)				X	X[m]	X[m]	X[m]	
Cognitive Testing (CogState)			X[n]	X	X[m]	X[m]	X[m]	
M.I.N.I.	X							
ATHF Score Card	X							
Adverse Events[o]	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Begin washout for medications for TRD		X						
Confinement to Unit[p]			X	X	X	X	X	
Resume treatment for depression							X[q]	

[a] The screening period will take place up to 30 days prior to Day 1 of the Treatment Period .

[b] The washout period for drugs used for treatment of depression will start 7 days before Day 1 of the Treatment Period, however if the patient is using fluoxetine or MAO inhibitors the washout period will be 14 days prior to Day 1 of the Treatment Period . Patients can be admitted to the CRC during the washout period based on worsening of their depressive symptoms (at the discretion of the investigator).

[c] Please see Table 2 for specific timings for all procedures scheduled for Day 1.

[d] Height will be evaluated at the Screening Visit only.

[e] If possible use the same arm for each blood pressure evaluation.

[f] The orthostatic blood pressure evaluation on Day-1 will serve as the baseline.

[g] Body temperature should be recorded in °C.

[h] Randomization will take place on Day 1 of the Treatment Period.

[i] The actual sample collection date and time for PK will be recorded in the eCRF. Two additional PK tubes will be collected, one at baseline and one at 24 hours for possible future research purposes.

[j] There will be 2 samples collected for exploratory BDNF evaluation. One sample will be collected Pre-Dose on Day 1 and one will be collected on Day 2.

[k] The blood sample for pharmacogenetics will only be collected 1 time during the study preferably on Day 1 of the Treatment Period.

[l] For the MADRS Evaluation, Day 1, pre-dose will be considered the baseline. The VAS Scale on Day-1 will be for training purposes.

[m] Suggested times for Day 2, 3 and 4 evaluations are approximately 24, 48 and 72 hours after dosing time completion. A window of approximately 1 hour will be given to complete the depression scales and cognition testing.

[n] On Day-1 cognitive testing will be performed 3 times, twice for training purposes followed by 1 time to establish the baseline. The interval between testing administrations will be at least 1 hour and no less than 30 minutes.

[o] AE's will be collected from Informed Consent signing through the Follow-Up Visit.

[p] Patients will be discharged from the CRC after completion of all evaluations on Day 4 of the Treatment Period.

[q] Patients can resume medications for treatment of depression upon discharge from the Treatment Period. At the discretion of the investigator, patients may remain in the CRC for the resumption of the depression medications.

Table 2 Timing of Procedures on Day 1 through 24 hours

Procedure and Procedure Time	**1.5 hrs. Pre-dose**	**0.25 hrs. Pre-dose**	**0 hr**	**0.25 hr**	**0.5 hr**	**0.75 hr**	**1.0 hr**	**2.0 hr**	**3.0 hr**	**3.5 hr**	**4.0 hr**	**8.0 hr**	**24 hr**
Semi-reclining blood pressure and pulse[a]	X				X					X			X
Orthostatic Blood Pressure and pulse[b]								X					
Digital ECG[c]		X		X	X	X		X		X			
Body Temperature[d]	X												
MADRS[e,f]	X						X				X		X
CGI[f]	X						X						X
BPRS[f]							X				X		X
CADDS[f]	X						X				X		X
BDI[f]							X				X		X
VAS[f]	X						X				X		X
Cognition Testing (CogState)	X						X				X		X
Randomization[g]			X										
Dose Administration (Start of Infusion)			X										
Optional Genetic Blood Sample Collection		X											
PK Sample Collection		X[h]					X[i]		X			X	X[h]
BDNF[j]		X											

[a] If possible the blood pressure should be evaluated using the same arm.

[b] The 2.0 hr. orthostatic blood pressure evaluation will be completed after the Digital ECG.

[c] Digital ECGs will be completed twice at 0.25 hr Pre-Dose, (~10 minutes apart). The 0.25 hr Pre-Dose evaluation will serve as the baseline. All Digital ECGs will be completed in triplicate at each time-point. The investigator will review the print-out for safety.

[d] Body temperature should be recorded in °C

[e] The Day 1 Pre-Dose MADRS evaluation will serve as the baseline.

[f] It is recommended that the depression scales be completed in the following order, MADRS,CGI, BPRS, CADSS, BDI, VAS and CogState. A window of approximately 1 hour will be given to complete the depression scales and cognition testing.

[g] Randomization will take place just prior to dosing on Day 1 of the Treatment Period.

[h] Two additional PK tubes will be collected, one at 0.25 hr pre-dose and one at 24 hrs post dose. These samples will be held for future exploratory analysis.

[i] The 1 hour PK sample will be collected at the end of the infusion.

[j] There will be 2 samples collected for exploratory BDNF evaluation. One sample will be collected Pre-Dose on Day 1, the second sample will be collected on Day 2.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The purpose of this study is to determine whether AZD6765 will give an adequate effect for patients suffering from treatment resistant depression who have not responded adequately to other antidepressant therapies. The results from this study will build upon existing clinical data observed with the use of NMDA antagonists.

A growing body of preclinical research suggests that brain glutamate systems may be involved in the pathophysiology of major depression and the mechanism of action of antidepressants. A double-blind, placebo controlled trial to assess the treatment effects of a single dose of ketamine, an N-methyl-D-aspartate (NMDA) receptor agonist was associated with robust decreases in depressive symptoms, emerging progressively within 3 days as compared to placebo (Berman et al., 2000.) see Section 9.

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

Please see Section 1.2 or the Investigator's Brochure (IB) for further information.

3.2.2 Risk/benefit and ethical assessment

The benefit of the study drug is that it may provide rapid relief from depression in patients diagnosed with TRD.

The major risks of participating in this trial are adverse events related to discontinuation of prescribed treatment for depression and adverse events related to the use of AZD6765. In previous human studies, lightheadedness was observed when 40 mg was administered over 15 minutes and when doses of 80 mg or greater were administered over one hour. Other adverse events noted were headache, blurred vision, hypoaesthesia, somnolence, stupor, and impaired concentration. An additional risk is worsening of symptoms of depression due to lack of response. Finally, there is a slight risk of infection or bruising that may occur as a result of phlebotomy and intravenous infusion.

Please refer to the Investigator's Brochure for additional information regarding risks.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrollment but never enrolled eg, subject screening log, according to local procedures. This information is necessary to establish that the subject population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria.

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

2. Male and female patients aged 21 to 65 years old inclusive. Women of child bearing potential must have a negative serum pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control the highly effective form of birth control includes but is not limited to: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, IUD/IUS (copper coils), Depo-Provera injections, low dose combined oral contraceptive only if used in TriCycle regime, and Evra Patch or Nuvaring use in TriCycle regime. Women should be on a stable method of birth control for a minimum of 3 months prior to study entry.

3. Documented clinical diagnosis meeting criteria from the DSM-IV (Appendix K) by the Mini-International Neuropsychiatric Interview (M.I.N.I.), (Appendix L) for either of the following 2:

   – 296.2X Major Depressive Disorder, Single Episode duration at least 1 year or
   296.3X Major Depressive Disorder, Recurrent,

   – and have a HAM-D score of >20.

4. Patients with a history of inadequate response to an adequate course of antidepressants (4 weeks) with at least 2 different antidepressants as determined by the ATHF score cards (Appendix N).

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

6. Outpatient status at screening.

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

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1 Patients with DSM-IV Axis II disorder which has a major impact on the patient's current psychiatric status.

2. Patients with DSM-IV Axis I bipolar disorder (I or II), psychotic disorder, or major depressive disorder with psychotic features.

3. Patients who are treatment refractory, defined as having failed adequate courses of treatment with 5 different classes of drug.

4. Patients who have failed past ECT.

5. History of substance or alcohol abuse in the past 6 months or dependence within 1 year of enrollment (except for caffeine or nicotine dependence), as defined in DSM IV criteria. Patients with a positive urine drug screen (UDS) for methamphetamines (including ecstasy), benzodiazepines, cocaine and/or metabolites, amphetamines, tetrahydrocannibinol (TCH), opiates, phencyclidine (PCP), and barbiturates will be excluded except for patients testing positive for prescribed medications. Patients can be retested if the initial UDS is positive, but should be excluded if the results are still positive, at the second test. Patients with a positive UDS for a drug(s) legally available by prescription, must provide evidence of the prescription for the drug(s).

6. Use of drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes within 2 weeks prior to randomization, eg, inducers: carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort. Eg.inhibitors: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluoxetine, nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir, and saquinavir.

7. Previous investigational treatment with ketamine for depression or participation in a clinical study with ketamine.

8. Pregnancy or lactation.

9. Evidence of clinically relevant diseases, eg, renal or hepatic impairment, symptomatic coronary artery disease, cerebrovascular disease, viral Hepatitis B or Hepatitis C, HIV infection or acquired immunodeficiency syndrome (AIDS).

10. QT interval corrected by the Fredericia Formula(QTcF) on screening ECG of >450 (msec).

11. Systolic Blood Pressure < 95 or >140 mm Hg at screening.

12. Heart Rate <50 or >100 beats per minute at screening.

13. Patients who have a Thyroid Stimulating Hormone (TSH) concentration more than 10% above the upper limit of normal (ULN) of the range of the laboratory used for the TSH sample analysis at screening whether or not the patient is being treated for hypothyroidism.

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

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

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

17. Current or past diagnosis of stroke or Transient Ischemic Attack (TIA).

18. History of head trauma, defined as closed head injury in which loss of consciousness occurred.

19. History of seizure (including febrile seizures) or family history of epilepsy.

20. Receipt of electroconvulsive therapy (ECT) within 90 days prior to randomization.

21. Use of mood stabilizers, antidepressants or other antipsychotic or psychoactive drugs within 7 days of Day 1, or use of fluoxetine or MAO inhibitors within 14 days of Day 1 of the Treatment Period.

22. Lifetime use of depot antipsychotics.

23. Patients who, in the investigator's judgment pose a current serious suicidal or homicidal risk, or have active suicidal ideation or gesture, or have made a suicide attempt within the past 6 months.

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

25. ECG results considered to be clinically significant as determined by the investigator or an experienced cardiologist interpreting the ECG.

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

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

28. Participation in a clinical study or compassionate use program within 60 days of randomization.

3.3.4 Restrictions

Subjects will be required to:

1. Discontinue use of current treatment for TRD for 7 days (14 days for MAO inhibitors or fluoxetine) prior to Day 1 of the Treatment Period and continue through completion of the Treatment period.

2. Abstain from the use of P450 3A4 inducers: (carbamazepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort) within 2 weeks of Day 1 of the Treatment Period through completion of the Treatment Period.

3. Abstain from the use of P450 3A4 inhibitors: (ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluoxetine, nefazodone, troleandomycin, indinavir, nelfinalvir, ritonavir, and saquinavir) within 2 weeks of Day 1 of the Treatment Period through completion of the Treatment Period.

4. Abstain from use of mood stabilizers, antidepressants, use of antipsychotics or psychoactive drugs within 7 days of Day 1 of the Treatment Period through completion of the Treatment Period.

5. Abstain from use of MAO Inhibitors and fluoxetine within 14 days of Day 1 of the Treatment Period through completion of the Treatment Period.

6. Abstain from consumption of alcoholic beverages for 48 hours prior to Day 1 of the Treatment Period.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient , who is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.
- Incorrect enrollment ie, the patient does not meet the required inclusion/exclusion criteria for the study

- Patient lost to follow-up

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 subject will not prejudice further treatment.

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up to a resolution if possible. Patients who discontinue from the study before completion should undergo, if possible, the assessments and procedures scheduled for the follow-up visit. Every effort should be made to follow-up with patients who discontinue from the study prior to the follow-up visit.

If a patient is being withdrawn due to a suspected infection in WHO risk categories 2, 3, and 4, no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site. For WHO risk categories refer to Appendix C.

3.3.5.3 Procedures for handling incorrect enrolled subjects

Patients not meeting the inclusion/exclusion criteria for a study should, under no circumstances, be enrolled into that study, there can be no exceptions to this rule. Where patients not meeting the study criteria are enrolled in error, incorrectly randomized, or where patients subsequently fail to meet the criteria for the study post randomization, then these patients should return, if possible, for the follow-up visit.

3.3.5.4 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 will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

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

In the case of any subject withdrawing consent for the genetic research, the principal investigator must notify the monitor using the "Withdrawal of Consent Form" (to be supplied). Requests for sample destruction should be forwarded by the monitor to the head of Clinical Genotyping Group (CGG), (address: Clinical Genotyping Group, Block, 17, Mereside, Alderly Park, Macclesfield, UK, SK10 4 TG: Tel: +44 (0) 1625 230959, Fax : +44 (0) 1625 230958) along with copies of the relevant documentation detailing study code and patient enrollment code. The Study Delivery Team and principal investigator will receive written confirmation from the CGG that the genetic sample has been destroyed.

3.4 Treatment(s)

3.4.1 Investigational product(s)

3.4.1.1 Identity of investigational product and Placebo

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

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

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

Table 3 Identity of investigational product

Investigational Product	Dosage form and strength	Manufacturer	Formulation number
AZD6765	15 mg/mL for IV infusion	AstraZeneca	2729-x-1

3.4.1.2 Labeling

All clinical trial material will be packaged and labeled by AstraZeneca. The treatment vials will be clearly marked according to national requirements regarding use for clinical trial investigation only and will also be labeled with the drug name, study reference number and storage conditions. The study site dispensary staff will dilute and dispense the investigational product according to the randomization scheme. Individual dosing containers will be labeled with the study number, patient number and study day.

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product vial label and the Investigator Brochure. All study drug will be stored in original containers in a lockable storage facility until dispensed to the patients.

3.4.1.4 Accountability

It is the investigator's responsibility to establish a system for handling study treatment, including investigational medicinal products, to ensure that:

- Deliveries of products from AstraZeneca are correctly received by the Investigator or his/her designee.
- Such deliveries are recorded on a drug log.
- Any unused products are accounted for and returned to a designated facility or AstraZeneca for destruction.

The investigator must maintain accurate records for accounting for the receipt of the investigational materials for the disposition of the material. This record keeping will consist of dispensing record including the identification of the person to whom drug is dispensed, the quantity and the date of dispensing. The record is in addition to any drug accountability information recorded in the CRFs. At the completion of this study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or designated responsible person. The responsible person must ensure:

- Study treatments are handled and stored safely and properly.
- Such treatments are only dispensed to study patients in accordance with this protocol.

The investigational materials are to be administered by a designated staff member. Under no circumstances will the Investigator allow the investigational product to be used other than directed by the protocol without prior AstraZeneca approval.

The investigator will retain all remaining study medication along with any study medication not dispensed. At the termination of the study or at the request of AstraZeneca or its designee, the Investigator must return any unused supplies to AstraZeneca or its designee. The return will be documented by using an Investigational Product Return Invoice (or equivalent form) supplied by AstraZeneca.

It is essential that all medication be accounted for by the investigator or institution, and that any discrepancies are explained and documented.

3.4.2 Doses and treatment regimens

On Day 1 of the Treatment Period, each patient will receive either Treatment A or Treatment B by a single IV infusion in a randomized fashion. Patients will be randomized to either AZD6765 (Treatment A) or Placebo (Treatment B) on a 1:1 ratio. Patients should be semi-reclining during the intravenous infusion.

> **Treatment A:** Treatment A will consist of 1 dose of 100 mg of AZD6765 given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute (1.67 mg/minute) over 60 minutes. (The dose may be reduced based on emerging safety data).
>
> **Treatment B:** Treatment B will consist of 1 dose of 0.9% saline (placebo) given as an intravenous infusion. The infusion will be a final volume of 30mL given at an infusion rate of 0.5 mL/minute over 60 minutes.

3.4.3 Method of assigning subjects to treatment groups

Written informed consent will be obtained before enrollment and the patients identified with an enrollment number starting with E0001001 for Site 1 and E0002001 for Site 2 etc. Patients fulfilling the eligibility criteria will be assigned randomization codes (patient numbers) starting with number 101 for Site 1 and 201 for Site 2 etc.

Patients will be assigned patient numbers strictly sequentially as patients are eligible for randomization within each site. If a patient discontinues from the study, the enrollment number and the patient number will not be re-used and the patient will not be allowed to re-enter the study.

3.4.4 Blinding and procedures for unblinding the study

3.4.4.1 Methods for ensuring blinding

The investigator, patient and study staff will be blinded. The pharmacist will be unblinded.

Both AZD6765 and 0.9 % saline will be prepared in advance and provided to the study staff on the morning of dosing. The labeling of the dose will not reveal the treatment to be administered.

The randomization schedule will be provided to the CRC pharmacy staff who will prepare the study drug for administration. This document will be kept in a secure location, not accessible to the blinded study staff. To ensure maintenance of the blind, at the end of the study, the pharmacist will mail the randomization scheme back to the AstraZeneca biostatistical associate in a tamper resistant envelope.

3.4.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the pharmacists at the study center.

The individual treatment codes must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the randomization treatment sequence and/or events that meet the criterion for possible dose reduction, refer to 3.1.5. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient has been made a documented. However, if deemed necessary, based on safety and tolerability data and/or exposure data obtained, the AstraZeneca Safety Review Committee (AZRC) may break the code during the study.

3.4.5 Concomitant medication

Any medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (CRF). Lifetime use of drugs for depression (collected on the ATHF score card) and pre-study medications for all other concomitant medication use from up to 60 days prior to enrollment will be recorded in the appropriate sections of the CRF.

Please see Appendix D for permitted/restricted/prohibited medications.

3.4.6 Treatment compliance

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

4. MEASUREMENT OF STUDY VARIABLES

The following study measurements will be obtained. The timing of these measurements is detailed in the study plan Table 1 and Table 2. The following 'priority order' will be in effect when more than one assessment is required at a particular time point:

- Digital ECGs
- Vital Signs
- Pharmacokinetic blood sampling. (Note: PK sampling must be performed at the precise protocol scheduled time and this time will be recorded in the CRF)
- Depression Scales
- Cognitive testing

4.1 Medical examination and demographic measurements

4.1.1 Enrollment medical examination and demographic measurements

Each subject will undergo an enrollment medical examination in the 30 days prior to the Treatment Period (Visit 2). This will consist of:

- Inclusion/exclusion criteria (Will be reviewed at screening and at admission to the Treatment Period).
- Recording of demographic data including: date of birth, sex, race.
- A standard medical history and physical examination including the cardiovascular and respiratory system.
- Diagnosis of depression by use of the M.I.N.I and severity of depression evaluated by the HAM-D.
- Review of concomitant medications for general use and use for depression. The ATHF card will be used for review of medications for depression.
- Recording of height and weight.
- CGI evaluationA blood sample for standard clinical chemistry, hematology assessments and (all female patients) a pregnancy test, a mid-stream urine sample for urinalysis and drugs of abuse screen.
- A blood sample for HIV and Hepatitis B and Hepatitis C serology.

- An ethanol (breath, serum or saliva) screen.
- Recording of oral body temperature.
- A resting 12 lead ECG (the patient should be in a semi-reclining for 10 minutes prior to the evaluation).
- A resting blood pressure and pulse rate (the patient should be resting in a semi-reclining position for 10 minutes prior to the evaluation).

4.1.2 Post-study medical examination

Each patient will undergo a post-study medical examination prior to discharge. This will consist of:

- A blood sample for standard clinical chemistry and hematology assessments and a pregnancy test (all female patients) and a mid-stream urine sample for urinalysis
- A resting blood pressure and pulse rate (the patient should be resting in a semi-reclining position for 10 minutes prior to the evaluation).
- Physical Examination
- Recording of weight
- A resting 12 lead ECG (the patient should be in a semi-reclining for 10 minutes prior to the evaluation).

4.2 Pharmacokinetic measurements

For timing of individual samples refer to Table 2. The actual date and time of the sample collection must be recorded on the appropriate eCRF page.

4.2.1 Determination of drug concentration in biological samples

Plasma samples for determination of AZD6765 concentrations will be analyzed by Global Drug Metabolism and Pharmacokinetics& Bioanalysis, AstraZeneca, Wilmington, DE, using fully validated bioanalytical methods. Details of the methods used will be provided in the clinical study report (CSR). Blood samples will be collected, labeled and shipped as detailed below.

4.2.2 Collection of biological samples

Venous blood samples (6 mL) will be taken at the times presented in Table 2 and Table 4. Individual venipunctures for each time point may be performed or an indwelling catheter may be used. If the site chooses to use an indwelling catheter, the first 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Heparin may **not** be used to flush the catheter.

Venous blood samples (6mL) will be collected into EDTA spray-dried tubes. One additional (6 mL) sample each will be collected at 0.25 hr pre-dose and 24 hrs for future research studies. All blood 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 of 1500Xg. The resulting plasma will be evenly divided into 2 transfer tubes (2.0 mL (Microcentrifuge Micro Tubes – Sterilized, Cat. #: 4204S, BIO Plas, Inc., USA, or a tube approved by AstraZeneca) and immediately frozen upright at or below -70°C 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 and will be shipped during a separate shipment. AstraZeneca will instruct the site when to ship the retention sample.

Table 4 Scheduled PK Blood Sampling

Scheduled Time Relative to Dose at Visit 2	Tube and Set Number
Pre-Dose (within 30 minutes of Dose)	**1 A/B/C/D**
1 Hr. Post Dose	**2 A/B**
3.0 Hr. Post Dose	**3 A/B**
8.0 Hr. Post Dose	**4 A/B**
24.0 Hr. Post Dose	**5 A/B/C/D**

4.2.2.1 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: D6702C00001
Patient Number
Site Number
Sample Number (Tube and Set Number)
Protocol Time
Analyte: AZD6765
Matrix: Plasma

4.2.2.2 Shipment of AZD6765 plasma samples

All AZD6765 plasma samples accompanied by the sample shipment logs will be shipped via an agreed upon courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for delays in the shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment. The primary contact, [redacted] 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 Wednesday. Do not ship on or within two days prior to a legal holiday.

Plasma samples should be shipped to:

[redacted]

4.3 Collection of samples for Brain Derive Neurotrophic Factor (BDNF)

Blood samples will be collected for the determination of serum BDNF levels. BDNF will be analyzed at the Yale Depression Research Laboratory, New Haven, CT. The details of the method used will be provided in the clinical study report (CSR).

4.3.1.1 Collection of blood samples for BDNF analysis

Venous blood samples (10mL) for the determination of BDNF will be taken at the times presented in Table 2. Blood samples will be collected according to site procedure. Individual venipuncture may be performed. If the site chooses to use an indwelling catheter, the 1st 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Venous blood samples (10mL) will be collected into a serum separator tiger topped tube. The sample will remain upright in a rack at room temperature and allowed to clot. The sample should be processed within 45 minutes after collection. The samples will be centrifuged for 10 minutes at 1500xG. The samples should be placed into a 5 mL cyrovial and immediately frozen in an upright position at -20°C or below and kept frozen at this temperature before, during and after transport to the designated laboratory.

4.3.1.2 Labeling of BDNF samples

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

Study Number: D6702C00001
Patient Number
Site Number
Protocol Day
Analyte: BDNF
Matrix: Serum

4.3.1.3 Shipment of BDNF samples

All serum samples for BDNF analyses accompanied by the sample shipment logs will be shipped via an agreed upon courier. The frozen samples must be packed securely to avoid breakage during transit, should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples remain frozen for at least 72 hours to allow for delays in the shipment. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included with the shipment. The primary contact, [redacted] 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 Wednesday. Do not ship on or within two days prior to a legal holiday.

Serum samples for BDNF should be shipped to:

[redacted]

4.4 Pharmacodynamic measurements

The pharmacodynamic measurements will include clinical interviews and self report scales to determine levels of depression and cognitive testing to determine cognitive effects of treatment.

4.4.1 Depression assessments

The following scales (MADRS, HAM-D, BDI and CGI-S) are to be utilized in this study and will be rated by the investigator or delegate, according to the schedule of events in Table 1 and Table 2.

When multiple scales are being performed at the same time point the order in which the scales will be performed is as follows: MADRS, CGI, BPRS, CADSS, BDI, VAS and CogState.

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 and HAM-D will receive training in conducting these assessments. In addition, certification will be required for MADRS scale administration. To reduce scoring variability, it is important that the same rater conduct the rater assessments for a given patient for a specific scale throughout the course of the study.

The back-up rater must meet the same qualifications as the primary rater and be authorized by the principal investigator 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 adverse events (AEs) if they fulfill the criteria for a SAE or are the reason for discontinuation from treatment with the investigational product.

Please see Table 1 and Table 2 for the timing the evaluations.

4.4.2 Montogomery-Åsberg Depression Rating Score (MADRS)

4.4.2.1 Methods of assessment

The MADRS is a 10-item scale for the evaluation of depressive symptoms (Montgomery S.A., Åsberg, M.A. 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 the Sponsor.

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 CRF.

A patient will be classified as a responder if the percentage change from baseline indicates ≥50% reduction in the MADRS total score. A patient will be classified as in remission if their MADRS total score is ≤8. (Appendix F).

The timing of the MADRS measurements can be found in Table 1 and Table 2.

4.4.2.2 Calculation or derivation of outcome variable

The MADRS total score will be calculated as the sum of the 10 individual item scores and the total score ranges from 0-60. Change from baseline to each assessment will be calculated for total MADRS total score as the visit score subtracted by the baseline score.

4.4.3 Hamilton Depression Rating Scale (HAM-D)

The HAM-D is a 21-item observer rated scale that assesses depressive symptoms **Error! Reference source not found.**(,Hamilton 1960) each of which is rated from 0-2 or 0-4, where 0 is none/absent. Depressive symptoms include depressed mood, feeling of guilt, suicide, insomnia-early, insomnia-middle, insomnia-late, work activities, retardation: psychomotor, agitation, anxiety psychic, anxiety somatic, somatic symptoms-GI, somatic symptoms-general, genital symptoms, hypochondriasis, loss of weight and insight. (Appendix E).

The HAM-D will be performed during the Screening Visit to determine depression severity.

4.4.4 Clinician Administered Dissociative Status Scale (CADSS)

The CADSS has self and interviewer administered items, and include 5 subscales, generated a priori, evaluating aspects of dissociative symptoms including: altered environmental perception, time perception, body perception, feelings of unreality, and memory impairment. (Appendix G).

The timing of the CADSS evaluations can be found in Table 1 and Table 2.

4.4.5 Brief Psychiatric Rating Scale (BPRS)

The BPRS is a 16-item scale with nine general symptom items, five positive-symptom items, and two negative-symptom items. Each item is scored by the investigator on a seven point severity scale, resulting in a range of scores from 16-112. (Appendix I).

The timing for the BPRS can be found in Table 1 and Table 2.

4.4.6 Beck Depression Inventory (BDI)

The Beck Depression Inventory, is a 21 question, multiple choice, self-report inventory(Beck Depression Inventory 1961). The questionnaire is designed for adults age 17-80 and is composed of items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings or being punished, as well as physical symptoms such as fatigue, weight loss and lack of interest in sex. (Appendix J).

The timing of the BDI measurement can be found in Table 1 and Table 2.

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

4.4.7.1 Methods of assessment

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

The first part, Severity of Illness scale (CGI-S), is scored to rate the patient's current clinical state. The second part, Global Improvement scale (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-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". 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 is administered at various times during the course of the study to assess patient progress. Higher CGI-S scores indicate greater illness severity. CGI-I scores greater than 4 indicate worsening, while scores less than 4 indicate improvement. The individual item scores will be recorded on a specifically designed eCRF. (Appendix H).

4.4.7.2 Derivation or calculation of outcome variable (CGI-S and CGI-I)

CGI-I will be evaluated at each assessment following randomization, and will be summarized by each rating as well as dichotomized into "Much or Very Much Improved" (a CGI-I rating ≤ 2), or "Not Much Improved" (a CGI-I >2).

The timing of the CGI measurements can be found in Table 1 and Table 2.

4.4.8 Bond-Lader Visual Analogue Scale (VAS)

The modified Bond-Lader Visual Analogue Scale (VAS) is a questionnaire completed by the patient consisting of 9 scales that assess changes in subjective alertness, subjective calmness and subjective contentment. (Appendix M).

The timing for the VAS measurement can be found in: Table 1, and Table 2.

4.5 Cognitive

4.5.1 CogState

CogState is a collection of computerized neurocognitive tests designed to maximize the signal and minimize the noise from cognitive recording taken in clinical trials. A battery has been assembled to meet the objectives of this study for brevity (8-12 minutes), sensitivity to the effects of AZD6765 (psychomotor speed, attention, working memory and short term memory) and is appropriate for a depressed population.

The timing of the CogState measurements can be found in Table 1 and Table 2.

4.6 Safety measurements

4.6.1 Vital Signs

4.6.2 Semi-reclining blood pressure and pulse

Blood pressure and heart rate will be measured while the patient is in a semi-reclining position using a semi-automatic blood pressure recording device with appropriate cuff size. The patient will be required to rest for 10 minutes prior to each blood pressure and pulse evaluation. Please refer to Table 1 and Table 2 for timing of these evaluations.

4.6.3 Orthostatic blood pressure and pulse

Orthostatic blood pressure and heart rate measurements will include semi-reclining blood pressure and heart rate (obtained after at least 10 minutes in a semi-reclining position) and a standing blood pressure and heart rate (obtained after 5 minutes in the standing position) and will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. The 2 hour orthostatic evaluation will be performed after the digital ECG evaluation. The baseline evaluation will be taken on Day-1 of the Treatment Period.

Please refer to Table 1 and Table 2.

4.6.4 Medical/surgical history

A detailed medical surgical history including medication history will be recorded for each patient during the Screening Visit. Significant medical conditions that have occurred within the past two years or conditions that are ongoing (ie, headache, backache, indigestion) will be recorded. Please refer to Table 1.

4.6.5 Body temperature

Oral body temperature will be measured in °C at Screening and on Day 1 during the Treatment Period. Please refer to Table 1.

4.6.6 Complete Physical Examination

The complete physical examination will include assessment of the following: general appearance, skin, head, neck (including eyes, ears, nose and throat), lymph nodes, thyroid,

musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems.

Complete physical examination data to be recorded on the CRF will include: 1) normal/abnormal and 2) a description of the abnormalities. Please refer to Table 1

4.6.7 12-Lead ECG

A 12-lead ECG will be obtained after the patient has been resting in a semi-reclining position for at least 10 minutes. Please refer to Table 1 and Table 2 for the timing of these procedures.

All ECGs will be documented in the CRF by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT and QTcF. (A conversion chart will be provided to the study site to assist in calculating QTcF).

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 CRF.

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 CRF.

Please refer to Table 1 and Table 2.

4.6.8 Digital ECGs

Digital ECGs will be obtained after the patient has been resting in a semi-reclining position for at lest 10 minutes. Please refer to Table 1 and Table 2 for the timing of these procedures. The baseline evaluation (0.25 hr. pre-dose)should be performed 2 times approximately 10 minutes apart. Each digital ECG will be performed in triplicate at each time-point.

All digital ECGs will be documented by recording date, time, heart rate, QRS duration, PR interval, RR interval, QT and QTcF. (A conversion chart will be provided to the study site to assist in calculating QTcF).

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 CRF.

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 CRF. Digital ECGs will be saved for the possibility of review by a central reader. AstraZeneca will inform the site whether a central reader will be used for the digital ECG evaluations.

4.6.9 Height and weight

Height will be measured in centimeters (cm) and weight will be measured in kilograms (kg). Measurements should be taken in light clothing without shoes. Please refer to Table 1.

4.6.10 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times given in the study plan Table 1, and Table 2. The date and time of collection will be recorded on the appropriate CRF.

The following laboratory variables will be measured:

Clinical chemistry	**Hematology**
Sodium	Red Blood Cells Count (RBC)
Potassium	Hemoglobin (HGB)
Chloride	Hematocrit (HCT)
BUN	White Blood Cell Count(WBC)
Creatinine	White Blood cell differential including: lymphocytes, basophils, monocytes, neutrophils and eosinophils
Glucose	Platelet Count
Calcium	**Urinalysis**
Uric Acid	pH
Triglycerides	Erythrocytes[a]
Total Bilirubin (Direct and Indirect)	White Blood Cells (WBC's)
Total Protein	Protein[a]
Albumin	Glucose
Alkaline Phosphatase	Bilirubin
AST	Ketones
ALT	
LDH	
T3[b]	
T4[b]	
TSH[b]	

[a] If a urine sample is positive for blood or protein, a microscopic examination of the urine sediment will be performed.
[b] Thyroid function tests will be performed at the screening visit only.

4.6.11 Pregnancy Test

A serum pregnancy test will be performed on all women at the Screening Visit, at admission on Day-1 of the Treatment Period and at the Follow-up Visit. If a pregnancy test is found to be positive at anytime, the patient will not be able to continue participation in the study. Please refer to Table 1 for the timing of pregnancy testing and 8.4 for procedures in case of pregnancy.

4.6.12 Urine Drug Screen

A urine sample will be evaluated during the Screening Visit and at admission to the CRC on Day –1 of the Treatment Period. If necessary the sample can be analyzed using a dip stick. If the dipstick method is used, any result that is indeterminate or positive will be confirmed with a full laboratory evaluation. The sample will be tested for the following drugs of abuse: methamphetamines (including ecstasy), benzodiazepines, cocaine and/or metabolites, amphetamines, tetrahydrocannibinol (THC), opiates, phencyclidine (PCP), and barbiturates. Patients with a positive urine drug screen will be excluded from participating except for patients testing positive for prescribed medication. If a patient tests positive during the initial drug screen, they can be retested but should be excluded if the second test is still positive. Patients who have a positive UDS for a drug(s) legally available by prescription, must provide evidence of the prescription for the drug(s). Please refer to Table 1.

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

4.6.13 Ethanol Screen

A breath, serum or saliva ethanol screen will be administered to all patients during the Screening Visit and at admission on Day-1 of the Treatment Period. If the result is positive at any time the patient will not be allowed to continue participation in the study. Please refer to Table 1.

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

4.6.14 Serology testing

Serology testing for HIV antibody, HbsAg and Hepatitis C antibody is performed on all patients during the Screening Visit only. If a test is positive the subject will not be allowed to participate in the study. Please refer to Table 1.

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 CRFs and will therefore not be recorded in the study database.

4.6.15 Additional Vital Signs

Vital signs assessments in addition to those discussed above can be made at the discretion of the investigator in order to follow the patient's clinical condition. These assessments should be entered as unscheduled assessments in the appropriate sections of the CRF.

4.7 Genetic measurements and co-variables

4.7.1 Collection of samples for optional genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (9mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labeled with the protocol study number, enrollment code and/or patient number and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at Visit 2 it may be taken until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.7.1.1 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory of collection and must remain frozen at all times.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, center number, enrollment number and/or patient number and date of sample collection, should accompany the shipment.

Genetic samples should be shipped to:

[redacted]

4.7.1.2 Storage and coding of DNA samples

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

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

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labeled with the study number and subject number. Only the investigator will be able to link the blood sample to the individual subject. The sample and data will not be labeled with a personal identifier. The link between the patient enrollment/randomization code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca, Alderley Park, UK. 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. Access to the link file will require written authorization from the Project Team Leader.

All DNA samples will be stored under secure conditions with restricted access at AstraZeneca and/or the contracted laboratory. The blood, DNA samples or data derived from the samples may be made available to groups or organizations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

4.7.1.3 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to AZD6765. The results of the genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on AZD6765 to generate hypotheses to be tested in future studies.

4.7.1.4 Derivation or calculation of genetic parameters

The number of patients who 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.

4.8 Volume of blood sampling

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

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	n of samples	Total volume (mL)
Pharmacokinetic		6 mL	7	42
HIV, Hepatitis B, Hepatitis C		10 mL	1	10
BDNF		10 mL	2	20
Optional Genetic		9 mL	1	9
Safety	Clinical chemistry	7mL	4	28
	Hematology	3 mL	4	12
Total				**121**

4.9 Adverse Events

The methods for collecting adverse events are described below.

4.9.1 Adverse Events

4.9.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An adverse event 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, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

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

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Pharmacology Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as 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. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.9.1.2 Recording of adverse events

Adverse event reporting will begin at the screening visit and last throughout the study. All AEs will be collected in the CRF. All SAEs must be reported according to the procedure described in 4.9.1.3.

The patient will be told to report any AE occurring during the study to the investigator or study site staff. Open, standardized AE questioning such as "Have you had any health

problems since your last visit or since you were last questioned? Will be done by the investigator or their personnel at each contact with the patient. The AE open, standardized questioning should be done discretely in order to prevent the patient's from influencing each other. Changes in intensity for an adverse event will be recorded as a new adverse event.

Any AE including clinical findings not resolved on the final scheduled protocol day will be followed up until resolved or explained, or until the investigator decides that no further follow-up is necessary. AstraZeneca may still request further information about such events.

The following variables will be recorded for each AE:

Description of the event, onset (date and time), resolution (date and time), change in intensity, action taken, outcome, causality (yes/no) and whether it constitutes and SAE or not.

The intensity is defined as:

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

A causality assessment must be recorded for all AEs. The CRF asks the question, "In your medical judgment, is there a reasonable possibility that the event may have been caused by the study drug?" If there is any valid reason, even if it is undetermined or untested, for the suspecting cause and effect relationship between the study drug and the occurrence of the AE then this should be answered as "yes". Otherwise, if no valid reason exists for suggesting a possible relationship, then this would be answered as "no". If more than one AE is identified, a causality assessment must be made for each AE.

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

The latest version of the Medical Dictionary of Regulatory Activities (MedDRA) will be used by AstraZeneca for the classification and analysis of adverse events in the study database. For regulatory reporting, SAEs will also be entered onto the global AstraZeneca drug safety database, Clintrace, and coded using MedDRA.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 8.3., regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 8.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Abnormal laboratory tests/ECGs/Vital Signs

Individual protocol-mandated laboratory and other safety-related test results should not be recorded as AEs unless they fulfill the criteria for an SAE or lead to discontinuation of treatment with the investigational product or if the investigator insists that it be considered an adverse event, but will be evaluated in the overall safety analysis. If an abnormal laboratory or other safety-related test result is associated with clinical signs or symptoms, the sign or symptom should be recorded as an AE, and the associated test result should be recorded in the appropriate CRF.

Rating Scales

Signs and symptoms revealed and recorded during the rating of any of the scales (MADRS, BDI, CADSS , etc) should not be reported as an AE, unless they fulfill the criteria for an SAE or lead to the discontinuation of treatment with the investigational product.

Disease under study (DUS)

Worsening of depression will not be considered an AE. However, if it is felt that the investigational product may have contributed to the deterioration, this would be treated as an AE. If the patient requires hospitalization (inpatient stays, in the CRC are not considered hospitalization) due to worsening of symptoms it should be recorded as a serious adverse event (SAE).

Adverse event of Special Interest-Suicidality

All AEs of suicidality will be carefully monitored. These include events of suicide attempts, suicide 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., a motor vehicle accident, or behaving in a dangerous and unsafe way and other self-injurious behavior. Instances of suicidality will be evaluated using a suicidality classification similar to the one established by Columbia University.

Investigators are required to provide detailed accounts of AEs related to, or possibly related to suicidality as described above to AstraZenenca in a prompt manner. Request 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, detailed information will be collected on a separate CRF.

For procedures in case of suicide attempt or suicide, see Section 8.5.

4.9.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study 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 AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the case report form. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

5. STUDY MANAGEMENT

5.1 Monitoring

5.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document “Good Clinical Practice: Consolidated Guideline”.

The specific requirements of the genetic part of the study will be discussed with the investigator(s) and other personnel involved with the study.

5.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the subject’s medical notes (permission from the subject will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

Monitoring including source data verification with the electronic data capture system will be performed on a timely basis during the study.

Source verification of the genetic consent of participating subjects will be performed to ensure that the investigational team is adhering to the specific requirements of the genetics aspects of the study.

5.2 Audits and inspections

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

5.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic testing with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the subjects' samples will also be made clear.

To ensure consistency throughout the study, investigators and study personnel will receive training and instructions for CogState and depression rating scales. Only certified investigators and study personnel will be permitted to conduct the assessments. There will be training and information on all study related processes at the Initiation Visit. AstraZeneca will supply more detailed instructions to site personnel as necessary before and during the study.

Before the first patient is entered into the study, the investigational staff will be trained to use the WBDC system by AstraZeneca personnel or delegates.

5.4 Changes to the protocol

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

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each IRB, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s) who in turn is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

5.5 Study agreements

The principal investigator at each center must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

Specific reference to genetics should be included in the agreement. The contractual obligations should not include any additional payment for collecting the samples, unless special processing is required.

5.6 Study timetable and end of study

The study is expected to start in July 2007 and to be completed by November 2007.

5.7 Data management

5.7.1 Case report forms

Paper CRFs (pCRFs) may be used to record all data not captured electronically. Data should be recorded legibly onto the pCRFs, if applicable, in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

The AstraZeneca Monitor will check data at the monitoring visits to the study site. The Investigator will ensure that the data in the pCRFs are accurate, complete and legible.

Data from the completed pCRFs, if applicable, will be entered onto the clinical study database and validated under the direction of the Data Manager. Any missing, impossible or inconsistent recordings in the pCRFs, if applicable, will be referred back to the Investigator using a data query form and be documented for each individual subject before clean file status is declared.

5.7.2 Electronic data capture (Immediate data entry)

Electronic CRFs will be used to record all data not captured electronically at bedside. Patient questionnaires will be completed by the patient. The data from the questionnaires will be entered into the electronic data capture system by site personnel.

The data entry screens used will be designed according to the AstraZeneca CRF Standard.

Data entry, editing and analyses will be performed by a vendor selected by AstraZeneca R&D. In cases where immediate data entry is not possible, data will first be recorded on a pCRF page, and thereafter entered into the database. The investigator will ensure that the recorded data are correct.

5.7.3 Genetic data

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

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the datasets from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

5.8 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to subjects, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The subject's DNA will not be used for any purpose other than those described in the study protocol.

Individual subjects will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the subject's name nor any other personal identifiers will appear in any publication or report.

6. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

6.1 Pharmacokinetic / pharmacodynamic evaluation

6.1.1 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic analyses will be performed by Clinical Pharmacology, AstraZeneca, Wilmington, DE. Plasma levels of AZD6765 will be determined for all patients dosed.

Pharmacokinetic parameters for AZD6765 will computed by standard non-compartmental methods of analysis using WinNonLin Professional Edition version 4.1 or higher, on a computer that meets or exceeds the minimum system requirement for this program.

Pharmacokinetic parameters to be calculated for each patient include, but is not limited to:

- Maximum AZD6765 plasma concentration at the end of the infusion (C_{max}),
- Time of maximum plasma concentration at the end of the infusion (t_{max}),
- Area under the plasma AZD6765 concentration-time curve from zero to 24 hours [$AUC_{(0-24h)}$].

C_{max} and t_{max} will be assessed by inspection of the AZD6765 plasma-concentration-time profile. Area under the plasma concentration-time curve [$AUC_{(0-24\ hr)}$] will be calculated by the linear trapezoid rule. Other PK parameters, such as partial AUCs, clearance, half-life, and volume of distribution may be calculated as appropriate.

Pharmacokinetic parameters will be calculated individually and summarized by descriptive statistics (n, arithmetic mean, arithmetic standard deviation, arithmetic CV%, geometric mean, geometric CV%, median, minimum, and maximum.

6.1.2 Calculation or derivation of pharmacodynamic variables

There will be no specific derivation of pharmacodynamic variables per se, however, the primary and secondary variables, which include the assessment of patient mood, anxiety, perception and cognitive function, may serve also as the pharmacodynamic endpoints.

6.1.3 Calculation or derivation or pharmacokinetics/pharmacodynamics

If the data are suitable, the relationship between the plasma AZD6765 concentration/exposure and efficacy/pharmacodynamic parameters will be explored either using graphical means or appropriate PK/PD software. Details of the pharmacokinetic analyses will be pre-defined in the Pharmacokinetic Analysis Plan prior to database lock.

6.1.4 Population analyses

The pharmacokinetic data from this study and other prior and/or future studies may be pooled and subjected to analysis using non-linear mixed effects modelling, in order to build a population model to describe the pharmacokinetics of AZD6765 in patients with Treatment Resistant Depression. Together with safety data and efficacy/pharmacodynamic data this may be subjected to exploratory population PK-PD analyses. A Pharmacokinetic Analysis Plan will be will be produced prior to any such investigations, and the analysis will be reported separately.

6.2 Safety evaluation

6.2.1 Calculation or derivation of safety data

Descriptive statistics will be used to present safety data.

6.2.1.1 Adverse events

The incidence of treatment-emergent adverse events reported will be summarized by treatment. Adverse events will be classified using the MedDRA system of nomenclature

(preferred term and system organ class (SOC)). The number and proportion of patients reporting treatment-emergent adverse events will be summarized for each treatment by SOC and preferred term. Adverse events reported before administration of study drug will be listed only and be referred to as 'pre-treatment'.

Similarly, the number of serious treatment-emergent adverse events, other significant treatment-emergent adverse events, adverse events that led to withdrawal, and drug related treatment-emergent adverse events will be summarized by treatment.

Patients reporting treatment-emergent adverse events will be categorized into one or more of the following categories:

- Adverse events
- Serious adverse events
- Other significant adverse events
- Drug related adverse events
- Adverse events leading to withdrawal
- Deaths

Patients' listing will also be provided for each of the above adverse events categories.

6.2.1.2 ECG

ECG data will be summarized by treatment using descriptive statistics. Patient listings will also be provided.

6.2.1.3 Vital signs

Change from baseline in blood pressure and pulse will be summarized at each scheduled measurement by treatment using descriptive statistics. Patient listings will also be provided.

6.2.1.4 Clinical laboratory

Clinical laboratory data will be summarized at each scheduled assessment time by treatment using descriptive statistics. Summary table will be presented for continuous data, and shift table will be presented for categorical data.

Patient listings will be provided and clinically significant laboratory results will be flagged. Due to discrete nature of the urinalyses, these will be summarized using counts and percents. All laboratory data will be presented by parameter group (i.e. clinical chemistry, hematology, urinalysis).

6.3 Genetics as a co-variate

6.3.1 Calculation or derivation of genetic variables

The number of subjects who 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.

6.4 Statistical methods and determination of sample size

6.4.1 Statistical evaluation

Statistical analysis will be conducted by Biostatistics at AstraZeneca, Wilmington, DE using SAS (Version 9). A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized prior to database unblinding.

6.4.2 Description of variables in relation to hypotheses

The primary objective is to determine whether a rapid antidepressant effect can be achieved with AZD6765 in patients with Treatment Resistant Depression (TRD) as determined by the change from baseline to 24 hour assessment in MADRS total score.

The secondary efficacy objectives are to investigate the effects of AZD6765 on subject mood, anxiety, perception and cognitive function using a battery of MADRS, VAS, CADSS, BPRS, CGI, BDI and CogState.

The safety objective is to assess the safety and tolerability of 100 mg IV doses of AZD6765. Safety will be assessed by AEs, vital signs, physical examinations, laboratory parameters and electrocardiograms (ECGs). In addition, safety will be assessed by the 10^{th} item MADRS score $\geq$4 at anytime after the 1^{st} dose of study medication or a treatment-emergent adverse event of suicidality/suicidal ideation/suicide attempt/suicide completion. Incidences of suicidality will also be evaluated using a suicidality classification similar to the one established by Columbia University

6.4.3 Description of analysis sets

Safety patient population will include all the randomized patients who received at least one dose of study medication, classified according to the treatment actually received. Safety population will be used for safety analyses.

Intent-to-treat (ITT) patient population will include all the randomized patients who received at least one dose of study medication, classified according to the treatment they were randomized to. ITT population will be used for efficacy analyses.

6.4.4 Methods of statistical analyses

All statistical tests will be 2-sided at the significance level of 5% unless otherwise specified.

Descriptive statistics will be used to present efficacy and safety variables. For continuous variables, n, mean, standard deviation, median, minimum and maximum will be presented. For categorical variables, n and % will be presented.

6.4.4.1 Primary efficacy variable

The change from baseline in MADRS total score will be compared between two treatment groups, at each scheduled assessment with LOCF in the ITT population, using ANCOVA model with the baseline MADRS as the covariate and treatment as fixed effect in the model. The analysis of the change from baseline to the 24 hour assessment in MADRS total score will be considered as the primary efficacy analysis.

Additionally, the MADRS response will be compared between two treatment groups, at each scheduled assessment with LOCF in the ITT population, using logistic regression with treatment and baseline MADRS in the model. The MADRS response is defined as a reduction of at least 50% from baseline in MADRS total score.

As sensitivity analyses, the above analyses will be repeated at each scheduled assessment (OC) in the ITT population.

For the analyses discussed above in this section, the statistical tests will be 2-sided at the significance of 10%.

6.4.4.2 Secondary efficacy variables

Descriptive statistics will be used to present secondary efficacy variables. Additionally for the key secondary efficacy variables, the ANCOVA model will be used for continuous variable, and the logistic regression will be used for binary variables. The statistical tests will be 2-sided at the significance level of 10%.

6.4.5 Determination of sample size

Based on the assumptions of treatment difference (in MADRS total score change from baselineto the 24 hour assessment) Δ=5, standard deviation σ=7.5, and 2-sided test at α=20%, then 40 completed patients (i.e. 20 completed patients per treatment group) will provide approximately 80% power.

6.5 Interim analyses (Not applicable)

6.6 Data presentation (Not applicable)

6.7 Data monitoring committee (Not applicable)

7. ETHICS

7.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

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

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the IRB. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

7.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

7.3 Informed Consent

The principal investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Informed Consent Form. A copy of the Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

The genetic research is optional and the subject may participate in 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 (non-genetic components of the 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 the genetic aspect of the study at any time.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

7.4 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by randomization code/study code/ initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority or an IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the subjects' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to subjects. 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, however, it must be recognized that there are exceptional circumstances where individuals may see both genetic data and a subject's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the subjects' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

8. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

8.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

[redacted]

For Serious Adverse event reporting

[redacted]

8.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.9.1.3.**

8.3 Procedures in case of overdose

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the CRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An Overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF.

- An Overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF. In addition, the Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An Overdose without associated symptoms should not be recorded as an AE in the CRF. The Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

While there is no specific antidote to AZD6765 that is known, lorazepam can be administered in the case anxiety reactions were to occur in patients.

8.4 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

8.5 Procedures in case of suicide or suicide attempt

Suicide or suicide attempt, irrespective of method, but in connection with the use of the investigational product, should be reported as an AE or SAE in accordance with the definition provided in Section 4.9. The event should be identified as a suicide or suicide attempt, and the method of the suicide or the suicide attempt should be provided. 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, a 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 describerd above, to AstraZeneca promptly according to the timeline for SAE's , please see Section 4.9.1.3 and preferably within 5 days for non-serious 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 CRF pages.

Any patient who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued form the study, please see Section 3.3.5.1 and Section 3.3.5.2. All efforts should be taken to minimize the risk of suicide and the investigator should carefully monitor the patient.

9. REFERENCES

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Clinical Study Protocol	
Appendix A	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix A
Signatures

Appendix A
Drug Substance AZD6765
Study Code D6702C00001
Appendix Edition Number 1.0
Appendix Date [redacted]

ASTRAZENECA SIGNATURE(S)

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Two-Way, Crossover Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

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

Appendix A
Drug Substance AZD6765
Study Code D6702C00001
Appendix Edition Number 1.0
Appendix Date [redacted]

ASTRAZENECA SIGNATURE(S)

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Two-Way, Crossover Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol

AstraZeneca Research and Development site representative

[redacted]

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

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Two-Way, Crossover Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol.

Centre No.: 001

Signature: [redacted]

SIGNATURE OF PRINCIPAL INVESTIGATOR

A Phase IIa, Multi-Center, Randomized, Double-blind, Placebo-controlled, Two-Way, Crossover Study to Assess the Antidepressant Effect and Onset of Effect of AZD6765 in Treatment-Resistant Major Depressive Disorder Patients

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol.

Centre No.:

Signature: [redacted]

Clinical Study Protocol: Appendix B

Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the 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).

Hospitalization

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

Important medical event or medical intervention

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

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

Examples of such events are*:*

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

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 recognized feature of overdose of the drug?

- Is there a known mechanism?

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

Clinical Protocol: Appendix C

Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix C
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4 no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix D
Tables of Permitted/Restricted and Prohibited Drugs

1.1.1 Summary of medications and treatments permitted and prohibited pre-study

Medication specifically prohibited or restricted and those permitted pre-study are listed in Table 1.

Table 1 Pre-study permitted, and prohibited, medications and treatments

Use category	Type of medication/treatment	Timelines and instuctions
Permitted	Non-psychoactive medications, including over-the-counter medications which are required to treat non psychiatric concurrent conditions or illnesses	
	Contraceptives (eg. oral contraceptive, implant, dermal contraceptive, long-term injectable contraceptive, intra-uterine device)	
Prohibited	Use of drugs that inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes including: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluoxetine, , nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir and saquinavir.	2 weeks prior to Day 1 Treatment Period 1
	Use of drugs that induce the hepatic metabolizing cytochrome P40 3A4 enzyme including: carbamzepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort	2 weeks prior to Day 1 Treatment Period 1

Use of psychoactive drugs including the following classes other than those allowed in a restricted manner:	7 days prior to Day 1 Treatment Period 1
MAOI's	14 days prior to Day 1 Treatment Period 1
Anxiolytic	14 days prior to Day 1 Treatment Period 1
Fluoxetine	14 days prior to Day 1 Treatment Period 1
Depot antipsychotics	Lifetime

1.1.2 Summary of medications and treatments permitted, restricted, and prohibited during the Treatment Period.

Medication specifically prohibited or restricted and those permitted during the treatment period are listed in Table 2.

Table 2 Permitted, prohibited, and restricted medications during Treatment Periods

Use Category	Type of medication /treatment
Permitted	Non-psychoactive medications including over the counter medications which are required to treat non psychiatric concurrent conditions or illnesses
	Contraceptives (eg., oral contraceptives, implant, dermal contraception, long-term injectable contraceptive, intrauterine device)
Restricted	Hydroxyzine (50-100 mg) and chlorpheniramine (4 mg) can be used for insomnia (at bedtime) up to the specified dosage per night at the discretion of the investigator.
Prohibited	Use of drugs that inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes including: ketoconazole (except for topical use), itraconazole, fluconazole, erythromycin, clarithromycin, fluoxetine, , nefazodone, troleandomycin, indinavir, nelfinavir, ritonavir and saquinavir.
	Use of drugs that induce the hepatic metabolizing cytochrome P40 3A4 enzyme including: carbamzepine, phenytoin, barbiturates, rifampin, rifabutin, glucocorticoids, thioridazine and St. John's Wort
	Depot antipsychotics
	Antipsychotics
	Mood Stabilizers
	Antidepressants
	MAOI's
	Anxiolytics
	Fluoexetine

Clinical Study Protocol Appendix E	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix E
Hamilton Rating Scale for Depression (HAM-D)

1. HAMILTON RATING SCALE FOR DEPRESSION (HAM-D)

E Code:_____ Date of Assessment_____

For each of the 21 items below, write the correct number on the line next to the item. (Only one response per item).

Depressed Mood

(Sadness, hopeless, helpless, worthless)

- 0= Absent
- 1= These feeling states indicated only on questioning
- 2=These feeling states spontaneously reported verbally
- 3= Communicates feeling states non-verbally-i.e., through facial expression, posture, voice and tendency to weep.
- 4= Patient reports Virtually Only these feeling states in his spontaneous verbal and non-verbal communication.

Feeling of Guilt_____

- 0=Absent
- 1= Self reproach, feels he has let people down
- 2= Ideas of guilt or rumination over past errors or sinful deeds
- 3= Present illness is a punishment. Delusions of guilt
- 4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

Suicide_____

- 0=Absent
- 1=Feels life is not worth living
- 2=Wishes he were dead or any thoughts of possible death to self
- 3=Suicidal ideas or gesture
- Attempts at suicide (any serious attempt rates 4)

Insomnia Early _____

- 0=No difficulty falling asleep
- 1=Complains of occasional difficulty falling asleep- ie, more than ½ hour.
- 2=Complains of nightly difficulty falling asleep.

Insomnia Middle _____

- 0=No difficulty
- 1=Patient complains of being restless and disturbed during the night.
- 2=Waking during the night-any getting out of bed rates 2 (except for purposes of voiding.

Insomnia Late_____

- 0=No difficulty
- 1=Waking in early hours of the morning but goes back to sleep
- 2=Unable to fall asleep again if he gets out of bed

Work and Activities _____

- 0=No difficulty
- 1=Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies.
- 2=Loss of interest in activity; hobbies or work-either directly reported by patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
- 3=Decrease in actual time spent in activities or decrease in productivity
- 4=Stopped working because of present illness

Retardation: Psychomotor (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)_____

- 0=Normal speech and thought
- 1=Slight retardation at interview
- 2=Obvious retardation at interview
- 3=Interview difficult
- 4=Complete stupor

Agitation _____

- 0=None
- 1=Fidgetiness
- 2=Playing with hands, hair etc.
- 3=Moving about, can't sit still
- 4=Hand wringing, nail biting, hair-pulling, biting of lips

Anxiety (Psychological) _____

- 0=No Difficulty
- 1=Subjective tension and irritability
- 2=Worrying about minor matters
- 3=Apprehensive attitude apparent in face or speech
- 4=Fears expressed without questioning

Anxiety Somatic: Physiological concomitants of anxiety, (ie, effects of autonomic overactivity, "butterflies", indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (ie, dry mouth, constipation).

_____

- 0=Absent
- 1=Mild
- 2=Moderate
- 3=Severe
- 4=Incapacitating

Somatic Symptoms (Gastrointestinal)_____

- 0=None
- 1=Loss of appetite but eating without encouragement from others. Food intake about normal.
- 2=Difficulty eating without urging from others. Marked reduction of appetite and food intake.

Somatic Symptoms General_____

- 0=None
- 1=Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability.
- 2=Any clear-cut symptom rates 2

Genital Symtoms (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)_____

- 0=Absent
- 1=Mild
- 2=Severe

Hypochondriasis _____

- 0=Not present
- 1=Self absorption(bodily)
- 2=Preoccupation with health
- 3=Frequent complaints, requests for help, etc
- 4=Hypochondriacal delusions

Loss of Weight_____ (When rating history)

- 0=No weight loss
- 1=Probably weight loss associated with present illness
- 2=Definite (according to patient) weight loss
- 3=Not assessed

Insight_____

- 0=Acknowledges being depressed and ill
- 1=Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest
- 2=Denies being ill at all

Diurnal variation_____**(**Note whether symptoms are worse in morning or evening. IF no diurnal variation, mark none)

- 0=No variation
- 1=Worse in A.M.
- 2=Worse in P.M.

If diurnal variation present, mark the severity of the variation. Mark "None" if No variation

- 0=None
- 1=Mild
- 2=Severe

Depersonalization and Derealization (Such as: Feelings of unreality; nihilistic ideas)
_____

- 0=Absent
- 1=Mild
- 2=Moderate
- 3=Severe
- 4=Incapacitating

Paranoid Symptoms _____

- 0=None
- 1=Suspicious
- 2=Ideas of reference
- 3=Delusions of reference and persecution

Obsessional and Compulsive Symptoms_____

- 0=Absent
- 1=Mild
- 2=Severe

Total Score_____

Clinical Study Protocol Appendix F	
Drug Substance	AZD6765
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Appendix Date	[redacted]

Appendix F
Montgomery Åsberg Rating Scale MADRS

1. MONTGOMERY-ÅSBERG RATING SCALE

MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS)

OVERALL SEVERITY

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise but this must be recorded.

Specify one of the reasons listed below by putting appropriate number in adjacent box.

1. APPARENT SADNESS

Representing despondency, gloom and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

☐

0 - No sadness
1
2 - Looks dispirited but does brighten up without difficulty
3
4 - Appears sad and unhappy most of the time
5
6 - Looks miserable all the time. Extremely despondent.

2. REPORTED SADNESS

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

☐

0 - Occasional sadness in keeping with the circumstances
1
2 - Sad or low but brightens up without difficulty
3
4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 - Continuous or unvarying sadness, misery or despondency

3. INNER TENSION

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.

Rate according to intensity, frequency, duration and the extent of reassurance called for.

☐

0 - Placid. Only fleeting inner tension
1
2 - Occasional feelings of edginess and ill-defined discomfort
3
4 - Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty
5
6 - Unrelenting dread or anguish. Overwhelming panic

MADRS Page 1

A11

4. REDUCED SLEEP

Representing the experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well.

☐

0 - Sleeps as usual
1
2 - Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
3
4 - Sleep reduced or broken by at least 2 hours
5
6 - Less than 2 or 3 hours sleep

5. REDUCED APPETITE

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

☐

0 - Normal or increased appetite
1
2 - Slightly reduced appetite
3
4 - No appetite. Food is tasteless
5
6 - Needs persuasion to eat at all

6. CONCENTRATION DIFFICULTIES

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.
Rate according to intensity, frequency, and degree of incapacity produced.

☐

0 - No difficulties in concentrating
1
2 - Occasional difficulties in collecting one's thoughts
3
4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
5
6 - Unable to read or converse without great difficulty

7. LASSITUDE

Representing a difficulty getting started or slowness initiating and performing everyday activities.

☐

0 - Hardly any difficulty in getting started. No sluggishness
1
2 - Difficulties in starting activities
3
4 - Difficulties in starting simple routine activities which are carried out with effort
5
6 - Complete lassitude. Unable to do anything without help

8. INABILITY TO FEEL

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

☐

0 - Normal interest in surroundings and in other people
1
2 - Reduced ability to enjoy usual interests
3
4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances
5
6 - The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends

9. PESSIMISTIC THOUGHTS

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

☐

0 - No pessimistic thoughts
1
2 - Fluctuating ideas of failure, self-reproach or self-depreciation
3
4 - Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 - Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable

10. SUICIDAL THOUGHTS

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

☐

0 - Enjoys life or takes it as it comes
1
2 - Weary of life. Only fleeting suicidal thoughts
3
4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention
5
6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide

Clinical Study Protocol Appendix G	
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Appendix G
Clinician-Administered Dissociative States Scales (CADSS)

The Clinician Administered Dissociative States Scale (CADSS)

J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Ecode: _____ Initials: _____ Treatment Period. _____

Date: _____ Time: _____

Subjective Items:

1. Do things seem to be moving in slow motion?
   0= Not at all.
   1= Mild, things seem slightly slowed down, but not very noticeable.
   2= Moderate, things are moving about twice as slow as normally.
   3= Severe, things are moving so slowly that they are barely moving.
   4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.

2. Do things seem to be unreal to you, as if you are in a dream?
   0= Not at all.
   1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   2= Moderate, things seem dreamlike, although I know I am awake.
   3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.

3. Do you have some experience that separates you from what is happening;
   for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   0= Not at all.
   1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   3= Severe, I feel extremely separated from what is going on, or I feel as if I am in a movie or a play.
   4= Extreme, I feel as if everyone around me is talking a foreign language, so that cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.

4. Do you feel as if you are looking at things from outside of your body?
0= Not at all.
1= Mild, I feel somewhat disconnected from myself, but I am basically all together. 2= Moderate, I feel like I am outside of my body, but not looking down upon myself from far above.
3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.

5. Do you feel as if you are watching the situation as an observer or a spectator?
0= Not at all.
1= Mild, I feel slightly detached from what is going on, but I am basically here.
2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in this room.
4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
0= Not at all.
1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
3= Severe, I feel detached from my own body, but not far removed from by body, and I feel as if it is me there.
4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
0= Not at all.
1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel that this is not my body.
4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small. Or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
   0= Not at all.
   1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
   0= Not at all.
   1= Mild, things seem slightly different than normal, although it is barely perceptible.
   2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   3= Severe, things are much more distorted, but I have no problems recognizing things around me.
   4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
    0= Not at all.
    1= Mild, things seem slightly paler than usual if I think about it.
    2= Moderate, colors are somewhat diminished, but still recognizable.
    3= Severe, colors are extremely pale, in no way as vivid as they usually are.
    4= Extreme, everything is black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.

12. Does this experience seem to take much longer than you would have expected?
0= Not at all.
1= Mild, it seems as if the interview has gone by for at least twice as long as the true elapsed time.
2= Moderate, it seems as if the interview has gone by for at least two hours.
3= Severe, it seems as if at least ten hours have gone by since the start of the interview.
4= Extreme, it seems as if time is standing still, so that we have been here at this point in time for ever.

13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
0= Not at all.
1= Mild, things are happening slightly faster than normal.
2= Moderate, things seem to be happening at least twice as fast as normal.
3= Severe, things seem to be happening at least 10 times faster than normal.
4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.

14. Do things happen that you later cannot account for?
0= Not at all.
1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
2= Moderate, at least once there were things which happened which now I can't account for.
3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.

15. Do you space out, or in some other way lose track of what was going on?
0= Not at all.
1= Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Do sounds almost disappear or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem to be very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make out anything around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

Clinical Study Protocol Appendix H	
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Appendix H
Clinical Global Impression (CGI)

CLINICAL GLOBAL IMPRESSION (CGI)

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

(Put appropriate code in box)

☐

0 = NOT ASSESSED

1 = NORMAL, NOT ILL AT ALL

2 = BORDERLINE MENTALLY ILL

3 = MILDLY ILL

4 = MODERATELY ILL

5 = MARKEDLY ILL

6 = SEVERELY ILL

7 = AMONG THE MOST EXTREMELY ILL PATIENTS

GLOBAL IMPROVEMENT

Compared to patient's condition **on admission,** how much has patient changed?

(Put appropriate code in box)

☐

0 = NOT ASSESSED

1 = VERY MUCH IMPROVED

2 = MUCH IMPROVED

3 = MINIMALLY IMPROVED

4 = NO CHANGE

5 = MINIMALLY WORSE

6 = MUCH WORSE

7 = VERY MUCH WORSE

Clinical **Study Protocol Appendix I**	
Drug Substance	AZD6765
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Appendix I
Brief Psychiatric Rating Scale (BPRS)

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, **1** = not present, **2** = very mild, **3** = mild, **4** = moderate, **5** = moderately severe, **6** = severe, **7** = extremely severe

1. SOMATIC CONCERN
Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.
SCORE ☐

2. ANXIETY
Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.
SCORE ☐

3. EMOTIONAL WITHDRAWAL
Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.
SCORE ☐

4. CONCEPTUAL DISORGANIZATION
Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.
SCORE ☐

5. GUILT FEELINGS
Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.
SCORE ☐

6. TENSION
Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.
SCORE ☐

7. MANNERISMS AND POSTURING
Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.
SCORE ☐

8. GRANDIOSITY
Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.
SCORE ☐

9. DEPRESSIVE MOOD
Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.
SCORE ☐

10. HOSTILITY
Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. *(Rate attitude toward interviewer under "uncooperativeness").*
SCORE ☐

11. SUSPICIOUSNESS
Belief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.
SCORE ☐

12. HALLUCINATORY BEHAVIOR
Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.
SCORE ☐

13. MOTOR RETARDATION
Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.
SCORE ☐

14. UNCOOPERATIVENESS
Evidence of resistance, unfriendliness, resentment and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.
SCORE ☐

15. UNUSUAL THOUGHT CONTENT
Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.
SCORE ☐

16. BLUNTED AFFECT
Reduced emotional tone, apparent lack of normal feeling or involvement.
SCORE ☐

17. EXCITEMENT
Heightened emotional tone, agitation, increased reactivity.
SCORE ☐

18. DISORIENTATION
Confusion or lack of proper association for person, place or time.
SCORE ☐

***Clinical* Study Protocol Appendix J**	
Drug Substance	AZD6765
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Appendix Date	[redacted]

Appendix J
Beck Depression Inventory (BDI)

BDI®-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

19 20 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

***Clinical* Study Protocol Appendix K**	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix K
DSM-IV Diagnostic Criteria for 296.2x Major Depressive Disorder, Single Episode and 296.3x Major Depressive Disorder, Recurrent

1. DSM-IV

Diagnostic criteria for 296.2x Major Depressive Disorder, Single Episode

A. Presence of a single Major Depressive Episode.

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 not 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 (see page 4).

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.

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

C. There has never been a Manic Episode (see page 4), a Mixed Episode (see page 4 and 5), or a Hypomanic Episode (see page 5). **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.

Diagnostic criteria for 296.3x Major Depressive Disorder, Recurrent

A. Presence of two or more Major Depressive Episodes.

Criteria for Major Depressive Episode (see above)

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 (see page 4), a Mixed Episode (see page 4), or a Hypomanic Episode (see page 5). **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.

Criteria for Manic Episode

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

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

(1) inflated self-esteem or grandiosity

(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

(3) more talkative than usual or pressure to keep talking

(4) flight of ideas or subjective experience that thoughts are racing

(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

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

(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode (see page 4).

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

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

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Criteria for Mixed Episode

A. The criteria are met both for a Manic Episode (see page 4) and for a Major Depressive Episode (see page 2) (except for duration) nearly every day during at least a 1-week period.

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

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

Note: Mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Criteria for Hypomanic Episode

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

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

(1) inflated self-esteem or grandiosity

(2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)

(3) more talkative than usual or pressure to keep talking

(4) flight of ideas or subjective experience that thoughts are racing

(5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

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

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

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

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

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

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

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

Clinical Study Protocol Appendix L	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix L
Mini International Neuropsychiatric Interview (M.I.N.I)

1. M.I.N.I

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10	
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	❐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	❐
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	❐
	Optional			296.30-296.36 Recurrent	F33.x	❐
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1	❐
C	SUICIDALITY	Current (Past Month) Risk: ☐ Low ☐ Medium ☐ High	☐			❐
D	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	❐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	❐
		Past	☐			
E	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	❐
		Lifetime	☐			
F	AGORAPHOBIA	Current	☐	300.22	F40.00	❐
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1	❐
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	❐
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	❐
J	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	❐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	❐
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	❐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	❐
L	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	❐
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9		
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/	❐
		Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39	❐
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	❐
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	❐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	❐

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	❐
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2	❐

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➨) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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A. MAJOR DEPRESSIVE EPISODE

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
		➨	
	IS **A1** OR **A2** CODED **YES?**	NO	YES

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES**?

NO **YES ***

MAJOR DEPRESSIVE EPISODE, CURRENT

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

A4	a	During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?	NO	YES
	b	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?		

NO **YES**

MAJOR DEPRESSIVE EPISODE, RECURRENT

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (**A3** = **YES**), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER **A5a** OR **A5b** CODED **YES**?	➨ NO	YES

A6		**Over the past two week period, when you felt depressed and uninterested:**		
	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED **YES**?

NO	**YES**
Major Depressive Episode **with** ***Melancholic Features Current***	

B. DYSTHYMIA

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1		Have you felt sad, low or depressed most of the time for the last two years?	➨ NO	YES
B2		Was this period interrupted by your feeling OK for two months or more?	NO	➨ YES
B3		**During this period of feeling depressed most of the time:**		
	a	Did your appetite change significantly?	NO	YES
	b	Did you have trouble sleeping or sleep excessively?	NO	YES
	c	Did you feel tired or without energy?	NO	YES
	d	Did you lose your self-confidence?	NO	YES
	e	Did you have trouble concentrating or making decisions?	NO	YES
	f	Did you feel hopeless?	NO	YES
		ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	➨ NO	YES
B4		Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?		

NO **YES**

DYSTHYMIA
CURRENT

C. SUICIDALITY

In the past month did you:

				Points
C1	Suffer any accident?	NO	YES	0
	IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:			
C1a	Plan or intend to hurt yourself in that accident either passively or actively?	NO	YES	0
	IF NO TO C1a, SKIP TO C2: IF YES, ASK C1b,:			
C1b	Did you intend to die as a result of this accident?	NO	YES	0
C2	Think that you would be better off dead or wish you were dead?	NO	YES	1
C3	Want to harm yourself or to hurt or to injure yourself?	NO	YES	2
C4	Think about suicide?	NO	YES	6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency	Intensity	
Occasionally ❒	Mild ❒	Can you control these impulses and state that you will not act on them while in this program? Only score 8 if the response is NO.
Often ❒	Moderate ❒	
Very often ❒	Severe ❒	

NO YES 8

C5	Have a suicide plan?	NO	YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
C7	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
C8	Attempt suicide?	NO	YES	10
	Hoped to be rescued / survive ❒			
	Expected / intended to die ❒			

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT C1) CODED **YES**?

NO **YES**

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

SUICIDE RISK CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

D. (HYPO) MANIC EPISODE

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling persistently irritable?	NO	YES
		➨ IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **D1b** AND **D2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

	Current Episode		Past Episode	
D3 (SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS **NO** (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **D3** SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.	NO	YES	NO	YES
D4 Did these symptoms last at least a week **and** cause significant problems at home, at work, socially, or at school, **or** were you hospitalized for these problems?	NO ↓	YES ↓	NO ↓	YES ↓
THE EPISODE EXPLORED WAS A:	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*

IS **D4** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
HYPOMANIC EPISODE	
CURRENT	❒
PAST	❒

IS **D4** CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	❒
PAST	❒

E. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**? IF YES TO E5, SKIP TO E7.	NO	YES ***PANIC DISORDER LIFETIME***
E6		IF **E5** = **NO,** ARE ANY E4 ANSWERS CODED **YES**? THEN SKIP TO **F1.**	NO	YES ***LIMITED SYMPTOM ATTACKS LIFETIME***
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES ***PANIC DISORDER CURRENT***

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2**.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➨ NO	YES
G2	Is this social fear excessive or unreasonable?	➨ NO	YES
G3	Do you fear these social situations so much that you avoid them or suffer through them?	➨ NO	YES
G4	Do these social fears disrupt your normal work or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

H. OBSESSIVE-COMPULSIVE DISORDER

(➨ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **H4**
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **H4**
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES **obsessions**
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES **compulsions**
	IS **H3** OR **H4** CODED **YES**?	➨ NO YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➨ NO YES
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➨ NO	YES
I2	Did you respond with intense fear, helplessness or horror?	➨ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➨ NO	YES

I4	**In the past month:**			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE **3** OR MORE **I4** ANSWERS CODED **YES**?	➨ NO	YES
I5	**In the past month:**			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE **2** OR MORE **I5** ANSWERS CODED **YES**?	➨ NO	YES

I6 During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?

NO	**YES**
POSTTRAUMATIC STRESS DISORDER CURRENT	

J. ALCOHOL ABUSE AND DEPENDENCE

(➨ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH AND MOVE TO THE NEXT MODULE)

		➨	
J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES

J2 **In the past 12 months**:

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF **YES** TO EITHER, CODE **YES**.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

NO **YES***

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

ALCOHOL DEPENDENCE
CURRENT

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

NO **N/A** **YES**

ALCOHOL ABUSE
CURRENT

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
K1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED) ☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:_____

K2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

***** IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

NO **YES ***

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **N/A** **YES**

SUBSTANCE ABUSE
CURRENT

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

					BIZARRE
		Now I am going to ask you about unusual experiences that some people have.			
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER**:** ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITIUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	NO	YES	
		IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO L6a:** have you heard these things in the past month? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES	YES ➡**L8b**

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO ➡**L13** YES

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **L1**a TO **L7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

LIFETIME

L12 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER, CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE

NO **YES**

MOOD DISORDER WITH *PSYCHOTIC FEATURES*

CURRENT

L13 ARE 1 OR MORE « b » QUESTIONS (1-10) CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS (1-10) CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

L14 IS **L13** CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS (1-10) FROM L1a TO L7a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS (1-10) FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

M. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1	a	How tall are you?	❑❑ft ❑❑in. ❑❑❑cm.	
	b.	What was your lowest weight in the past 3 months?	❑❑❑lbs. ❑❑❑kgs.	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	NO	YES

In the past 3 months:

M2		In spite of this low weight, have you tried not to gain weight?	NO	YES
M3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	NO	YES
M4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
M5		ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**?	NO	YES
M6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	NO	YES

FOR WOMEN: ARE **M5 AND M6** CODED **YES**?

FOR MEN: IS **M5** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

N. BULIMIA NERVOSA

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➨ NO	YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	➨ NO	YES
N3	During these binges, did you feel that your eating was out of control?	➨ NO	YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➨ NO	YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	➨ NO	YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	YES ↓ Skip to N8
N7	Do these binges occur only when you are under (_____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

N8 IS **N5** CODED **YES** AND IS EITHER **N6** OR **N7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **N7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

O. GENERALIZED ANXIETY DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO ➨	YES
	b	Are these worries present most days?	NO ➨	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES ➨
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO ➨	YES
O3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO **YES**

GENERALIZED ANXIETY DISORDER
CURRENT

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES

➨

ARE **2** OR MORE **P1** ANSWERS CODED **YES**? NO YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO **YES**

ANTISOCIAL PERSONALITY DISORDER
LIFETIME

THIS CONCLUDES THE INTERVIEW

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Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:**
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
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Gujarati		M. Patel, B. Patel
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
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Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
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Portuguese	P. Amorim	P. Amorim, T. Guterres
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Urdu		A. Taj, S. Gambhir

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Clinical Study Protocol Appendix M	
Drug Substance	AZD6765
Study Code	D6702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix M
Modified Bond-Lader Visual Analogue Scale (VAS)

1. VISUAL ANALOGUE SCALE (VAS)

This visual analog scale test will be administered at the times given in Table 1 and Table 2 to assess self-rated depression. The first test on Day -1 will be a training session to overcome practice effects and ensure optimal performance for the baseline measurements taken at pre-dose on Day 1.

The modified test being used for this study consists of a questionnaire with 24 visual analog scales (VAS). The scale uses a 100 mm line, each with a set of opposing adjectives at either end, as listed below:

Alert – Drowsy

Troubled – Tranquil

Mentally slow – Quick-witted

Contented – Discontented

Tense – Relaxed

Attentive – Dreamy

Happy – Sad

Calm – Excited

Fuzzy – Clear-Headed

At specified time points during the study, subjects will be asked to record how they are feeling at the moment by making a vertical mark on the line. Standardized instructions will be given to each subject before he completes the questionnaire. Study site personnel will check that the scale has been completed by the subject when collecting the questionnaire. The questionnaires will be evaluated using the same ruler for each subject. Date and time of collection and the distance from beginning of the line and the mark made by the subject on the VAS scale will be recorded in mm in the CRF. If the mark occurs in between two hash marks on the ruler, the more conservative distance, i.e., the longer distance will be recorded in the CRF.

AstraZeneca

Clinical Study Protocol Appendix N	
Drug Substance	AZD6765
Study Code	D06702C00001
Appendix Edition Number	1.0
Appendix Date	[redacted]

Appendix N
A Computer Algorithm for Calculating the Adequacy of Antidepressant Treatment of Unipolar and Bipolar Depression (ATHF Score Cards)

A Computer Algorithm for Calculating the Adequacy of Antidepressant Treatment in Unipolar and Bipolar Depression

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Background: Major depression is often treated with medications in doses that are too low or too short in duration. We published an early version of the Antidepressant Treatment History Form (ATHF) that rates the adequacy of antidepressant treatment. The updated ATHF presented here includes newer medications and a computer algorithm to automate the evaluation of the adequacy of pharmacotherapy or electroconvulsive therapy for depression.

Method: The computer algorithm was written in MS-DOS Q-BASIC and in Visual Basic 5.0. Treatment data from 47 depressed (Structured Clinical Interview for DSM-III-R) patients were scored by the computer algorithm and assigned a number from 0 to 5 for the adequacy of antidepressant treatment. A psychiatrist blinded to the computer ratings manually rated the treatment using the ATHF.

Results: The computer algorithm, based on an updated version of the ATHF, estimates the adequacy of treatment of unipolar and bipolar depression. Computer algorithm results agreed with those generated by a clinician completing the form manually ($\kappa = 0.88$ to 1.00).

Conclusion: The computer algorithm can be used to analyze large databases and may help reduce the morbidity and mortality associated with major depression by improving the assessment of adequacy of pharmacologic treatments for research and quality assurance purposes. The availability of the updated ATHF on the Internet for downloading allows for modifications according to the user's purposes.

(J Clin Psychiatry 2003;64:825–833)

Major depression results in extensive morbidity and mortality estimated at $43.7 billion annually in terms of health care dollars spent, loss of productivity, and days of work lost[1] and carries the risk and consequences of suicidal behavior.[2] However, major depression is inadequately treated in the community,[3–6] general psychiatric settings,[7,8] and academic psychiatry university settings.[9]

Recently, algorithms for the treatment of unipolar and bipolar depression have been generated.[10] However, a computer-assisted search did not uncover published algorithms to evaluate the strength of prescribed antidepressant treatments. We report the development of a computer algorithm based on an updated version of the Antidepressant Treatment History Form (ATHF),[11] a rating scale based on community standards for antidepressant treatment and suggestions by Keller et al.[12] for the evaluation of medication or electroconvulsive therapy (ECT) in the treatment of mood disorders.

METHOD

The Rating Form

The ATHF rates the adequacy of antidepressant treatment based on diagnosis (unipolar or bipolar depression, with or without psychotic features). The ATHF was originally written in 1990 (J.P., H.A.S.)[11] and last updated in 1999 (M.A.O., A.K.)[7] to include medications that became available in the intervening time period. Developed to classify research subjects presenting with major depression as treatment refractory, the ATHF uses stringent dose ranges to define treatment adequacy. The scale, including details regarding cutoff doses and how administration of multiple medications is rated, appears in Appendix 1, Appendix Tables A–J.

The ATHF assigns a score from 0 to 5, scaled for each type of treatment (specific medication or ECT), and takes into account dose, duration of treatment, and patient compliance with the treatment. A 0 indicates that no psychopharmacologic treatment was prescribed, and a rating of 1 or 2 indicates inadequate treatment. Treatment receives a rating of 1 if the medication dose is less than 50% of an adequate dose; a rating of 3 or greater indicates not only adequacy, but also increasing strength of antidepressant prescription (see Appendix 1, Appendix Tables A–J for exact cutoff doses). The increasing ratings above adequate rating reflect the fact that in clinical practice psychopharmacologists often increase the dose above that considered minimally effective in an attempt to maximize response. A method for rating aggressive treatment may be especially helpful in evaluating treatment-refractory patients.

For a treatment to be considered adequate, it must be taken for at least 4 weeks except in the case of ECT (see Appendix 1, Appendix Tables A–J). The ATHF only rates as adequate treatments those approved by the U.S. Food and Drug Administration for major depression or for which there is substantial evidence of antidepressant efficacy in the literature. Lithium and carbamazepine are rated differently for unipolar and bipolar depression. Only lithium is considered an augmenting agent.

Computer Algorithm

The computer algorithm was written in MS-DOS Q-BASIC (Microsoft, Redmond, Wash.) and in Visual Basic 5.0 (Microsoft, Redmond, Wash.) (V.K., A.K., E.B.G.) and implements the rules of the ATHF. It requires the availability of the following data: (1) subject identification number; (2) type of major depression (unipolar or bipolar); (3) assessment of psychosis (present/absent); (4) date of onset of current episode; (5) patient compliance with treatment; (6) name of medication (generic or commercial) or ECT (bilateral or unilateral); (7) dose or, preferably, blood level; (8) date of onset of treatment; and (9) date of treatment discontinuation. In the case of missing data, when treatment is with a standard antidepressant, the ATHF assigns a rating of 1 by default. When data are missing regarding patient characteristics, the program defaults to unipolar depression, nonpsychotic episode. If patient compliance ratings are missing, the program assumes 100% compliance. The program does not account for treatment response in calculating adequacy of response.

Table 1. Number of Pharmacologic Agents Used in Antidepressant Treatments

Medication Category	Number of Medications		Maximum Number of Medications
	Mean	SD	
Antidepressant	1.16	.77	3
Antipsychotic	0.18	.39	1
Benzodiazepines	0.20	0.46	2
Lithium	0.08	0.28	1
Mood stabilizers	0.47	0.54	2
Other	0.14	0.35	1

Subjects

Subjects were recruited at a university teaching hospital as part of a larger study and gave informed consent as approved by the Institutional Review Board. Subjects were 47 patients with either major depressive disorder (i.e., unipolar subtype) (N = 38) or bipolar (N = 9) major depressive episode diagnosed using the Structured Clinical Interview for DSM-III-R (SCID).[13] Only 3 patients had psychotic features as part of the major depressive episode. Patients were interviewed and characterized in terms of their diagnosis (bipolar or unipolar), episode characteristics (psychotic or nonpsychotic), and date of onset of the depressive episode. Data regarding the drug name, dose or blood drug levels, duration of treatment, and compliance were also recorded for all medications reportedly taken by the patient in the 3 months prior to study entry. In some cases, information from medical records and treating physicians was also recorded.

Evaluation of Treatment Adequacy

Data from the ATHF were scored by the computer algorithm and assigned a number from 0 to 5 for the adequacy of antidepressant treatment. An experienced psychiatrist (M.A.O.) blinded to the computer ratings manually rated the adequacy of treatment of depressed patients using the ATHF.

Statistical Analysis

All data are expressed as means and standard deviations. The ratings conducted by the clinician were compared with those generated by the computer algorithm using a weighted kappa.

RESULTS

Table 1 summarizes the pharmacologic agents used for the treatment of major depressive episode. The scores for

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Table 2. Depressed Subjects (N = 47) Receiving Treatments of Each Adequacy Rating[a]

Adequacy	N	%
1	20	42.6
2	5	10.6
3	8	17.0
4	14	29.8
5	0	0

[a]A rating of 1 or 2 indicates inadequate treatment. A rating of 3 or greater indicates not only adequacy, but also increasing strength of antidepressant prescription.

the adequacy of the antidepressant treatments received by the study group are indicated in Table 2.

The kappa score was 1.00 for the unipolar subjects and 0.88 for the bipolar subjects (0.98 for the combined group), reflecting a single disagreement between the assessment by the clinician and the computer assessment. This disagreement led to the discovery of an error in the computer algorithm, which was subsequently corrected. Thus, the adjusted kappa after the correction of the computer algorithm was 1 for both groups. The computer algorithm proved to be equivalent to manual generation of adequacy scores by an experienced clinician. The adequacy of treatment data (Table 2) showed a bimodal distribution.

DISCUSSION

Major depression is often inadequately treated psychopharmacologically, even in situations in which patients seek care from a psychiatrist.[9] Patients treated with tricyclics or monoamine oxidase inhibitors have been reported to receive inadequate somatic therapies (51% of inpatients, 81% of outpatients) even in academic centers.[9] Although one study showed that adequate doses of selective serotonin reuptake inhibitors (SSRIs) are given by both psychiatrists (83%) and other physicians (79%) more often than tricyclics (53% for psychiatrists and 68% for other physicians) or atypical antidepressants,[14] lower doses than the ones used in the ATHF were considered adequate. A survey of prescribing practices, which also defined adequate treatment at lower doses than our criteria, found that 87% of SSRI prescribing practices fell in the adequate range, compared with 29% for tricyclics.[15] In contrast, we found that patients received equally inadequate treatment regardless of the agent used (18% received adequate treatment).[7]

Some subgroups of patients may be at risk for receiving poor somatic treatment. Patients with psychotic depression did not receive an antipsychotic 47% of the time and only 4% received at least 1 adequate medication trial before being referred for ECT.[16] Clinicians either failed to recognize psychotic symptoms or prescribed subtherapeutic doses of antipsychotic medication. A prospective study from the Netherlands[17] found that elderly, depressed inpatients received inadequate antidepressant treatment in 55% of cases, more often when receiving tricyclic medications (82%) than other antidepressants including SSRIs (36%). Although this report[17] did not make explicit what was considered an adequate treatment, Heeren et al.[17] documented that low doses were often prescribed because of side effects (21%) or patient's refusal to increase the dose (7%). Only in 21% of cases was dosing low because of reluctance on the part of the physician. Of interest, in 45% of cases in which a low dose was prescribed, the physician reported that a "good response" had been attained although the physician also reported a less than full recovery.[17] Depressed elderly patients hospitalized for medical problems also received inadequate antidepressant treatment.[18] Close to 60% of those patients received no antidepressants at all, despite chart documentation of major depression. Antidepressants were prescribed in adequate doses in only 29% of cases.[18]

Similarly, in a study of outpatient mental health community clinics,[19] white patients received a recommendation for antidepressant medications more often than Hispanic and black patients (84%, 56%, and 30%, respectively). This was true even though there were no differences in depressive subtype, suicidality, severity of depression, or length of current episode when minority and white groups were compared.[19]

Like the ATHF, the algorithm presented here considers the issue of compliance in addressing adequacy of treatment. Noncompliance with medication treatment has been reported to range from 15% to 44%.[20] Perhaps newer, better-tolerated antidepressants such as the SSRIs lead to fewer problems with compliance. One study showed that patients were more likely to refill their antidepressant prescriptions if they were prescribed an SSRI rather than a tricyclic medication.[13] However, other factors influence compliance as well.[21] Research that attends to compliance in a rigorous way may lead to further understanding of patient characteristics such as diagnosis, age, body weight, and ethnicity that may influence compliance with certain antidepressants.

Retrospective use of our algorithm for the ATHF may aid in the analysis of existing databases to evaluate outcome variables that depend on treatment adequacy, such as length of hospital stay, reduction in symptoms, or reduction of suicidal behaviors. The computer algorithm can also be used to categorize patients as treatment resistant.[11] Prospectively, the algorithm may serve as a way of verifying adequacy of treatment as it evolves, thereby alerting the pharmacist and/or physician if the prescribed treatment appears inadequate. The clinician can then verify the need for lower doses in cases such as slower metabolism in an individual or briefer duration of treatment if there are intolerable side effects leading to trial discontinuation. On a larger scale, this type of algorithm may assist drug utilization review methods currently in

use by health maintenance organizations or federal programs such as Medicaid.[22]

Practically, this computerized version of the ATHF has clinical and research uses and can be downloaded from the Internet (http://excalibur.cpmc.columbia.edu/intensity/Intensity.zip). The simplicity of the program allows for modification for the user's purposes, making it an important research and clinical tool. Evaluating adequacy of treatment in a methodical fashion, this algorithm may further knowledge about how clinicians select and use currently available treatments with efficacy for major depression.

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Appendix appears on pages 829–833.

Appendix 1. Antidepressant Treatment History Form (ATHF) Instruction Guide

Introduction

The ATHF was developed to organize information from various sources about the treatment history of patients with major depression and to rate the antidepressant potency of medication trials and/or electroconvulsive therapy (ECT) that a patient may have received in the current or previous episodes.

Raw Data

Raw data consist of such items as a photocopy of a patient's medical record, pharmacy computer output, etc. These should be obtained with patient consent and incorporated into the research record. In general, a record will be more accurate than a verbal report from memory. For interviews of the patient, family members, and prescribing psychiatrists, the treatment history form itself serves as the raw data, with a separate form completed for each individual interviewed, for each episode of depression. Repeat interviews (e.g., following remission of the acute episode) require completion of a new form.

Treatment History Form

The treatment history forms consist of a face sheet and a continuation form. One set should be used for each available source of information in a particular episode. A separate summary form is used for each episode to evaluate and collapse information from multiple sources.

Identifying information about the characteristics of a particular episode should be ascertained and recorded as accurately and in as much detail as possible. The RDC or DSM diagnosis, the designation of unipolar/bipolar and psychotic/nonpsychotic, and the duration of episode will be critical to later determinations of the potency of drug trials and the relative resistance to treatment.

For ECT, the possibility of recording detailed information, even though it may not always be available, has been incorporated into the form. Evidence of inadequate seizure duration should be explicitly noted.

For each medication trial, each change of dose and each blood level should be recorded on its own line. The purpose is to provide a time line for each trial of the alterations in oral dose and the documentation of blood levels. The date that blood was drawn for levels should be recorded, if available. The reason for stopping the trial should be identified, with particular reference to relapse after acute response, limiting side effects, lack of efficacy, and noncompliance. The final outcome of the trial and compliance with the prescribed regimen should be rated using the scales at the top of the form. In addition, it should be indicated whether each trial was conducted on an inpatient or outpatient basis.

Rating Antidepressant Trials

Each drug or drug combination should be considered separately and rated on the summary form. Information concerning ratings of specific agents is contained in the section "Criteria for Rating Medication Trials for Antidepressant Strength."

Episodes designated as nonpsychotic can be rated without considering the antipsychotic equivalency scales. Please note that lithium and carbamazepine have differing ratings for depressive episodes in unipolar versus bipolar patients. When blood levels are available for imipramine, desipramine, or nortriptyline, they take precedence in ratings relative to oral dose.

Episodes diagnosed as psychotic depression should be considered in the following manner. First, rate antidepressant therapies. Then consider the concurrent antipsychotic treatment ratings for the drug trial. A chlorpromazine (CPZ) equivalency list is provided.

General Principles

Nonpsychotic depression trials for medication groups 100–300 and medications 402 and 602 (medications with demonstrated antidepressant activity) with a duration less than 4 weeks or missing duration receive a score of "1." For selective heterocyclic antidepressants (HTCs), information regarding blood levels takes precedence over oral dosage. *Nonpsychotic depression* trials for medication groups 400–1200 (excluding 402, 602, and 900) receive score "1" independent of dose or duration.

If the duration of a *nonpsychotic depression* trial equals or exceeds 4 weeks and the medication belongs to group 100–300 or is 402, 602, or 900, the trial receives a score between 2 and 5, depending on the dose of antidepressant (see Tables C–G), and diagnosis. For combination trials (e.g., HTC and SSRI), each medication is rated separately. An exception is made for lithium augmentation. The ratings for these trials are increased by 1 point if lithium was administered for at least 2 weeks and the score for the antidepressant met the threshold for an adequate trial (antidepressant adequacy > 2).

Monotherapy with medications without established efficacy for unipolar depression receive a score of "1" independent of dosage or duration (e.g., antipsychotics, benzodiazepines, sedatives, stimulants, thyroid hormones), while for other agents with uncertain efficacy the maximum score could be "2" (alprazolam, specific anticonvulsants, lithium).

Group 1300 receives score "0" independent of dose, duration, and diagnosis.

Psychotic depression trials first should be rated in accordance with the rules for nonpsychotic depression trials. Then all medications that belong to group 500 should be calculated in terms of the CPZ equivalence. If the group 500 medications are prescribed in doses equivalent to ≥ 400 mg of CPZ and the duration of the trial is ≥ 3 wk, then the adequacy should be rated separately (if used alone) or in combination with 100–300, 402, and 602 if used with antidepressants.

See Calculation of Adequacy of Treatment When Antipsychotic Trials Overlap and Table B for instructions.

Psychotic depression trials with combined antidepressant-antipsychotic therapy should be scored as separate trials for each antidepressant (100–300, 402, and 602).

900 ECT is rated separately and is not augmented by 209 (Li) or 500 (neuroleptics).

Only a simultaneous combined treatment trial can be considered augmented; any combined treatment given in sequential order must be rated separately.

For bipolar patients, carbamazepine and lithium treatment alone can receive a maximum rating of 3.

Evidence of noncompliance diminishes the rating of trial strength. Abandoning a trial because of side effects in the context of significant clinical improvement diminishes the rating of trial strength.

continued

Appendix 1. Antidepressant Treatment History Form (ATHF) Instruction Guide (cont.)

Calculation of Adequacy of Treatment When Antipsychotic Trials Overlap

If there is more than one antipsychotic medication, the following rules should apply:

If the AP1 CPZ > 400 and > 3 wk

And

If the AP2 CPZ > 400 or > 3 wk then it is considered as an adequate trial and rated as 2

Or

It can be rated as 2–5 if there is a combination of AP1, AP2 + AD1 + . . . rated as 1–5

If the AP1 CPZ < 400 or < 3 wk

And

If the AP2 CPZ < 400 or < 3 wk

Then

If the trials are consecutive, the duration of the trials should be added and the lowest dose should be used:

Example:
AP1 CPZ = 600 and D = 2 wk

And

AP2 CPZ = 400 and D = 1 wk

Then

AP1 + AP2 = CPZ 400 and D 3 wk, Adequacy = 2

If the trials are overlapping and the D of overlapping wk ≥ 3, then CPZ equivalents should be added.

If D overlapping < 3 wk, then duration of the 2 trials should be added.

Compliance

If information about compliance (C) is missing or not available, it is assumed that C = 100%.

The compliance should be calculated by the following equation:

$$C = \frac{\text{Total Medication Given} \times \text{Daily Dose Prescribed}}{\text{Total Medication Prescribed}}$$

Total Medication Given: Total amount of medication that the patient took during the treatment (e.g., sum of total number of milligrams taken over the course of treatment).

Daily Dose Prescribed: Dose after induction phase of treatment (e.g., 30 mg per day).

Total Medication Prescribed: Total amount of medication prescribed during the treatment (e.g., 30 mg per day for 28 days = 840 mg).

A separate summary form should be completed for each episode of major depression. Review all sources of information regarding each trial in making these determinations giving greatest weight to medical documentation, blood levels, and multiple sources of confirmation. The starting and stop dates for the period of the trial for which the patient is being rated (e.g., maintained oral dose or blood level for 4 weeks or greater) should be indicated, followed by the generic name(s) of the medication. Note explicitly combination trials and provide a separate rating for each agent in HTC/MAOI combinations and HTC/SSRI combinations. In rating relative antidepressant resistance, note that noncompliance or instances of good therapeutic response followed by rapid relapse in the absence of continuation therapy at adequate levels or due to noncompliance prevent rating a trial at level 3 or higher. For each trial, provide a global confidence score for the antidepressant resistance rating. This score should reflect the rater's certainty regarding dose, duration, compliance, and clinical outcome of the medication trial. For ECT trials, the confidence rating should reflect certainty regarding the number of ECTs given and the outcome of the treatment. At this time, confidence in reports of dosage of ECT is not being rated, and compliance with treatment is usually 100% (patient was present at the treatment). The scale to be used for this judgment is provided below.

1. No Confidence Rating: Discrepant or clearly unreliable information regarding dose, duration, compliance, and outcome of a medication trial or number and outcome of ECT trial.
2. Low Confidence Rating: Information is marginal. Evidence of contradictions in information or significant doubt exists regarding dose, duration, compliance, and outcome of a medication trial or number and outcome of ECT trial.
3. Moderate Confidence Rating: Adequate information is available but based largely on one source that appears reliable. Areas of doubt not critical in medication or ECT resistance rating.
4. Strong Confidence Rating: Adequate information is available from more than one reliable source without significant discrepancy regarding dose, duration, compliance, and outcome of a medication trial or number and outcome of ECT trial.
5. High Confidence Rating: Trial dose, duration, compliance, and outcome or number and outcome of ECT trial confirmed by multiple sources, with excellent documentation (blood levels, medication orders), strong evidence of compliance, and outcome certain.

After the global confidence rating is made for the rating of relative medication or ECT resistance, specific confidence ratings should be made with respect to dose, duration, compliance, and outcome of the trials. The same 1–5 rating scale as used for the global confidence rating should be applied to these specific ratings.

Equivalent Doses of Antipsychotic Drugs*

Generic name (trade names)	Equivalent Doses		
Phenothiazines			
Chlorpromazine (Thorazine)	100 mg	200 mg	400 mg
Thioridazine (Mellaril)	100 mg	200 mg	400 mg
Mesoridazine (Serentil)	50 mg	100 mg	200 mg
Trifluoperazine (Stelazine)	4 mg	8 mg	16 mg
Fluphenazine (Prolixin, Permitil)	1.5 mg	3 mg	6 mg
Fluphenazine decanoate	0.25 cc/mo	0.5 cc/mo	1 cc/mo
Perphenazine (Trilafon)	10 mg	20 mg	40 mg
Prochlorperazine (Compazine)	15 mg	30 mg	60 mg
Thioxanthenes			
Thiothixene (Navane)	5 mg	10 mg	20 mg
Chloprothixene (Taractan)	50 mg	100 mg	200 mg
Butyrophenone			
Haloperidol (Haldol)	2 mg	4 mg	8 mg
Haloperidol decanoate		0.25 cc/mo	0.5 cc/mo
Dibenzoxazepine			
Loxapine (Loxitane)	15 mg	30 mg	60 mg
Amoxapine (Asendin)	125 mg	250 mg	500 mg
Dibenzazepine			
Clozapine (Clozaril)	60 mg	120 mg	240 mg
Dihydroindolone			
Molindone (Moban)	10 mg	20 mg	40 mg
Diphenylbutylpiperidine			
Pimozide (Orap)	2 mg	4 mg	8 mg
Risperidone (Risperdal)	1.5 mg	3 mg	6 mg
Sulpiride	300 mg	600 mg	1200 mg
Olanzapine (Zyprexa)	5 mg	10 mg	20 mg
Quetiapine (Seroquel)	100 mg	200 mg	400 mg

*Please note the rating for amoxapine.

Appendix Table A. Medication Names and Codes[a,b]

Group Class	Drugs in Class	Drugs in Class	Drugs in Class
0 = none			
100 = Norepinephrine agonists	101 desipramine (Norpramin) 102 maprotiline (Ludiomil)	103 bupropion (Wellbutrin, Zyban) 104 nortriptyline (Pamelor)	105 protriptyline (Vivactil)
200 = Serotonin agonists	201 trazodone (Desyrel) 202 fluoxetine (Prozac) 203 fluvoxamine (Luvox)	204 paroxetine (Paxil) 206 sertraline (Zoloft) 207 nefazodone (Serzone)	208 buspirone (BuSpar) 209 lithium (Eskalith, Lithobid) 210 citalopram (Celexa)
300 = Combined norepinephrine and serotonin agonists	301 amitriptyline (Elavil, Endep) 302 imipramine (Tofranil) 303 amoxapine (Asendin) 304 venlafaxine (Effexor)	305 clomipramine (Anafranil) 306 doxepin (Sinequan, Zonalon) 307 tranylcypromine (Parnate) 308 phenelzine (Nardil)	309 isocarboxazid (Marplan) 310 mirtazapine (Remeron)
400 = Mood stabilizers	401 valproic acid (Divalproex Na, Valproate, Depakene, Depakote)	402 carbamazepine (Tegretol) 403 gabapentin (Neurontin)	404 lamotrigine (Lamictal) 405 topiramate (Topamax)
500 = Neuroleptics	501 haloperidol (Haldol) 502 perphenazine (Trilafon) 503 clozapine (Clozaril) 504 risperidone (Risperdal) 505 chlorpromazine (Thorazine)	506 pimozide (Orap) 507 fluphenazine (Prolixin, Permitil) 508 trifluoperazine (Stelazine) 509 thiothixene (Navane) 510 loxapine (Loxapac, Loxitane)	511 thioridazine (Mellaril) 512 olanzapine (Zyprexa) 513 quetiapine (Seroquel) 514 ziprasidone (Geodon) 515 molindone (Moban)
600 = Tranquilizers	601 lorazepam (Ativan) 602 alprazolam (Xanax) 603 clonazepam (Klonopin)	604 temazepam (Restoril) 605 hydroxyzine (Atarax, Vistaril) 606 flurazepam (Dalmane)	607 oxazepam (Serax)
700 = Stimulants	701 dextroamphetamine (Dexedrine)	702 methylphenidate (Ritalin)	703 pemoline (Cylert)
800 = Antihistamines/ anticholinergics	801 diphenhydramine (Benadryl, Dephedril)	802 benztropine (Cogentin) 803 trihexyphenidyl (Artane)	804 promethazine (Phenergan)
900 = ECT	900 unknown	901 unilateral ECT	902 bilateral ECT
1100 = Hypnotics	1101 chloral hydrate 1102 amobarbital Na (Amytal Na) 1103 butibel 1104 butabarbital Na (Butisol Na)	1105 methobarbital (Mebaral) 1106 methohexital Na (Brevital) 1107 pentobarbital Na (Nembutal, Pentobarb) 1108 phenobarbital (Phenob, Luminal)	1109 primidone (Mysoline) 1110 zolpidem (Ambien) 1111 secobarbital Na (Seconal Na, Tuinal)
1200 = MWADA	1201 clonidine (Catapres) 1202 L-tryptophan	1203 thyroid hormones (Cytomel, Synthroid) 1204 estrogens 1205 fenfluramine (Pondimin)	1206 phototherapy 1207 Ca channel blockers
1300 = MWNADA	1301 acetylsalicylic acid (aspirin) 1302 acetaminophen (Tylenol) 1303 indomethacin (Indocin) 1304 antibiotics 1305 cardiac glycosides	1306 stool softeners, laxatives 1307 vitamins 1308 H_2 blockers 1309 glucose-lowering (Sulfonurea class) 1310 insulin	1311 antiacid medication 1312 β-blockers 1313 pseudoephedrine

[a]All medications are encoded with 3- or 4-digit codes in accordance with their antidepressant activity.
[b]The first number in 3-digit codes or first 2 numbers in 4-digit codes encode the medication type; the second 2 digits encode the medication name.
Abbreviations: ECT = electroconvulsive therapy, MWADA = medication with antidepressant activity, MWNADA = medication with no antidepressant activity.

Appendix Table B. Trial Adequacy Calculation for Psychotic Depression

Adequacy	Categories	Definition of Rating
0	Medications with no known psychotropic actions or no medication	No treatment
1	AD alone AP alone CPZ < 400 or D < 3 wk AD rated as 1 + AP CPZ < 400 or D < 3 wk	Minimal treatment
2	AD rated 2–5 + AP CPZ < 400 or D < 3 wk AP alone CPZ ≥ 400 and D ≥ 3 wk AD rated 1–2 + AP CPZ ≥ 400 and D ≥ 3 wk	Treatment of uncertain efficacy
3	AD rated 3 + AP CPZ ≥ 400 and D ≥ 3 wk	Adequate moderate treatment
4	AD rated 4 + AP CPZ ≥ 400 and D ≥ 3 wk	Adequate intensive treatment
5	AD rated 5 + AP CPZ ≥ 400 and D ≥ 3 wk	Aggressive treatment

Abbreviations: AD = antidepressant, AP = antipsychotic, CPZ = chlorpromazine equivalent, D = trial duration.

Appendix Table C. Heterocyclic Antidepressants (HTC)[a,b,c]

Drug Rating	HTC Dose	HTC Blood Level	Nortriptyline Dose	Nortriptyline Blood Level	Protriptyline Dose
1	Any drug < 4 wk or Any drug < 100 mg/d		NT < 4 wk or 4 wk or more and NT < 50 mg/d	NT < 4 wk	Drug < 4 wk or 4 wk or more and dosage < 30 mg/d
2	4 wk or more and 100–199 mg/d		4 wk or more and NT 50–75 mg/d	4 wk or more and level < 50 ng/mL	4 wk or more and dosage 31–40 mg/d
3	4 wk or more and 200–299 mg/d	4 wk or more and DMI level 125 ng/mL or greater	4 wk or more and NT 76–100 mg/d	4 wk or more and level < 50–99 ng/mL	4 wk or more and dosage 41–60 mg/d
4	4 wk or more and 300 mg/d or greater	4 wk or more and DMI + IMI level > 224 ng/mL	4 wk or more and NT > 100 mg/d	4 wk or more and level 100–150 ng/mL	4 wk or more and dosage > 60 mg/d

[a]For HTC-MAOI combinations, score each agent alone, as a separate trial.
[b]For HTC-paroxetine/fluoxetine combination trials: after 1 week on 20 mg of paroxetine or fluoxetine, the dosage equivalent of the HTC should be doubled to determine adequacy rating.
[c]Amitriptyline (Elavil, Endep), imipramine (Tofranil), desipramine (Norpramin, Pertofrane), trimipramine (Surmontil), clomipramine (Anafranil), maprotiline (Ludiomil), doxepin (Sinequan, Adapin), nomifensine, nortriptyline (Pamelor, Aventyl), protriptyline (Vivactil).
Abbreviations: DMI = desipramine, IMI = imipramine, MAOI = monoamine oxidase inhibitor, NT = nortriptyline.

Appendix Table D. Selective Serotonin Reuptake Inhibitors (SSRIs)[a]

Drug Rating	Fluoxetine, Citalopram	Fluvoxamine	Paroxetine	Sertraline
1	Drug < 4 wk or 4 wk or more and dosage 1–9 mg/d	Drug < 4 wk or drug < 100 mg/d	Less than 4 wk or 4 wk or more and dosage < 1–9 mg/d	Drug < 4 wk or 4 wk or more and dosage < 50 mg/d
2	4 wk or more and dosage 10–19 mg/d	4 wk or more and 100–199 mg/d	4 wk or more and dosage 10–19 mg/d	4 wk or more and dosage 50–99 mg/d
3	4 wk or more and dosage 20–39 mg/d	4 wk or more and 200–299 mg/d	4 wk or more and dosage 20–29 mg/d	4 wk or more and dosage 100–199 mg/d
4	4 wk or more and dosage ≥ 40 mg/d	4 wk or more and 300 mg/d or greater	4 wk or more and dosage 30 mg/d	4 wk or more and dosage ≥ 200 mg/d

[a]Fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

Appendix Table E. Novel Antidepressants[a]

Drug Rating	Bupropion	Mirtazapine	Nefazodone	Trazodone, Amoxapine	Venlafaxine
1	Drug < 4 wk or 4 wk or more and dosage < 150 mg/d	Less than 4 wk or 4 wk or more and dosage < 15 mg/d	Drug < 4 wk or 4 wk or more and dosage < 150 mg/d	Drug < 4 wk or 4 wk or more and dosage < 200 mg/d	Less than 4 wk or 4 wk or more and dosage < 75 mg/d
2	4 wk or more and dosage 150–299 mg/d	4 wk or more and dosage 15–29 mg/d	4 wk or more and dosage 150–299 mg/d	4 wk or more and dosage 200–399 mg/d	4 wk or more and dosage 75–224 mg/d
3	4 wk or more and dosage 300–449 mg/d	4 wk or more and dosage 30–44 mg/d	4 wk or more and dosage 300–599 mg/d	4 wk or more and dosage 400–599 mg/d	4 wk or more and dosage 225–374 mg/d
4	4 wk or more and dosage 450 mg/d	4 wk or more and dosage 45 mg/d or greater	4 wk or more and dosage 600 mg/d or greater	4 wk or more and dosage 600 mg/d	4 wk or more and dosage 375 mg/d

[a]Bupropion (Wellbutrin), mirtazapine (Remeron), nefazodone (Serzone), trazodone (Desyrel), amoxapine (Asendin), venlafaxine (Effexor and Effexor XR).

Appendix Table F. Monoamine Oxidase Inhibitors (MAOIs)[a,b,c]

Drug Rating	Phenelzine	Moclobemide	Selegiline	Isocarboxazid
1	Drug < 4 wk or 4 wk or more and dosage < 30 mg/d	Less than 4 wk or 4 wk or more and dosage < 150 mg/d	Drug < 4 wk or 4 wk or more and dosage < 20 mg/d	Drug < 4 wk or 4 wk or more and dosage < 20 mg/d
2	4 wk or more and dosage 31–60 mg/d	4 wk or more and dosage 150–299 mg/d (100–200 = 30 Nardil)	4 wk or more and dosage 21–40 mg/d	4 wk or more and dosage 21–40 mg/d
3	4 wk or more and dosage 61–90 mg/d	4 wk or more and dosage 300–599 mg/d (300 = 60 Nardil)	4 wk or more and dosage 41–59 mg/d	4 wk or more and dosage 41–60 mg/d
4	4 wk or more and dosage 91 mg/d or greater	4 wk or more and dosage 600 mg/d or greater (600 = 90 Nardil)	4 wk or more and dosage 60 mg/d or greater	4 wk or more and dosage 61 mg/d

[a]MAOI inhibition: 80% inhibition will rate 4.
[b]For HTC-MAOI combinations, score each agent considered alone.
[c]Phenelzine (Nardil), moclobemide, selegiline (Eldepryl), tranylcypromine (Parnate), isocarboxazid.
Abbreviation: HTC = heterocyclic antidepressant.

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Appendix Table G. Lithium or Carbamazepine Alone[a,b]

Drug Rating	Lithium for Bipolar Patients: Levels Take Precedence Over Dosage	Carbamazepine
1	Drug < 4 wk or 4 wk or more and level: < 0.4 mEq/L or 4 wk or more and dosage: < 600 mg/d for any duration	Carbamazepine < 4 wk or 4 wk or more and level < 6
2	4 wk or more and level: 0.41–0.6 mEq/L or 4 wk or more and dosage: 600–899 mg/d	4 wk or more and level 6–7.9
3	4 wk or more and level: > 0.6 mEq/L or 4 wk or more and dosage: > 900 mg/d	4 wk or more and level 8 or more

[a]Unipolar patients can receive a maximum rating of 2 for lithium alone.
[b]Unipolar patients can receive a maximum rating of 2 for carbamazepine alone.

Appendix Table H. Lithium as an Augmenting Agent

Drug Rating	Lithium as an Augmenting Agent
4	Antidepressant drugs rated level 3 and lithium for at least 2 wk; carbamazepine rated level 3 and lithium for at least 2 wk
5	Antidepressant drugs rated level 4 and lithium for at least 2 wk

Appendix Table I. Electroconvulsive Therapy (ECT)[a,b]

Drug Rating	Number of Treatments: Unilateral or Unknown ECT	Number of Treatments: Bilateral ECT
1	1–3	1–3
2	4–6	4–6
3	7–9	
4	10–12	7–9
5	13 or more	10 or more

[a]A point is added to an ECT trial if the patient has had ≥ 7 adequate bilateral treatments. The highest rating is a 5.
[b]If ECT and antidepressant medication are given simultaneously, this does not constitute a combination/augmentation trial. Each should be rated separately.

Appendix Table J. Others

Drug Rating[a,b,c]	Alprazolam	Antipsychotics	Sedatives	Other Benzodiazepines[d]	Not Considered Augmenting Agents: Stimulants, eg, *d*-Amphetamine, Methylphenidate, Pemoline	Not Considered Augmenting Agents: Antipsychotics	Not Considered Augmenting Agents: Clonidine, L-tryptophan, Thyroid Hormones, Estrogen, Fenfluramine
1	< 4 wk or 4 wk or more and dosage < 4 mg/d	When used in nonpsychotic patients and should be rated together into 1 continuous trial, no matter how many different neuroleptics were given	Any dosage for any duration when used as a psychotropic	Any dosage for any duration	Any dosage for any duration	Any dosage for any duration	Any dosage for any duration
2	4 wk or more and dosage 4 mg/d or greater						

[a]HTC/SSRI and any other combinations, e.g., SSRI/bupropion, should be treated as HTC/MAOI combinations: rate each medication separately.
[b]If the patient uses different sedatives, with the exception of alprazolam, they should be rated as one continuous trial.
[c]Phototherapy in any form: 1.
[d]Clonazepam (Klonopin) and valproic acid (Depakene) can be rated 1 if used alone; they are not considered augmenting agents.
Abbreviations: HTC = heterocyclic antidepressant, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.