STUDY PROTOCOL

PROTOCOL NUMBER:	**ARX 1006**
PROTOCOL TITLE:	A 12-Week, Randomized, Double-Blind, Controlled Evaluation Followed by an Open-Label 12-Week Follow-up Period of the Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering from a Major Depressive Disorder (MDD) and Having Had – Within the Current Episode - an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic
TEST ARTICLE:	GeneSight Psychotropic
SPONSOR:	AssureRx Health, Inc. (Assurex)
SPONSOR CLINICAL MONITOR:	**7** Bryan Dechairo, PhD
ISSUE DATE:	**04/21/15**
VERSION:	**5**

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1.0 PROCEDURES IN CASE OF EMERGENCY

Table 1. Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Medical Monitor	Vicki Brown	910-679-1573 (office) 910-231-3681 (mobile) 910-398-5910 (Blackberry) email: vikki.brown@incresearch.com
Clinical Development Associate	Lindsey Burns	513-701-5068 (office) 513-284-0608 (mobile) email: lburns@assurexhealth.com

2.0 SYNOPSIS

Name of Sponsor/ Company: Assurex

Name of Test Product: GeneSight Psychotropic (Pharmacogenomic based psychotropic treatment decision support tool; see Appendix 1 for list of psychotropic medications included in GeneSight Psychotropic)

Name of Active Ingredient: Not Applicable

Title of Study: A 12-week, randomized, double-blind, controlled evaluation followed by an open-label 12-week follow-up period of the impact of GeneSight Psychotropic on response to psychotropic treatment in outpatients suffering from a major depressive disorder (MDD) and having had – within the current episode - an inadequate response to at least one psychotropic medication included in GeneSight Psychotropic.

Study Center(s) and Countries: Multicenter, sites in the US will participate in this study. Investigators should be GeneSight Psychotropic naïve.

Principal Investigators:
John Greden, MD and Melvin McInnis, MD

Study period (years): 3 years Estimated first patient enrolled: April 2014 Estimated last patient completed: November 2016 Completion of data analysis: February 2017	**Development Phase:** IV

Objectives:

Primary Objective:
Evaluate the impact of GeneSight Psychotropic on response to psychotropic treatment as judged by the mean change in the 17-item Hamilton Depression ($HAM\text{-}D_{17}$) score from baseline to end of Week 8 of the study.

Secondary Objectives:

1. Mean change in the 16-item Quick Inventory of Depression Symptomology ($QIDS\text{-}C_{16}$) scale or the 9-item Patient Health Questionnaire (PHQ-9) from baseline to end of Week 8 of the study;
2. Mean change in $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, PHQ-9, or Clinical Global Impression of Severity (CGI-S) scale from baseline to end of Week 12 of the study;
3. Percentage of responders at Week 8 in each treatment group on the $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, or PHQ-9; for each rating scale, a responder is defined as a participant with 50% change from baseline in total scale score;
4. Percentage of responders at Week 12 (defined as above) in each treatment group on the $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, PHQ-9, CGI-S (defined as a change in category of severity of at least 1 point), Clinical Global Impression of Improvement (CGI-I; defined as a score from 1 to 3), or Clinical Global Impression of Efficacy (CGI-EI; defined as a scores of 01, 02, 05, or 06);
5. Percentage of remitters at Week 12 defined as $HAM\text{-}D_{17} \leq 7$, $QIDS\text{-}C_{16} \leq 5$, PHQ-9 <5, or CGI-S ≤1 in each treatment group;
6. Percentage of remitters at Week 8 defined as $HAM\text{-}D_{17} \leq 7$, $QIDS\text{-}C_{16} \leq 5$, or PHQ-9 <5 in each treatment group;
7. Time to response/remission of depressive symptoms over 8 and 12 weeks;
8. Mean change in symptoms, percent response and percent remission from baseline to week 24

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and from week 12 to week 24 across all scales in each treatment group.

Exploratory Objectives:

1. The mean change in Generalized Anxiety Disorder 7-item (GAD-7) scale from baseline to week 8 and week 12, and from week 12 to week 24 in each treatment group.

Methodology:

This protocol describes a 2-part study. The first part will be a randomized, multicenter, double-blind (raters and participants), 12-week, controlled study in parallel balanced groups of depressed patients to evaluate the impact of GeneSight Psychotropic on response to psychotropic treatments listed in Appendix 1 of this protocol. Patients enrolled in this study will be required to have Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of MDD, a total score ≥11 on the QIDS-C_{16} and QIDS-SR_{16}, and an inadequate response within the current episode to at least 1 psychotropic treatment. For the purpose of this protocol, inadequate response is defined as inadequate efficacy after 6 weeks of treatment or discontinuation of a psychotropic treatment due to adverse events (AEs) or intolerability. Upon completion of the double-blind part of the study, participants will continue in a 12-week open-label part of the study to evaluate the long-term impact of the use of GeneSight Psychotropic.

Patients suffering from MDD will be enrolled in the study and randomized on a 1:1 basis to treatment as usual or to treatment decision utilizing GeneSight Psychotropic.

Screening Period

Screening procedures will include GeneSight Psychotropic genotyping (buccal swab). After signing an informed consent form (ICF), patients will be evaluated for inclusion in the study not more than 2 weeks, and preferably 3 days prior to enrollment (results of the buccal swab will be available within 3 days).

Screening evaluations will include: demographics, medical history, medication history and response including previous and current psychotropic treatment, physical examination, vital signs, height, weight, psychiatric assessments including Mini International Neuropsychiatric Interview, DSM-IV-TR criteria for Major Depressive Disorder, QIDS-SR_{16}, QIDS-C_{16}, laboratory parameters (to exclude hepatic insufficiency), pharmacogenomic blood sample and Urine Drug Screen.

Patients' psychotropic medication should not be modified (in terms of type and dosage) during the screening period.

Randomization

Upon completion of the screening procedures, patients will be evaluated for eligibility against the inclusion/exclusion criteria. Eligible patients will be enrolled in the study and randomized to one of two groups (treatment as usual or to treatment decision utilizing GeneSight Psychotropic).

Upon inclusion into the study, participants will be evaluated with HAM-D_{17}, QIDS-C_{16}, PHQ-9,

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GAD-7, CGI-S, and SF-36. Upon inclusion in the study, investigators will be given the results of the GeneSight Psychotropic test for the participants randomized to the treatment decision utilizing GeneSight Psychotropic group. Investigators will be unblinded and use the report to support their treatment decisions for patients in the GeneSight Psychotropic group. However, raters and participants will be blinded. Sites should use the same blinded Site-Rater to conduct the QIDS-C_{16} throughout the trial. Each site should have a qualified back-up Rater for the QIDS –C_{16} in the event they must conduct ratings in the absence of the primary rater. The Treating Clinician should never conduct the QIDS-C_{16}. Double-Blind Treatment Period Throughout the 12-week double-blind treatment period, participants will be followed up (in-clinic visit) for efficacy, tolerability, and safety, at the end (± 3 days) of Weeks 4, 8, and 12. During the in-clinic visits, participants will be evaluated with HAM-D_{17}, QIDS-C_{16}, PHQ-9, and GAD-7. At the end of Week 12 visit, participants will also be evaluated with CGI-S, CGI-I, CGI-EI, and SF-36.
12-Week Open-Label Extension Following completion of the double-blind period, participants will continue in the study for an additional 12 weeks to evaluate the longer term impact of GeneSight Psychotropic. At the start of the open-label extension all participants will be given the results of their GeneSight Psychotropic test and will therefore be unblinded and treating clinicians can utilize GeneSight Psychotropic for treatment decision support of all participants. This phase of the study will have an in-clinic visit at the end (± 2 weeks) of Week 24, and evaluation with HAM-D_{17}, QIDS-C_{16}, PHQ-9, GAD-7, CGI-S, CGI-I, CGI-EI, and SF-36. Early Termination Visit If early termination occurs after Visit 2, the subject should attend an in-clinic visit as soon as possible to complete early termination procedures that will consist of all procedures scheduled for Week 24. Duration of Study for Individual Participants Individual participation in the double-blind period will last a maximum of approximately 26 weeks (up to 2 weeks screening; 12-week double-blind treatment and a 12-week follow-up period).
Number of Participants Planned: A sufficient number of participants will be enrolled in the study to have at least 1200 participants complete the Week 8 visit.
Study Population: Males and females, outpatients, ≥18 years of age, diagnosed with MDD having had an inadequate response to at least 1 psychotropic treatment within the current depressive episode will be enrolled in the study. Inadequate response is defined as lack of efficacy after 6 weeks of

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treatment or discontinuation of a psychotropic treatment due to AEs or intolerability.

Inclusion Criteria

To be eligible, all patients must:

1. Be able to understand the requirements of the study and provide written informed consent to participate in this study; signed and dated informed consent will be obtained from each patient before participation in the study;
2. Have provided written authorization for the use and disclosure of their protected health information;
3. Be ≥18 years of age;
4. Suffer from Major Depressive Disorder meeting DSM-IV-TR criteria;
5. Have had an inadequate response within the current episode to at least 1 psychotropic treatment (listed in Appendix 1 of this protocol). Inadequate response is defined as inadequate efficacy after 6 weeks of a psychotropic treatment or discontinuation of a psychotropic treatment due to AEs or intolerability;
6. Have a total baseline score on the QIDS-C_{16} and QIDS-SR_{16} rating scales ≥11;
7. Agree to abide by the study protocol and its restrictions and be able to complete all aspects of the study, including all visits and tests.

Exclusion Criteria

Any of the following conditions are cause for exclusion from the study:

1. Patients posing a serious suicidal risk and/or in need of immediate hospitalization as judged by the investigator;
2. Patients with a diagnosis of Bipolar I or II disorder;
3. Patients with a current Axis I diagnosis of:
    a. Delirium,
    b. Dementia,
    c. Amnestic and other cognitive disorder,
    d. Schizophrenia or other psychotic disorder;
4. Patients having experienced hallucinations, delusions, or any psychotic symptomatology within the current depressive episode or during prior depressive episodes;
5. Patient is currently in an inpatient facility;
6. Patients with a history of hypothyroidism unless taking a stable dose of thyroid medication and asymptomatic or euthyroid for 6 months;
7. Patients who meet DSM-IV-TR criteria for any significant current substance use disorder;
8. Patients with significant unstable medical condition; life threatening disease; hepatic insufficiency (3X ULN for AST and/or ALT); liver transplant recipient; cirrhosis of the liver; need for therapies that may obscure the results of treatment and/or of the study; malignancy (except basal cell carcinoma) and/or chemotherapy within 1 year prior to screening; malignancy more than 1 year prior to screening must have been local and

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without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications; 9. Participation in another clinical trial within 30 days of the screening visit; 10. Anticipated inability to attend scheduled study visits; 11. Patients who in the judgment of the Investigator may be unreliable or uncooperative with the evaluation procedure outlined in this protocol; 12. Patients with a history of prior pharmacogenomic testing; 13. Any change in psychotropic medication (including change in dosage) between screening and randomization; 14. Patients receiving ECT, DBS, or TMS treatment(should a subject receive any of these treatments they must be discontinued from the study); 15. Patients who self-report to be pregnant or lactating; 16. Patients with a history of gastric bypass surgery.
Investigational Product: Antidepressant Pharmacogenomic Algorithm (GeneSight Psychotropic). This test covers 38 psychotropic medications (Appendix 1) and informs physicians on the likelihood for a patient to respond to one or more of the listed psychotropic medications.
Concomitant Medications **Allowed Concomitant medications:** All concomitant medications are allowed at the Investigator's discretion.

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Criteria for Evaluation:

Primary Efficacy Variable
17-item Hamilton Depression ($HAM\text{-}D_{17}$) rating scale

Secondary Efficacy Variables
Clinician 16-item Quick Inventory of Depression Symptomology ($QIDS\text{-}C_{16}$) rating scale;
Clinical Global Impression of Severity (CGI-S);
9-item Patient Health Questionnaire (PHQ-9);
Clinical Global Impression of Improvement (CGI-I);
Clinical Global Impression Efficacy Index (CGI-EI);
Generalized Anxiety Disorder 7-item (GAD-7);
Short Form (36) Health Survey (SF-36).

Safety and Tolerability Variables
AEs

Statistical and Analytical Plan:
Continuous variables (defined in section 12) will be summarized with standard descriptive statistics including means, standard deviations, medians, and ranges. Categorical variables (defined in section 12) will be summarized with frequencies and percentages. Relative risk of response and remission will be determined between groups. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted.

Diagnostics will be performed on the data to determine appropriate statistical modeling prior to all analyses. When standard modeling assumptions of normality, independence, and heterogeneity of variance are met for continuous outcomes, statistically significant differences between groups will be determined with repeated measures ANOVA models when modeling change in outcome scores across all time points or with 1-way independent ANOVA models when modeling change in outcome scores using week 8, week 12, and baseline scores. Generalized estimating equations (GEEs) will be applied when standard modeling assumptions are not met.

Comparisons between composite phenotype subgroups will be conducted with independent t-tests when standard modeling assumptions are met, or with z-tests using GEEs when assumptions are not met.

Time to response/remission will be plotted using Kaplan-Meier curved and statistically significant differences in time to response/remission will be tested using Cox proportional hazard models.

3.0 TABLE OF CONTENTS

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-HT	Serotonin
AE	adverse event
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-EI	Clinical Global Impression Efficacy Index
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7-item
HIPAA	Health Insurance Portability and Accountability Act
IEC	Independent Ethics Committee
IRB	Institutional Review Board
HAM-D_{17}	17-item Hamilton Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MINI	MINI International Neuropsychiatric Interview
NCI	National Cancer Institute
NE	Norepinephrine
PHQ-9	9-item Patient Health Questionnaire
QIDS-C_{16}	16-item Quick Inventory of Depression Symptomology
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic or tetracyclic antidepressant
US	United States

5.0 INTRODUCTION AND STUDY RATIONALE

5.1 Background on Major Depression

Major depressive disorder (MDD) is a highly prevalent (Hasin et al., 2005) mental disorder and a leading source of disease burden worldwide (Lopez et al., 2006). Epidemiological studies estimate 12-month and lifetime prevalence for MDD in the United States to be 5.3% and 13.2%, respectively (reviewed in Blanco et al., 2010). MDD is expected to be the second greatest cause of disability by 2020 and has been shown to cause significant morbidity, affecting people's ability to work, function in relationships, and engage in social activities. Moreover, MDD increases the risk of suicidal ideation, attempted suicide, and death by completed suicide.

Prospective longitudinal studies of patient samples show that MDD is a chronic illness, characterized by remitting and recurrent depressive episodes (Solomon et al., 1997; Mueller et al., 1999). A major depressive episode is characterized by a low mood or an inability to experience pleasure (anhedonia), or both, for more than 2 weeks, combined with several cognitive and vegetative symptoms and the occurrence of distress or impairment (reviewed in Rot et al., 2009). In the US, nearly 1 in 5 people will experience a major depressive episode at some point in their lives (reviewed in Rot et al., 2009).

Drugs currently available to treat depression fall into the categories of those that have their main effect by increasing norepinephrine (NE) (the tricyclic or tetracyclic antidepressants [TCAs]), those that increase serotonin (5-HT) (the selective serotonin reuptake inhibitors [SSRIs]), and those that increase both NE and 5-HT (the monoamine oxidase inhibitors [MAOIs] and the serotonin and norepinephrine reuptake inhibitors [SNRIs]). While all antidepressants achieve similar levels of efficacy, treatment failures are relatively high ranging from 30 to 60% (Simpson and DePaulo). Additionally, many of these compounds are associated with significant adverse events (AEs).

5.2 Background on GeneSight Psychotropic

The GeneSight Psychotropic product is a pharmacogenomic decision support tool that helps clinicians to make informed, evidence-based decisions about proper drug selection, based on the testing for clinically important genetic variants in multiple pharmacokinetic and pharmacodynamic genes that affect a patient's ability to tolerate or respond to medications. The GeneSight Psychotropic product contains the most commonly prescribed antidepressant and antipsychotic medications, including a full representation of the SSRI and SNRI drug classes. Tricyclic antidepressants, an MAOI, and typical and atypical antipsychotics are also represented.

The clinical utility of GeneSight Psychotropic has been evaluated in three previous prospective trials. Hall-Flavin et al reported the results of an open-label pilot study (n = 44) comparing GeneSight guided treatment to treatment as usual (TAU) without the benefit of pharmacogenomic testing (2012). The GeneSight guided arm demonstrated a 30.8%

improvement in HAM-D17 score by the end of the 8 week treatment period, compared to an 18.2% improvement in the TAU arm ($p = 0.04$). Results of the larger ($n = 165$) open-label trial (Hall-Flavin, et al 2013) mirrored these findings, demonstrating a 46.9% improvement in HAM-D17 score in the GeneSight arm, compared to a 29.9% improvement in the TAU arm ($p < 0.0001$). The third trial used a randomized, double-blind trial design ($n = 51$). Due to the small sample size, the trial was underpowered to detect a significant difference in improvement between the two arms (TAU and GeneSight). However, effect sizes of improvement reflected those seen in previous trials. The GeneSight group experienced a 30.8% improvement in HAM-D17, compared to 20.7% in TAU. Odds ratios for response were calculated, showing that GeneSight-guided subjects had a 2.14 times greater likelihood of response compared to TAU subjects, which was similar to the 4.67 (smaller trial) and 2.06 (larger trial) odds ratios calculated for the other two studies.

5.3 Study Rationale

Previous studies utilizing an open-label design have shown significant improvement in patient outcomes following use of the GeneSight test. However, although effect sizes were similar to those seen in the open-label studies, a small ($n = 51$) blinded, randomized controlled trial did not detect a statistically significant outcome. Therefore, the primary rationale for this trial is to replicate previous findings of improvement in clinical outcomes in subjects treated with the benefit of GeneSight testing utilizing a double-blind, randomized control trial (RCT) design.

It is expected that results from this trial will be used to inform guidelines for the use of pharmacogenomic testing for the treatment of major depressive disorder. Results may also be shared with regulatory bodies in the United States and abroad.

5.4 Known and Potential Benefits and Risk

There is a potential risk that a patient's protected health information be identified despite all the measures taken to protect such information

A potential benefit of the study consists of patients understanding their gene-drug interactions by receiving the GeneSight Psychotropic test.

6.0 OBJECTIVES

6.1 Primary Objective

The primary objective of this study is to evaluate the impact of GeneSight Psychotropic on response to psychotropic treatment as judged by the mean change in the 17-item Hamilton Depression ($HAM\text{-}D_{17}$) score from baseline to end of Week 8 of the study.

6.2 Secondary Objectives

The secondary objectives of this study are to evaluate the:

1. Mean change in the 16-item Quick Inventory of Depression Symptomology ($QIDS\text{-}C_{16}$) scale or the 9-item Patient Health Questionnaire (PHQ-9) from baseline to end of Week 8 of the study;
2. Mean change in $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, PHQ-9, or Clinical Global Impression of Severity (CGI-S) scale from baseline to end of Week 12 of the study;
3. Percentage of responders at Week 8 in each treatment group on the $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, or PHQ-9; for each rating scale, a responder is defined as a participant with 50% change from baseline in total scale score;
4. Percentage of responders at Week 12 (defined as above) in each treatment group on the $HAM\text{-}D_{17}$, $QIDS\text{-}C_{16}$, PHQ-9, CGI-S (defined as a change in category of severity of at least 1 point), Clinical Global Impression of Improvement (CGI-I; defined as a score from 1 to 3), or Clinical Global Impression of Efficacy (CGI-EI; defined as scores of 01, 02, 05, or 06);
5. Percentage of remitters at Week 12 defined as $HAM\text{-}D_{17} \leq 7$, $QIDS\text{-}C_{16} \leq 5$, PHQ-9 <5, or CGI-S ≤1 in each treatment group;
6. Percentage of remitters at Week 8 defined as $HAM\text{-}D_{17} \leq 7$, $QIDS\text{-}C_{16} \leq 5$, or PHQ-9 <5 in each treatment group;
7. Time to response/remission of depressive symptoms over 8 and 12 weeks:
8. Mean change in symptoms, percent response and percent remission from baseline to week 24 and from week 12 to week 24 across all scales in each treatment group.

6.3 Exploratory Objectives

The exploratory objectives of this study are to evaluate:

1. The mean change in Generalized Anxiety Disorder 7-item (GAD-7) scale from baseline to week 8 and week 12, and from week 12 to week 24 in each treatment group.

7.0 INVESTIGATIONAL PLAN

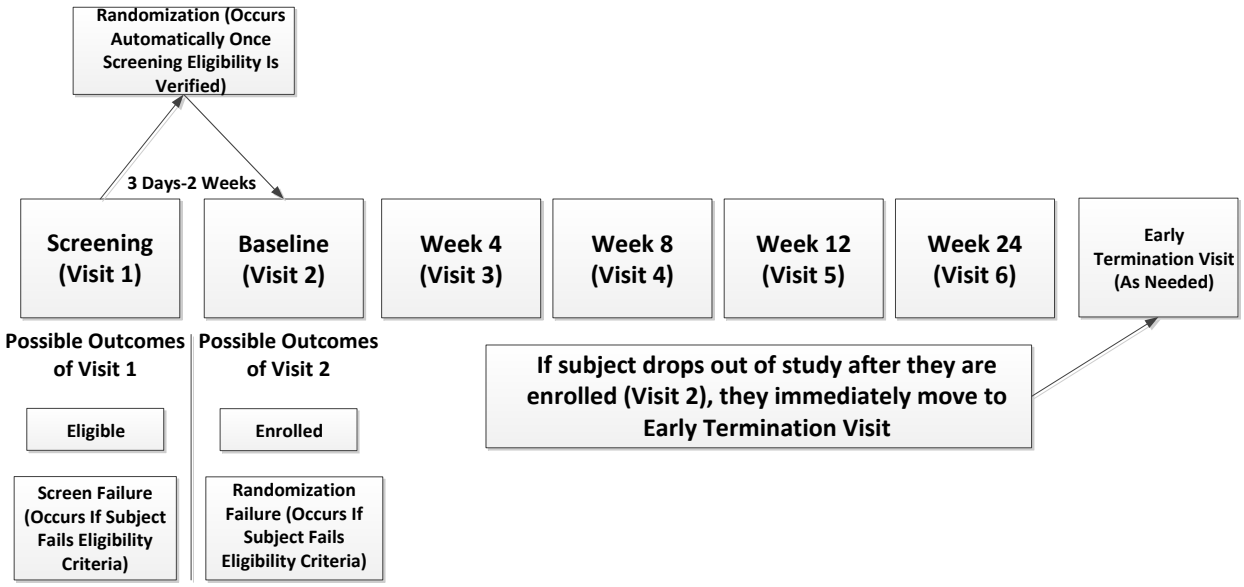
7.1 Overall Study Design and Plan

This protocol describes a 2-part study. The first part will be a randomized, multicenter, double-blind (raters and participants), 12-week, controlled study in parallel balanced groups of depressed patients. The study will evaluate the impact of GeneSight Psychotropic on response to psychotropic treatments listed in Appendix 1 of this protocol. Patients enrolled in this study will be required to have Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of MDD, a total QIDS-C_{16} score ≥11, a total QIDS-SR_{16} score ≥11, and an inadequate response within the current episode to one or more psychotropic treatments. For the purpose of this protocol, inadequate response is defined as lack of efficacy after at least 6 weeks of treatment or discontinuation of a psychotropic treatment due to AEs or intolerability. Only patients treated for their MDD with at least one of the psychotropic medications listed in Appendix 1 will be enrolled in the study.

Upon completion of the double-blind part of the study, participants will continue in a 12-week open-label extension of the study to evaluate the long-term impact of the use of GeneSight Psychotropic.

A Subject Visit Timeline is provided in the following Figure 1.

7.1.1 Figure 1: Subject Visit Timeline



7.1.2 Screening Procedures and Period

Screening procedures will include GeneSight Psychotropic genotyping (buccal swab). After signing an informed consent form (ICF), patients will be evaluated for inclusion in the study not

more than 2 weeks, and preferably 3 days prior to enrollment (results of the buccal swab will be available within 3 days).

Screening evaluations will include:

- Demographics
- Medical history
- Medication history and response including previous and current psychotropic treatment
- Physical examination;
- Vital signs, height, weight
- Psychiatric assessments including:
  - Mini International Neuropsychiatric Interview (by treating clinician or qualified delegated personal)
  - DSM-IV-TR criteria for Major Depressive Disorder (by treating clinician or qualified delegated personal)
  - QIDS-C_{16} (to be performed by the blinded Site- Rater only)
  - QIDS-SR_{16}
- Urine drug screen
- Urinalysis
- Laboratory blood test (to exclude hepatic insufficiency)
- Buccal sample
- Pharmacogenomic blood sample
- Collection of AEs

Patients' psychotropic medication should not be modified (in terms of type and dosage) during the screening period, except for treatment with benzodiazepines.

7.1.3 Randomization and Inclusion in the Study

Upon completion of the screening procedures, patients will be evaluated for eligibility against the inclusion/exclusion criteria. Patients who meet all the inclusion/exclusion criteria will be enrolled in the study and randomized on a 1:1 basis to one of two groups: treatment as usual or to treatment decision utilizing GeneSight Psychotropic. Randomization occurs before the Baseline visit to ensure that the GeneSight report is available at the Baseline visit, if applicable.

Upon inclusion in the study, investigators will be given the results of the GeneSight Psychotropic test for the participants randomized to the treatment decision utilizing GeneSight Psychotropic group. Investigators will use the report to support their treatment decision based on this information. However, raters and participants will be blinded. Sites should use the same Rater for the QIDS-C_{16} throughout the trial. Each site should have a qualified back-up Rater in the event they must conduct ratings in the absence of the primary rater.

Upon inclusion into the study, participants will be evaluated in the following manner (in chronological order):

- HAM-D_{17} (administered using a centralized phone-based rater system).
- QIDS-C_{16} (onsite blinded rater administrated),
- PHQ-9, SF-36 and GAD-7 (patient-rated using a paper-based or electronic system),
- CGI-S (administered by the treating clinician only),
- Medication reconciliation (including medication switching and augmentation).

7.1.4 Double-Blind Treatment Period

Throughout the 12-week double-blind treatment period, participants will be followed up (in-clinic visit) for efficacy, tolerability, and safety at the end (± 3 days) of Weeks 4, 8, and 12.

During the in-clinic visits, participants will be evaluated with HAM-D_{17}, QIDS-C_{16}, PHQ-9, and GAD-7 in the same manner utilized at the baseline visit. At the end-of Week 12 visit, participants will also be evaluated with CGI-S, CGI-I, SF-36, and CGI-EI. All assessments will be administered by the site with the exception of the HAM-D_{17}, which will be administered by a central rater.

7.1.5 12-Week Open-Label Extension

Following completion of the double-blind period, participants will continue participation in the study for an additional 12 weeks to evaluate the longer term impact of GeneSight Psychotropic. All participants will be given the results of their GeneSight Psychotropic test and will therefore be unblinded and treating physicians can utilize GeneSight Psychotropic for treatment decision support of all participants starting at the 12 week visit after all 12 week assessments have been completed.

Those who enroll in this additional follow-up phase of the study will be followed up (in-clinic visit) at the end (± 2 weeks) of Week 24, and evaluated with HAM-D_{17}, QIDS-C_{16}, PHQ-9, GAD-7, CGI-S, CGI-I, CGI-EI, and SF-36.

7.1.6 Early Termination Visit

If early termination occurs after Visit 2, the subject should attend an in-clinic visit as soon as possible to complete early termination procedures that will consist of all procedures scheduled for Week 24, namely: HAM-D_{17}, QIDS-C_{16}, PHQ-9, GAD-7, CGI-S, CGI-I, SF-36, and CGI-EI.

7.1.7 Unscheduled Visits

Investigators are able to bring Subjects to the site for clinical management of their depression at any time. There will be no "Unscheduled Visit" in the CRF but source documentation in the patient chart should be recorded of the visit.

7.2 Study Activities

7.2.1 Schedule of Assessments

The schedule of assessments is provided in the following Table 2

Table 2. Study Flow Chart – Time and Events Schedule

ASSESSMENTS	Screening Visit 1	Baseline/ Randomization Visit 2	Double-Blind Treatment In-Clinic End (±3 Days) of: Week 4 Visit 3	Week 8 Visit 4	Week 12 Visit 5	Open-Label Follow-Up In-Clinic Visits End (±2 weeks) of: Week 24 Visit 6
Informed Consent	X					
Demographics	X					
Clinician Demographics	X					
Treating Clinician	X	X	X	X	X	X
GeneSight Psychotropic Buccal Sample	X					
Medical History	X					
Urine Drug Screen and urinalysis	X					
Psychotropic Medication History previous and current including response questionnaire	X					
Current psychotropic medication and psychotropic medication trials since last visit		X	X	X	X	X
Other (within 1 month) Previous Medications	X					
Other Concomitant Medications	X	X	X	X	X	X
Physical Examination	X				X	X
Vital Signs	X				X	X
MINI for Axis I (by Treating Clinician or qualified delegated personal)*	X					
DSM-IV-TR (by treating clinician or qualified delegated personal)	X	X				
Phlebotomy for Laboratory Panel & biobank sample	X					
Inclusion/Exclusion Criteria	X	X				
Randomization		X				
QIDS-C_{16} (Blinded Site Rater)	X	X	X	X	X	X
QIDS-SR_{16} (Patient Reported)	X					
HAM-D_{17} (Central Rater)		X	X	X	X	X
CGI-S (Treating Clinician)		X			X	X
PHQ-9 (Patient Reported)		X	X	X	X	X
GAD-7 (Patient Reported)		X	X	X	X	X
CGI-I (Treating Clinician)					X	X
CGI-EI (Treating Clinician)					X	X
Adverse Events (AEs)	X	X	X	X	X	X
SF-36 (Patient Reported)		X			X	X
Dose Changes		X	X	X	X	X
Switching		X	X	X	X	X
Augmentation		X	X	X	X	X
Discontinuation		X	X	X	X	X
Compliance			X	X	X	X

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders IV, Fourth Edition, Text Revision; Vital signs: sitting blood pressure and pulse rate, height, weight; QIDS-C_{16}=Quick Inventory of Depression Symptomology; HAM-D_{17}=Hamilton Depression scale; CGI-S=Clinical Global Impression of Severity; PHQ-9=Patient Health Questionnaire; CGI-I=Clinical Global Impression of Improvement; CGI-EI=Clinical Global Impression Efficacy Index; Short Form (36) Health Survey (SF-36)
1. All Subjects will have a buccal swab collected at the Screening Visit. All Subjects will receive the results report at Study Week 12.
* All MINI for Axis I assessments must be verified by Treating Clinician if assessed by Site Rater.

7.2.2 Screening Visit Procedures (Visit 1)

Patients should be screened for inclusion/exclusion criteria within 2 weeks prior to inclusion, and preferably within 3 days of enrollment.

Written informed consent will be obtained prior to performing any study procedures. In addition, the Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per applicable regulations (i.e., Health Insurance Portability and Accountability Act [HIPAA] in the US) from each patient. The ICF must contain language relating to HIPAA.

The following will be performed at the screening visit:

- Obtain informed consent
- Perform buccal swab for GeneSight Psychotropic gene test
- Record demographics
- Record clinician demographics
- Review and record medical history
- Review and record psychiatric history
- Review and record current psychotropic medications
- Review and record past psychotropic medications including response
- Review and record past (within 4 weeks) other concomitant medication (other than psychotropic medication)
- Review and record other current medications (other than psychotropic medications)
- Perform physical examination
- Obtain vital signs, body weight and height
- Perform psychiatric assessments including:
  - Mini International Neuropsychiatric Interview (MINI) for Axis 1 (by treating clinician or qualified delegated personal)
  - DSM-IV-TR criteria for MDD (by treating clinician or qualified delegated personal)
  - QIDS-C_{16} (Blinded Site Rater)
  - QIDS-SR_{16} (Patient Reported)
- Collect AEs
- Collect blood for safety laboratories (hematology, and serum biochemistry)
- Collect blood for de-identified pharmacogenomic research biobank

- Collect urine sample for drug screen
- Evaluate patient against the inclusion/exclusion criteria

7.2.3 Baseline/Randomization Visit (Visit 2)

Following screening procedures, patients who meet the inclusion/exclusion criteria will be enrolled and randomized 1:1 to "treatment as usual" or "treatment guided by GeneSight Psychotropic." Randomization occurs before the Baseline visit to ensure that the GeneSight report is available at the Baseline visit, if applicable.

Upon study entry (baseline/randomization visit), and prior to any change or adjustment in antidepressant medication, participants will be evaluated on the following:

- Inclusion/Exclusion criteria
- DSM-IV-TR criteria for MDD (by treating clinician or qualified delegated personal)
- The following psychiatric evaluations:
  - QIDS-C_{16} (Blinded Site Rater)
  - HAM-D_{17} (Central Rater)
  - CGI-S (Treating Clinician)
  - PHQ-9 (Patient Reported)
  - GAD-7 (Patient Reported)
  - SF-36 (Patient Reported)

In addition the following will be recorded:

- Current psychotropic medication
- Current concomitant medication (other than psychotropic)
- Medication adjustments including:
  - Dose changes
  - AEs
  - Switching
  - Augmentation
  - Discontinuation

7.2.4 End of Week 4 Visit (Visit 3)

Participants will return to the study center at the End of Week 4 ± 3 days of the double-blind phase of the study (Visit 3) and will be evaluated on the following:

- Psychiatric evaluations:
  - QIDS-C_{16} (Blinded Site Rater)
  - HAM-D_{17} (Central Rater)

  - PHQ-9 (Patient Reported)
  - GAD-7 (Patient Reported)
- Current psychotropic medication
- Current concomitant medication (other than psychotropic)
- Medication adjustments including:
  - Dose changes
  - AEs
  - Switching
  - Augmentation
  - Discontinuation
- Compliance

7.2.5 End of Week 8 Visit (Visit 4)

Participants will return to the study center at the End of Week 8 ± 3 days of the double-blind phase of the study (Visit 4) and will be evaluated on the following:

- Psychiatric evaluations:
  - QIDS-C_{16} (Blinded Site Rater)
  - HAM-D_{17} (Central Rater)
  - PHQ-9 (Patient Reported)
  - GAD-7 (Patient Reported)
- Current psychotropic medication
- Current concomitant medication (other than psychotropic)
- Medication adjustments including:
  - Dose changes
  - AEs
  - Switching
  - Augmentation
  - Discontinuation
- Compliance

7.2.6 End of Week 12 Visit (Visit 5)

Participants will return to the study center at the End of Week 12 ± 3 days of the double-blind phase of the study (Visit 5) and will be evaluated on the following:

- Psychiatric evaluations:
  - QIDS-C_{16} (Blinded Site Rater)
  - HAM-D_{17} (Central Rater)
  - CGI-S (Treating Clinician)
  - PHQ-9 (Patient Reported)

  - GAD-7 (Patient Reported)
  - CGI-I (Treating Clinician)
  - CGI-EI (Treating Clinician)
  - SF-36 (Patient Reported)
- Current psychotropic medication
- Current concomitant medication (other than psychotropic)
- Perform physical examination
- Obtain vital signs, body weight and height
- Compliance

Following completion of the double-blind period, participants will continue participation in the study for an additional 12 weeks to evaluate the longer term impact of GeneSight Psychotropic. At the 12 week visit following completion of all assessments above, all participants will be given the results of their GeneSight Psychotropic test and will therefore be unblinded and treating physicians can utilize GeneSight Psychotropic for treatment decision support of all participants.

Following unblinding the following will be evaluated:

- Medication adjustments including:
  - Dose changes
  - AEs
  - Switching
  - Augmentation
  - Discontinuation

This phase of the study will have an in-clinic visit at the end (± 2 weeks) of Week 24, and evaluated on HAM-D_{17}, QIDS-C_{16}, PHQ-9, CGI-S, CGI-I, CGI-EI, and SF-36.

7.2.7 End of Week 24 Visit (Visit 6)

Participants will return to the study center at the End of Week 24 ± 2 weeks of the open-label extension phase of the study (Visit 6) and will be evaluated on the following:

- Psychiatric evaluations:
  - QIDS-C_{16} (Blinded Site Rater)
  - HAM-D_{17} (Central Rater)
  - CGI-S (Treating Clinician)
  - PHQ-9 (Patient Reported)
  - GAD-7 (Patient Reported)
  - CGI-I (Treating Clinician)
  - CGI-EI (Treating Clinician)
  - SF-36 (Patient Reported)

- Current psychotropic medication
- Current concomitant medication (other than psychotropic)
- Perform physical examination
- Obtain vital signs, body weight and height
- Medication adjustments including:
    - Dose changes
    - AEs
    - Switching
    - Augmentation
    - Discontinuation
- Compliance

8.0 SELECTION AND WITHDRAWAL OF PATIENTS

8.1 Study Population

At least 1,400 males and females, outpatients, ≥18 years of age, diagnosed with MDD having had an inadequate response to at least one psychotropic medication within the current depressive episode will be enrolled in the study. Inadequate response is defined as lack of efficacy after 6 weeks of psychotropic treatment or discontinuation of psychotropic treatment due to AEs or intolerability.

Participants will be randomized to either "treatment as usual" or "treatment guided by GeneSight Psychotropic" using a 1:1 allocation. Under the assumption of a 16.7% rate of premature discontinuation by Week 8 (primary endpoint), it is anticipated that approximately 1,200 fully evaluable patients will be available for primary endpoint analyses, roughly 600 in the "treatment as usual" and 600 in the "treatment guided by GeneSight Psychotropic" (see Section 12 for justification of patient numbers and power calculation).

8.2 Patient Inclusion Criteria

To be eligible, all patients must:

1. Be able to understand the requirements of the study and provide written informed consent to participate in this study; a signed and dated ICF will be obtained from each patient before participation in the study;
2. Have provided written authorization for the use and disclosure of their protected health information;
3. Be ≥18 years of age;
4. Suffer from a Major Depressive Episode meeting DSM-IV-TR criteria;
5. Have had an inadequate response within the current episode to at least 1 psychotropic treatment (listed in Appendix 1 of this protocol). Inadequate response is defined as inadequate efficacy after 6 weeks of a psychotropic treatment or discontinuation of a psychotropic treatment due to AEs or intolerability;
6. Have a total baseline score on the QIDS-C_{16} and QIDS-SR_{16} rating scale ≥11;
7. Agree to abide by the study protocol and its restrictions and be able to complete all aspects of the study, including all visits and tests.

8.3 Exclusion Criteria

Any of the following conditions are cause for exclusion from the study:

1. Patients posing a serious suicidal risk and/or in need of immediate hospitalization as judged by the investigator;
2. Patients with a diagnosis of Bipolar I or II disorder;

3. Patients with a current Axis I diagnosis of:
   - Delirium
   - Dementia
   - Amnestic and other cognitive disorder
   - Schizophrenia or other psychotic disorder;
4. Patients having experienced hallucinations, delusions, or any psychotic symptomatology within the current depressive episode or during prior depressive episodes;
5. Patient is currently in an inpatient facility;
6. Patients with a history of hypothyroidism unless taking a stable dose of thyroid medication and asymptomatic or euthyroid for 6 months;
7. Patients who meet DSM-IV-TR criteria for any significant current substance use disorder;
8. Patients with significant unstable medical condition; life threatening disease; hepatic insufficiency (3X ULN for AST and/or ALT); liver transplant recipient; cirrhosis of the liver; need for therapies that may obscure the results of treatment and/or of the study; malignancy (except basal cell carcinoma) and/or chemotherapy within 1 year prior to screening; malignancy more than 1 year prior to screening must have been local and without metastasis and/or recurrence, and if treated with chemotherapy, without nervous system complications;
9. Participation in another clinical trial within 30 days of the screening visit;
10. Anticipated inability to attend scheduled study visits;
11. Patients who in the judgment of the Investigator may be unreliable or uncooperative with the evaluation procedure outlined in this protocol;
12. Patients with a history of prior pharmacogenomic testing;
13. Any change in psychotropic medication (including change in dosage) between screening and randomization;
14. Patients receiving ECT, DBS or TMS treatment (should a Subject receive any of these treatments they must be discontinued from the study);
15. Patients who self- report to be pregnant or lactating;
16. Patients with a history of gastric bypass surgery.

8.4 Patient Discontinuation Criteria

Patients may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any patient who requests to be withdrawn. A patient's participation in the study may be discontinued at any time at the discretion of the Investigator and/or Sponsor, in accordance with his/her best professional judgment. However, it is encouraged that the Investigator contact the Sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a patient from the study.

The Sponsor must be notified of all patient withdrawals as soon as possible. The Sponsor reserves the right to discontinue the study at any time for medical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or Sponsor may withdraw a patient from the study include, but are not limited to, the following:

1. Patient wishes to withdraw;
2. Investigator judges that for any reason continuation of the study is inappropriate for the patient.

The reason for any early discontinuation will be stated on the case report form (CRF) as one of the following:

- AE
- Termination of study by the Sponsor
- Protocol violation: (specify)
- Lost to follow-up
- Withdrawal of consent
- Lack of efficacy
- Other: (specify)

The Investigator should immediately notify the designated medical monitor when a patient is discontinued.

If early termination (ET) occurs, the patient should attend a visit as soon as possible to complete all procedures scheduled for Visit 6 (End of Week 24/ End of Open-Label Follow-Up visit). If a patient fails to return for scheduled visits, a documented effort must be made to determine the reason. If the patient cannot be reached by telephone after two attempts, a certified letter should be sent to the patient requesting contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and the IRB/ IEC. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per applicable regulations (i.e., HIPAA in the US) from each patient. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient and the patient will be removed from the study.

8.5 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for any reason at any time.

8.6 Rescheduling a Screening of Study Visit

The Investigator should contact the medical monitor if the rescheduled visit will extend either the screening beyond 2 weeks or a treatment period visit beyond the allowed window.

8.7 Patient Identification

Each patient will be assigned a unique patient identifier. At the Screening Visit, each patient will be assigned a screening number upon signing the ICF. All screening numbers will be assigned by the site in strict numerical sequence and no numbers will be skipped or omitted (e.g., each patient will be assigned to the lowest screening number available). Upon enrollment (baseline Visit), all qualified patients will be assigned a patient number. Patient numbers will be assigned in a strict numerical sequence and no numbers will be skipped or omitted. This unique identifier will be on all case report form (CRF) pages.

9.0 TREATMENT OF PATIENTS

9.1 Treatments Administered

During the study, patients will continue treatment with psychotropic medication as judged best in terms of type of medication(s), dose, and dose regimen by the treating physician.

Patients will be required to not have any change in psychotropic medication during the screening period prior to randomization.

After completing screening procedures, patients will be randomized to "treatment as usual" or "treatment guided by GeneSight Psychotropic" for 12 weeks, followed by a 12-week open-label extension in which all patients may receive treatment guided by GeneSight Psychotropic.

Upon randomization, the treating physician will receive the results of the GeneSight Psychotropic test for patients randomized to "treatment guided by GeneSight Psychotropic." Guided by these results, the treating physician may decide to modify a participant's psychotropic medication, in terms of type of medication, dose, dose regimen or number of medications.

9.2 Blinding

This study will be conducted under double-blind conditions so that neither the patient nor study staff members involved in patient assessments will know whether the patient is receiving "treatment as usual" or "treatment guided by GeneSight Psychotropic."

At randomization, the treating physician will receive the results of the GeneSight Psychotropic test for patients allocated to "treatment guided by GeneSight Psychotropic" and may decide to change the participant's treatment based on the results of the test. The treating physician will therefore not be blind.

9.3 Treatment Compliance with Prescribed Psychotropic Medication

Site personnel will assess treatment compliance at each visit. Noncompliance will be defined as taking less than 80% or more than 120% of psychotropic medication prescribed by the treating physician during any outpatient evaluation period (visit to visit). Assessment of compliance will be done as per medical judgment; no pill counting or other formal compliance measure will be used to assess for compliance other than the general guidelines outlined above.

9.4 Description of the GeneSight Psychotropic Test

A buccal swab of the patient's cheek is taken by the clinician and mailed to the lab in a secure envelope labeled with a unique identifier to ensure accuracy and validity. Once received, the GeneSight Psychotropic lab analyzes the sample and determines the patient's genotypes and phenotypes for each of the tested genes. These phenotypes will provide a clear picture of how

functional each gene is with respect to drug metabolism (for CYP450 genes) or drug response (for neurotransmitter transporter and receptor genes).
After laboratory testing is completed and phenotypes are assigned, GeneSight Psychotropic technology integrates the genetic data with the pharmacology for each medication on the GeneSight Psychotropic panels, incorporating data gleaned from FDA-approved labels and published literature.

Within three days of sample receipt at the laboratory, results are returned to clinicians in the form of an interpretive report that categorizes medications into three independent bins titled "Use as Directed" or the Green Bin, "Use With Caution" or the Yellow Bin, and "Use with Increased Caution And With More Frequent Monitoring" or the Red Bin. Medications in the Green Bin are likely to be unaffected by any genetic polymorphisms the tested individual may possess. Medications in the Yellow Bin are at risk for a gene-drug interaction that may necessitate alternative dosing or medication selection. Medications in the Red Bin are at high risk for a gene-drug interaction that may necessitate alternative dosing or medication selection.

9.5 Concomitant Medications

During the study, patients will be allowed to use concomitant medications at the Investigators' discretion. The dose and dose regimen of concomitant medications should be recorded on the CRF.

10.0 ASSESSMENTS AND PROCEDURES

10.1 Endpoints

During the study participants will be evaluated on the following endpoints:

Primary Efficacy Variable
17-item Hamilton Depression ($HAM\text{-}D_{17}$) rating scale.

Secondary Efficacy Variables
Clinician 16-item Quick Inventory of Depression Symptomology ($QIDS\text{-}C_{16}$) rating scale (Blinded Site Rater);
Clinical Global Impression of Severity (CGI-S) (Treating Clinician);
9-item Patient Health Questionnaire (PHQ-9) (Patient Reported);
Clinical Global Impression of Improvement (CGI-I) (Treating Clinician);
Clinical Global Impression Efficacy Index (CGI-EI) (Treating Clinician);
Short Form (36) Health Survey (SF-36) (Patient Reported).

Exploratory Variables
Generalized Anxiety Disorder 7-item (GAD-7) (Patient Reported)

10.2 Descriptions of Assessments

10.2.1 Screening Only Assessments

10.2.1.1 Demographics

Patients' age, gender, race, smoking frequency, education, and annual income will be recorded on the CRF.

10.2.1.2 Clinician Demographics

Clinician's age, gender, and education will be recorded on the CRF at Screening and the treating clinician will be captured at each visit. The initial clinician should be the treating clinician throughout the duration of the study at each visit unless of an emergency or vacation.

10.2.1.3 Rater Demographics

Rater's age, gender, and education will be recorded on the CRF at Screening and the rater will be captured at each visit. The rater should be the rater throughout the duration of the study at each visit unless of an emergency or vacation.

10.2.1.4 Medical History

The complete medical history will be conducted with a review of all body systems and the patient's past and concurrent illnesses, drug use (including urine drug test), alcohol use, drug allergies, and family medical history.

Particular attention will be paid to past psychiatric history, in particular age at first depressive episode, frequency of relapses, response to previous treatments, and other concomitant psychiatric disorders and their treatment.

10.2.1.5 Physical Examination

At Screening, a complete physical examination, including an evaluation of general appearance, head, ears, eyes, nose, and throat, neurological, heart/cardiovascular, lungs, abdomen, gastrointestinal, endocrine, extremities, musculoskeletal, lymphatic, and skin systems will be performed by the Investigator.

In addition, height (without shoes) and body weight will be recorded.

10.2.1.6 Vital Signs

Vital signs, including temperature, heart rate, sitting systolic and diastolic arterial blood pressure and radial artery pulse rate will be measured at screening. Vital signs should be measured with the patient seated and rested (at least 5 minutes).

10.2.1.7 GeneSight Psychotropic Test

The following genes and polymorphisms are detected by the GeneSight Psychotropic assay:

- Cytochrome P450 2D6 (*CYP2D6*): *1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, gene duplication
- Cytochrome P450 2C19 (*CYP2C19*): *1, *2, *3, *4, *5, *6, *7, *8, *17
- Cytochrome P450 2C9 (*CYP2C9*): *1, *2, *3, *4, *5, *6
- Cytochrome P450 1A2 (*CYP1A2*): 3497G>A, 2499A>T, 558C>A, 5166G>A, -2467T>delT, 5347C>T, 2473G>A, 5090C>T, -163C>A, 125C>G, 3533G>A, 2116G>A, -739T>G, -729C>T, -3860G>A

- Cytochrome P450 3A4 (*CYP3A4*): *1, *13, *15A, *22
- Cytochrome P450 2B6 (*CYP2B6*): *1, *4, *6, *9
- Serotonin transporter (*SLC6A4*): 44 bp promoter indel (5-HTTLPR)
- Serotonin 2A receptor (*HTR2A*): rs7997012 (-1438G>A)

AssureRx's laboratory isolates DNA by utilizing MagMAX magnetic bead-based technology on MagMAX Magnetic Particle Processor (Life Technologies). The GeneSight test is analyzed by QuantStudio 12K Flex Real-Time PCR System and comprises of two distinct assays –

a) **OpenArray Assay** – The TaqMan OpenArray Genotyping chip is a 63-mm x 19-mm mid-density reaction plate containing 3072 reaction through-holes with each hole preloaded with a dried down TaqMan assay.
b) **2D6 Copy Number Assay** – TaqMan copy number assay is a real-time PCR reaction designed to detect and measure variation in the copy number of CYP2D6 gene and a reference gene (human RNase P H1 RNA gene).

The QuantStudio™ 12K Flex Real-Time PCR System uses TaqMan R 5'-nuclease assay chemistry to perform the genotyping of single nucleotide polymorphisms (SNPs) of CYP2D6, CYP2C9, CYP2C19, CYP1A2, CYP3A4, CYP2B6 (516G>T) and HTR2A. Each predesigned TaqMan® SNP Genotyping Assay includes two allele-specific TaqMan® MGB probes containing distinct fluorescent dyes and a PCR primer pair to detect specific SNP targets. These TaqMan® probe and primer sets (assays) are spotted on to a high density chip to provide unmatched specificity for the allele of interest and ability to process samples in a high throughput manner. CYP2D6 copy number is determined by running TaqMan® Copy Number Assays simultaneously with a TaqMan® Copy Number Reference Assay (for example, the human RNase P H1 RNA gene) in a duplex real-time polymerase chain reaction (PCR). The number of copies of the target sequence in each test sample is determined by relative quantitation (RQ) using the comparative CT method (also known as deltadeltaCT, where CT is cycle threshold and is defined as the number of cycles required for the fluorescent signal to exceed background level). This method measures the CT difference (ΔCT) between target and reference

sequences, and then compares the ΔCT values of test samples to a calibrator sample(s) known to have two copies of the target sequence.

CYP2B6 (785A>G) genotype is determined using PCR-RFLP assay by amplifying the relevant genomic regions with polymerase chain reaction (PCR) and subsequent restriction digest of PCR products and detection of DNA fragments using capillary electrophoresis on QIAxcel (QIAGEN).

Alternatively, CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP1A2, CYP2B6 and HTR2A genotypes are determined using multiplex xTAG® assays (Luminex Molecular Diagnostics). Luminex xTAG® assays incorporate multiplex Polymerase Chain Reaction (PCR) and multiplex Allele Specific Primer Extension (ASPE) with Luminex's Universal Tag sorting system on the Luminex® 100/200™ xMAP®platform. Target gene regions are amplified in a multiplexed PCR reaction(s) that are then treated with Exonuclease 1 and shrimp alkaline phosphatase to remove excess nucleotides and primers. Treated PCR products are extended using allele-specific primers that contain xTAG® universal tag sequence at the 5' end. The 5' universal tag sequences are then hybridized to the complementary anti-tag sequences coupled to the color-coded microspheres that are read on a Luminex xMAP instrument and results are analyzed using data analysis software.

Assurex detects specific mutations with in SLC6A4 by amplifying the relevant genomic regions with polymerase chain reaction (PCR) and detecting PCR fragments with gel electrophoresis.

10.2.1.8 Laboratory Tests

Clinical laboratory tests will be performed at screening only.

Blood samples will be collected for the following clinical laboratory tests:

- **Hematology:** hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.
- **Serum chemistry:** calcium, sodium, chloride, potassium, blood urea nitrogen, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase (AST), alpha-fetoprotein (AFP), alanine aminotransferase (ALT), creatinine, uric acid, phosphorous, total protein, albumin, and globulin.

An additional aliquot of blood will be collected and stored for future pharmacogenomic research at Assurex Health, Inc. The sample will be deidentified, but matched to clinical data.

Urine samples will be collected for drug screening and the following tests: glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, leukocytes, and, if necessary, microscopic examination.

Any abnormal laboratory value must be assessed, with written notation, by the Investigator. If an abnormal laboratory value is clinically significant, the Investigator must immediately contact the medical monitor to discuss the patient's continued eligibility in the trial.

Any information obtained at screening that appears to conflict with a patient's eligibility for participation must be addressed by the Investigator in source documentation prior to randomization.

ACM Contact Information:
Company Name: ACM Medical Laboratory, Inc.
Parent Company Name: Unity Health System
Headquarters Address: 160 Elmgrove Park, Rochester NY, 14624
Headquarters Phone Number: 1-800-525-5227
Headquarters Fax Number: 585-247-7735

10.2.1.9 MINI for Axis I

The MINI was developed as a short and efficient diagnostic interview to be used in clinical as well as research settings (Sheehan et al., 1998). It follows DSM-IV and the ICD-10 criteria for psychiatric disorders, screening for 17 Axis I disorders, with brief suicidality and antisocial personality modules. The Axis I disorders included in the MINI were selected based upon the 12-month prevalence reported in the Epidemiologic Catchment Area Study (Regier et al., 1984) and the National Comorbidity Survey (Kessler et al., 1994). The MINI has been validated in the U.S. and Europe (reviewed in Jana et al., 2005). Administration time ranges from approximately 15-20 minutes for individuals with few positively endorsed symptoms to 20-30 minutes for individuals who meet criteria for current diagnoses.

10.2.1.10 Medication History

Previous medications and medications taken at screening, psychotropic or other, will be collected in the CRF.

For the psychotropic medications used to treat depression, the generic name of the medication, the doses used, start and end date, as well as response to treatment (efficacy and adverse events) will be recorded.

For other medications, the CRF will specify the generic name of the medication, the doses used, start and end date.

10.2.2 Efficacy Assessments

10.2.2.1 Primary Efficacy Endpoint: 17-Item Hamilton Depression Scale (HAM-D_{17}; Appendix 3)

The 17-item Hamilton Depression Rating Scale (HAM-D_{17}) is the primary efficacy endpoint for this study and assesses mood, feelings of guilt, insomnia, agitation or retardation, anxiety, weight loss and somatic symptoms. The 17-item questionnaire is administered by a qualified rater at Baseline and at End of Weeks, 4, 8, 12 and 24.

10.2.2.2 16-Item Quick Inventory of Depressive Symptomology (QIDS-C_{16}; Appendix 4)

The clinician-rated, 16-item Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) has been extensively evaluated in patients with major depressive disorder (MDD; Rush et al, 2003; Trivedi et al, 2004). The scale assesses the nine DSM-IV criteria symptom domains for major depression: sad mood, concentration, self-outlook, suicidal ideation, involvement, energy/fatigability, sleep disturbance (4 items: initial, middle, late insomnia, and hypersomnia), appetite/weight increase/decrease (4 items), and psychomotor agitation/retardation (2 items).

10.2.2.3 9-Item Patient Health Questionnaire (PHQ-9; Appendix 5)

The PHQ-9 consists of nine questions, rated 0–3 according to the increased frequency of difficulty experienced in each area covered. Scores, with a possible range of 0–27, are summed and can then be interpreted as follows: no depression (0), minimal (1–5), mild (6–9), moderate (10–14), moderately severe (15–19), or severe (>20) depression.

10.2.2.4 Clinical Global Impression (CGI; Appendix 6)

The Clinical Global Impression Scale (CGI) is a brief clinician-rated instrument that consists of three different global measures. 1. Severity of illness: overall assessment of the current severity of the patient's symptoms (CGI-S); 2. Global improvement: overall comparison of the patient's baseline condition with his current state (CGI-I); 3. Efficacy index: overall comparison of the patient's baseline condition to a ratio of current therapeutic benefit and severity of side effects (CGI-EI).

10.2.2.5 SF-36 Health Survey (SF-36; Appendix 7)

The SF-36 Health Survey (SF-36), which assesses functional health and well-being from a patient’s point of view, is an exploratory endpoint for this study. The 36-item questionnaire is a self-rated measure that will be administered at Baseline and at of the Week 12 and Week 24 visits.

10.2.2.6 Generalized Anxiety Disorder 7-item (GAD-7; Appendix 8)

The Generalized Anxiety Disorder 7-item (GAD-7) is a self-reported questionnaire for screening and measuring severity of generalized anxiety disorder. The GAD-7 questionnaire is an exploratory endpoint of this study and will be administered at Baseline, Week 4, Week 8, Week 12, and Week 24 visits.

11.0 SAFETY ASSESSMENT

The GeneSight Psychotropic is not a drug intervention, and this study is an evaluation of the impact of the results report on a patient's major depression.

Investigators should follow the FDA process for reporting untoward events to of marketed medications. INC will provide training on submission of MedWatch reports at the Investigator Meeting, and when a report is filed with the FDA a copy should be printed and kept in the Subjects' source documentation for review by the study sponsor, or representative.

The INC Medical Monitor should be contacted for questions related to inclusion of Study Subjects. Contact information for the Medical Monitor for this study is as follows:

Vikki Brown, MD FACOG
Senior Medical Director. INC Research
910-679-1573 (office)
910- 398-5910 (mobile)
910- 231-3681 (mobile back-up)
Email: vikki.brown@incresearch.com

Contact information for questions regarding GeneSight Psychotropic for this study is as follows:

Medical Information
Office Phone: 513-701-5036
Fax: 513-492-7946
Email: MedInfo@assurerxhealth.com

Definitions

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Any worsening of a preexisting condition (i.e., any clinically significant adverse change in frequency and/or intensity) which is temporally associated with the use of the investigational product, is also an adverse event.

Evaluating and Recording of Adverse Events

At each visit all adverse events that are observed, elicited by the Investigator, or reported by the subject, will be recorded in the appropriate section of the AE eCRF and evaluated by the Investigator.

Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study drug, action taken, and outcome.

Severity of AEs will be graded by the Investigator using the following criteria as guidelines:

1. Mild: Nuisance, barely noticeable.
2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
3. Severe: Symptoms significantly interfere with daily activities or sleep.

The relationship of the AE to the study drug should be specified by the Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with study drug.
2. Unlikely Related: The event has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.
3. Possibly Related: The event follows a reasonable temporal sequence from administration of study drug but which could also be explained by concurrent disease or other factors or medications
4. Probably Related: The event follows a reasonable temporal sequence from administration of study drug, unlikely to be attributed to concurrent disease or other factors or medications. A clinically reasonable response may be observed if the study drug is withdrawn or dose reduced.
5. Definitely Related: the event follows a reasonable temporal sequence from administration of study drug and is definitive pharmacologically; cannot to be attributed to concurrent disease or other factors or medications. A clinically reasonable response should be observed if the study drug is withdrawn or dose reduced.

If discernible at the time of completing an AE eCRF, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded on the AE eCRF. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE eCRF (clinically significant laboratory abnormalities are those that are identified as such by the Investigator and/or those that require intervention).

Investigators should follow the FDA process for reporting untoward events to of marketed medications by submitting a MedWatch for a Serious Adverse Event:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose (including overdose) that meets one or more of the following criteria:

- Is fatal, as a direct outcome of the AE
- Is life threatening

  This serious criterion applies if the subject, in the view of the Investigator, is at substantial risk of dying from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization

  This serious criterion applies if the reported AE necessitates an inpatient admission (in the US) or a minimum 24-hour inpatient hospitalization (outside US) or, if in the opinion of the Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure, a routinely scheduled treatment or a social admission is not an SAE.
- Results in permanent or significant disability/incapacity

  This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.
- Results in a congenital anomaly/birth defect

  This serious criterion applies if a subject exposed to the investigational product gives birth to a child with congenital anomaly or birth defect.

Important medical events that do not meet any of the criteria above may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.0 STATISTICS

Sample Size
The sample size required for this study was calculated using effect size estimates drawn from a previous study conducted by Hall-Flavin et al (2013, *Pharmacogenetics and Genomics*). Assuming an effect size of .30 favoring the treatment group, statistical power of 90%, and an alpha level of 0.05, a total of 1400 subjects are required to detect the same effect in this study. However, due to expected subject attrition (see below) and to support an interim analysis with adequate power, a total of 1200 subjects will be enrolled in the study.

Hall-Flavin et al experienced significant subject attrition during the course of their investigation. Post hoc analyses using ITT analyses, however, revealed little differences between the observed data and inputed data (e.g., LOCF and EM algorithm imputation). Therefore, to account for subject attrition in the current study, ITT with LOCF and EM algorithm imputation will be employed to account for missing data, assuming the data is missing completely at random.

Data Analysis
Descriptive Statistics Continuous variables will be summarized with standard descriptive statistics including means, standard deviations, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted.

Diagnostics Prior to formal statistical analyses, diagnostics will be conducted to determine appropriate statistical models. The independence assumption of ANOVA will be tested by examining the correlation between error terms for each dependent variable across levels of the indicator variable. To this end, the Durbin-Watson test statistic will be used to determine if the independence assumption was upheld. Values approaching 2.0 from the left or right were considered to be an indication of independence. The normality assumption will be tested by plotting residuals against the normal probability plot and by deriving the Shapiro-Wilk (S-W) test statistic. The dependent variable will formally be considered to be non-normally distributed if the p-value for the S-W test was < 0.05. Homogeneity of variance will be tested by employing the statistic derived by Brown and Forsythe. If the associated p-value for the test statistic is < 0.05, then the dependent variable will be assumed to exhibit non-constant variance. If a given dependent variable did not meet the above mentioned assumptions (e.g., clustering due to study site), generalized estimating equations (GEEs) will be employed to account for the lack of independence between outcomes using an autoregressive correlation structure and identity link function.

Continuous outcomes If the Hamilton Depression ($HAM\text{-}D_{17}$) scores from baseline to end of Week 8 of the study meet the assumptions of ANOVA modeling, repeated-measure (i.e., mixed) ANOVA models will be used to model the outcome scores over time. This model accounts for a between-group and within-individual effect, which allows for the examination of average differences between groups while also accounting for the correlation between subject scores between each measurement. If the $HAM\text{-}D_{17}$ scores do not meet standard ANOVA assumptions, GEEs will be used to model repeated measurements of outcome scores over time, as these

models are more robust to departures from the standard assumptions and also allow the investigator to specify the correlation structure of the repeated measurements. Mean change for all continuous measures will be calculated using the standard formula ($\frac{y2-y1}{y1}$)*100. For all continuous measures, a responder will be defined as a participant with 50% change from baseline in total scale score. Remitters at week 8 and at week 12 will be defined as HAM-D_{17} ≤7, QIDS-C_{16} ≤5, PHQ-9 <5, or CGI-S ≤1 in each treatment group. Differential time to response/remission of depressive symptoms over 8 and 12 weeks will be plotted using Kaplan-Meier curves and Cox proportional hazard models will test the null hypothesis of no difference in time to response/remission between groups.

Categorical Outcomes Categorical outcomes (i.e., remission, response) will be analyzed with 2x2 contingency tables, logistic regression, or loglinear models, where appropriate. Relative risk of response and remission will be determined between groups using the standard formula $\frac{a/(a+b)}{c/(c+d)}$, where *a* is the number of responders/remitters in the GeneSight group, *b* is the number of non-responders/non-remitters in the GeneSight group, *c* is the number of responders/remitters in the TAU group, and *d* is the number of non-responders/non-remitters in the TAU group. Standard chi-square tests will be used to determine if the relative risk of response/remission is statistically significant between groups. If expected frequencies are too small for asymptotic assumptions, Fisher's exact tests will be employed to test for differences in categorical outcomes between groups. Ninety-five percent confidence intervals will be calculated and provided for the relative risk of response/remission between groups.

Within-Group and Between-Group Composite Phenotype Analyses A three-level indicator variable will be created using a proprietary algorithm which combines genotype, phenotype, and drug metabolism information for each subject with respect to CYP1A2, CYP2D6, CYP2C19, CYP2C9, SLC6A4, and HTR2A in an effort to reduce the dimensionality inherent to such data to arrive at a single composite phenotype for each subject. The final indicator variable will be labeled 'composite_phenotype,' with the first level scored as 'green,' (e.g., use medication(s) as directed) the second level scored as 'yellow,' (e.g., use medication(s) with caution) and the third level scored as 'red' (e.g., use medication(s) with caution and frequent monitoring). If parametric assumptions are upheld, 1-way independent ANOVA models will employed to test the independent ability of the composite phenotype variable to predict each respective continuous outcome (i.e., percent improvement from baseline for QIDS-C17, HAMD-17, PHQ-9, respectively) between study groups. If parametric (i.e., standard) assumptions are not met, GEEs will be employed test the independent ability of the composite phenotype variable to predict each respective continuous outcome. Three tests will be conducted for each continuous outcome: an overall ANOVA test and two planned contrasts involving the comparison of the first level to that of the third, and the first two levels of the composite phenotype variable to that of the third level. To account for multiple testing, the Sidak correction will be employed using the formula $1 - (1-\alpha)^{1/n}$ where n is the number of independent tests and α is the nominal level (i.e., 05) of statistical significance

Decision Rule An overall alpha-level of 0.05 will be used to determine statistical significance and all statistical tests will be two-sided. All data will be analyzed using SAS (SAS Institute, Inc., Version 9.3).

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study Monitoring

INC is responsible for monitoring the sites and study activities. They will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on patient enrollment and on study site performance. Among others, the following items will be reviewed:

- study progress
- compliance with the protocol
- completion of CRFs
- source data verification
- AEs and SAEs
- Essential documents contained within the regulatory binder.

Source data verification (verification of data by comparing CRF entries with patient records) include: patient identification, informed consent (procedure, signature, and date), selection criteria, and primary efficacy and safety parameters (i.e., AEs).

13.2 Data Generation and Analysis

Once the completed CRFs are monitored, INC and the Sponsor (or designee) will further check the CRFs for completeness and plausibility of the data. INC will utilize quality systems in order to verify accurate entry and completeness of the data, including additional checks of the data upon computerization (e.g., range checks, cross checks, and other edit checks). Where required, the Investigator will be asked for supplementary information or CRF corrections upon a data clarification form or query. After all data is entered and checked, a Quality Control audit will be conducted to verify accuracy of the data entry. The database will then be locked and a biostatistician will complete the analyses of the data in accordance with the SAP.

13.3 Audits and Inspections

Audits and inspections may be carried out by the Sponsor's quality assurance department or designee, Food and Drug Administration (FDA), or other regulatory authorities to whom information on this study has been submitted. All documents pertinent to the study must be made available for such inspection. Informed consent of patients participating in this study must include the authorization to access these source documents.

14.0 ETHICS

14.1 Ethics Review

This study is to be conducted in accordance with IRB regulations (i.e., US 21 Code of Federal Regulations [CFR] Part 56.103) and GCP. Prior to initiating the study, the Investigator will obtain written confirmation that the IRB or IEC is properly constituted and compliant with ICH Guidelines and GCP requirements, applicable laws and local regulations.

Prior to initiating the study, the Investigator will provide the IRB/IEC with all appropriate material, including the protocol, Investigator's Brochure, the ICF including compensation procedures, and any other written information provided to the patients, including all consent forms. The study will not be initiated until appropriate documents from the IRB/IEC confirming unconditional approval of the protocol, the ICF and all patient recruitment materials are obtained in writing by the Investigator and copies are received at Sponsor or designee. The approval document should refer to the study by protocol title and protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. Study re-approval by the IRB/IEC must be made at least annually.

14.2 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- US CFR, Title 21
- ICH Consolidated Guideline for GCP (E6)
- SOPs

Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

14.3 Written Informed Consent

The informed consent process must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each patient prior to enrollment into the study. All ICFs must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's

responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor or designee prior to submission to the governing IRB and that it is read, signed and dated by all patients subsequently enrolled in the study as well as those currently enrolled in the study if directed by the IRB.

14.4 Patient Confidentiality

All personal study patient data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors, and other authorized representatives of the Sponsor, the IRB/IEC approving this study, the FDA, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the GeneSight may ultimately be marketed, but the patients' identities will not be disclosed in these documents.

15.0 DATA HANDLING AND RECORDKEEPING

15.1 Case Report Forms and Study Records

Study data will be recorded on electronic case report forms (eCRFs). Each authorized study staff member will receive a unique access account which will indicate individual use.

Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to the CRF via a secure internet access. Each completed set of CRFs will be reviewed by the Investigator who will then sign and date the Investigator's Statement of Verification CRF confirming that all data for the patient is complete and correct.

No electronic signatures can be used on this form.

All source document information must be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

15.2 Inspection of Records

Monitors, auditors, and other authorized representatives of the Sponsor, the IRB/IEC approving this study, the FDA, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient’s original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

15.3 Retention of Records

The Investigator shall retain study records for a period of 2 years following the date a marketing application is approved for GeneSight Psychotropic for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, for a period of 2 years after all investigations with the test are discontinued and the FDA is notified. The Sponsor will inform the Investigator when the study records can be destroyed.

The study records must include a copy of Investigator’s medical license, each CRF, patient charts/source documents, Investigator’s Brochure, protocol, protocol amendments, correspondence with the sponsor and the IRB/IEC, test receipts and dispensing records, Screening and Enrollment Log, advertisements, written information provided to patients and patients completed ICFs. If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g.,

Sponsor, other investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

15.4 Financial Disclosure

Sites will ensure that prior to their participation in the study, the principal investigators and any sub-investigators (as listed on Form FDA 1572) complete and return to the Sponsor the Financial Disclosure Statement form provided by the Sponsor. The principal investigator and any sub-investigators will promptly notify the site and Sponsor of any required revision to their Financial Disclosure Statement during the term of this Agreement and for 1 year following completion of the study. Upon Sponsor's written request following completion of the study, the principal investigator and any sub-investigators will provide an updated Financial Disclosure Statement form to the Sponsor.

15.5 Publication and Disclosure Policy

The objectives, the content and the results of the present clinical study as well as all further information must be handled as strictly confidential. All data and results are the exclusive property of Assurex.

After completion of the study or when the study data are adequate (in the Sponsor's reasonable judgment), the Investigator may prepare the data derived from the Study for publication or presentation at a medical-scientific meeting. Such data will be submitted to the Sponsor for review and comment prior to publication. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least 60 days prior to submission for publication, public dissemination, or review by a publication committee.

The Investigator agrees that all reasonable comments made by the Sponsor in relation to a proposed publication by the Investigator will be incorporated by the Investigator into the manuscript.

During the period for review of a proposed publication, the Sponsor shall be entitled to delay publication in order to protect proprietary information. No publication of any material related to the study may be published without the prior written consent of the Sponsor.

Except as requested by law neither the Sponsor nor the Investigator will reveal the results of the study to a third party without a mutual agreement about the analysis and interpretation of the data.

16.0 REFERENCES

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APPENDICES

Appendix 1. List of Psychotropic Medications Included in GeneSight Psychotropic

Psychotropic

Amitriptyline
Aripiprazole
Asenapine
Bupropion
Chlorpromazine
Citalopram
Clomipramine
Clozapine
Desipramine
Desvenlafaxine
Doxepin
Duloxetine
Escitalopram
Fluoxetine
Fluphenazine
Fluvoxamine
Haloperidol
Iloperidone
Imipramine
Levomilnacipran
Lurasidone
Mirtazapine
Nortriptyline
Olanzapine
Paliperidone
Paroxetine
Perphenazine
Quetiapine
Risperidone
Selegiline
Sertraline
Thiorizadine
Thiothixene
Trazodone
Venlafaxine
Vilazodone
Vortioxetine
Ziprasidone

Appendix 2. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Criteria

DIAGNOSTIC CRITERIA FOR 296.2X OR 296.3X
MAJOR DEPRESSIVE DISORDER, SINGLE OR RECURRENT

A. The presence of one or more major depressive episodes.

B. The major depressive episodes are not better accounted for by Schizo-affective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified (NOS).

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode (Note: This exclusion does not apply if any 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).

Appendix 3. 17-Item Hamilton Depression Rating Scale (HAM-D$_{17}$)

1. 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 nonverbally—i.e., through facial expression, posture, voice, and tendency to weep
4 Patient reports VIRTUALLY ONLY these feeling states in his/her spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT
0 Absent
1 Self-reproach, feels he/she 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

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

4. INSOMNIA, EARLY
0 No difficulty falling asleep
1 Complains of occasional difficulty falling asleep—i.e., more than ½ hour
2 Complains of nightly difficulty falling asleep

5. 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)

6. 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/she gets out of bed

7. 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/she has to push self to work or activities)
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores or if patient fails to perform ward chores unassisted

Appendix 3. 17-Item Hamilton Depression Rating Scale (continued)

8. RETARDATION (*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

9. 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

10. ANXIETY PSYCHIC
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

11. ANXIETY (SOMATIC)
Physiological concomitants of anxiety such as: Gastrointestinal—dry mouth, wind, indigestion, diarrhea, cramps, belching; Cardiovascular—palpitations, headaches; Respiratory—hyperventilation, sighing; Urinary frequency; Sweating
0 Absent
1 Mild
2 Moderate
3 Severe
4 Incapacitating

12. SOMATIC SYMPTOMS, GASTROINTESTINAL
0 None
1 Loss of appetite but eating without staff encouragement; heavy feelings in abdomen
2 Difficulty eating without staff urging; requests or requires laxatives or medication for bowels or medication for GI symptoms

13. 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

14. GENITAL SYMPTOMS
Symptoms such as: loss of libido, menstrual disturbances
0 Absent
1 Mild
2 Severe

Appendix 3. 17-Item Hamilton Depression Rating Scale (continued)

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

16. LOSS OF WEIGHT
0 No weight loss
1 Probable weight loss associated with present illness
2 Definite (according to patient) weight loss
3 Not assessed

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

Appendix 4. 16-Item Quick Inventory of Depression Symptomology (QIDS-C16)

1. Sleep Onset Insomnia
0 Never takes longer than 30 minutes to fall asleep.
1 Takes at least 30 minutes to fall asleep, less than half the time.
2 Takes at least 30 minutes to fall asleep, more than half the time.
3 Takes more than 60 minutes to fall asleep, more than half the time.

2. Mid-Nocturnal Insomnia
0 Does not wake up at night.
1 Restless, light sleep with few awakenings.
2 Wakes up at least once a night, but goes back to sleep easily.
3 Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.

3. Early Morning Insomnia
0 Less than half the time, awakens no more than 30 minutes before necessary.
1 More than half the time, awakens more than 30 minutes before need be.
2 Awakens at least one hour before need be, more than half the time.
3 Awakens at least two hours before need be, more than half the time.

4. Hypersomnia
0 Sleeps no longer than 7-8 hours/night, without naps.
1 Sleeps no longer than 10 hours in a 24 hour period (include naps).
2 Sleeps no longer than 12 hours in a 24 hour period (include naps).
3 Sleeps longer than 12 hours in a 24 hour period (include naps).

Enter the highest score on any 1 of the 4 sleep items (1-4 above) _____

5. Mood (Sad)
0 Does not feel sad.
1 Feels sad less than half the time.
2 Feels sad more than half the time.
3 Feels intensely sad virtually all the time.

6. Appetite (Decreased)
0 No change from usual appetite.
1 Eats somewhat less often and/or lesser amounts than usual.
2 Eats much less than usual and only with personal effort.
3 Eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others.

7. Appetite (Increased)
0 No change from usual appetite.
1 More frequently feels a need to eat than usual.
2 Regularly eats more often and/or greater amounts than usual.
3 Feels driven to overeat at and between meals.

8. Weight (Decrease) Within The Last Two Weeks
0 Has experienced no weight change.
1 Feels as if some slight weight loss occurred.
2 Has lost 2 pounds or more.
3 Has lost 5 pounds or more.

9. Weight (Increase) Within The Last Two Weeks
0 Has experienced no weight change.
1 Feels as if some slight weight gain has occurred.

Appendix 4. 16-Item Quick Inventory of Depression Symptomology (QIDS-C16) (continued)

2 Has gained 2 pounds or more.
3 Has gained 5 pounds or more.

Enter the highest score on any 1 of the 4 appetite/weight change items (6-9 above) _____

10. Concentration/Decision Making
0 No change in usual capacity to concentrate and decide.
1 Occasionally feels indecisive or notes that attention often wanders.
2 Most of the time struggles to focus attention or make decisions.
3 Cannot concentrate well enough to read or cannot make even minor decisions.

11. Outlook (Self)
0 Sees self as equally worthwhile and deserving as others.
1 Is more self-blaming than usual.
2 Largely believes that he/she causes problems for others.
3 Ruminates over major and minor defects in self.

12. Suicidal Ideation
0 Does not think of suicide or death.
1 Feels life is empty or is not worth living.
2 Thinks of suicide/death several times a week for several minutes.
3 Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.

13. Involvement
0 No change from usual level of interest in other people and activities.
1 Notices a reduction in former interests/activities.
2 Finds only one or two former interests remain.
3 Has virtually no interest in formerly pursued activities.

14. Energy/Fatiguability
0 No change in usual level of energy.
1 Tires more easily than usual.
2 Makes significant personal effort to initiate or maintain usual daily activities.
3 Unable to carry out most of usual daily activities due to lack of energy.

15. Psychomotor Slowing
0 Normal speed of thinking, gesturing, and speaking.
1 Patient notes slowed thinking, and voice modulation is reduced.
2 Takes several seconds to respond to most questions; reports slowed thinking.
3 Is largely unresponsive to most questions without strong encouragement.

16. Psychomotor Agitation
0 No increased speed or disorganization in thinking or gesturing.
1 Fidgets, wrings hands and shifts positions often.
2 Describes impulse to move about and displays motor restlessness.
3 Unable to stay seated. Paces about with or without permission.

Enter the highest score on either of the 2 psychomotor items (15 or 16 above) _____

TOTAL SCORE: _____ (RANGE 0-27)

Appendix 5. 9-Item Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (circle one number on each line)

	Not at all	Several days	More than half the days	Nearly everyday
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

Appendix 6. Clinical Global Impression Scale

1. SEVERITY OF ILLNESS (CGI-S)

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

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill patients

2. GLOBAL IMPROVEMENT (CGI-I)

Rate total improvement compared to baseline, whether or not, in your judgment, it is due entirely to drug treatment.

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

3. EFFICACY INDEX (CGI-EI)

Rate this item on the basis of DRUG EFFECT ONLY Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as "Moderate" and side effects are judged "Do not significantly interfere with patient's functioning." Record 06

THERAPEUTIC EFFECT	**SIDE EFFECTS**			
	None	**Does not significantly interfere with patient's functioning**	**Significantly interfere with patient's functioning**	**Outweigh therapeutic effect**
MARKED – Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
MODERATE – Decided improvement. Partial remission of symptoms	05	06	07	08
MINIMAL – Slight improvement which doesn't alter status of care of patient	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16

Appendix 7. SF-36 Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

1. In general, would you say your health is:
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor

2. Compared to one year ago, how would you rate your health in general now?
   - Much better now than a year ago
   - Somewhat better now than a year ago
   - About the same as one year ago
   - Somewhat worse now than one year ago
   - Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

c. Lifting or carrying groceries.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

d. Climbing several flights of stairs.
   - Yes, limited a lot.
   - Yes, limited a little.
   - No, not limited at all.

e. Climbing one flight of stairs.
   - Yes, limited a lot.

Appendix 7. SF-36 Health Survey (continued)

Yes, limited a little.
No, not limited at all.

f. Bending, kneeling or stooping.
Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

g. Walking more than one mile.
Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

h. Walking several blocks.
Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

i. Walking one block.
Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

j. Bathing or dressing yourself.
Yes, limited a lot.
Yes, limited a little.
No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?
Yes No

b. Accomplished less than you would like?
Yes No

c. Were limited in the kind of work or other activities
Yes No

d. Had difficulty performing the work or other activities (for example, it took extra time)
Yes No

Appendix 7. SF-36 Health Survey (continued)

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?
Yes No

b. Accomplished less than you would like
Yes No

c. Didn't do work or other activities as carefully as usual
Yes No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
Not at all
Slightly
Moderately
Quite a bit
Extremely

7. How much bodily pain have you had during the past 4 weeks?
Not at all
Slightly
Moderately
Quite a bit
Extremely

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
Not at all
Slightly
Moderately
Quite a bit
Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?
All of the time
Most of the time
A good bit of the time

Appendix 7. SF-36 Health Survey (continued)

Some of the time
A little of the time
None of the time

b. have you been a very nervous person?
All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time

c. have you felt so down in the dumps nothing could cheer you up?
All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time

d. have you felt calm and peaceful?
All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time

e. did you have a lot of energy?
All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time

f. have you felt downhearted and blue?
All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time

Appendix 7. SF-36 Health Survey (continued)

g. did you feel worn out?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

h. have you been a happy person?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

i. did you feel tired?
- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

11. How TRUE or FALSE is each of the following statements for you?
a. I seem to get sick a little easier than other people
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

b. I am as healthy as anybody I know
- Definitely true
- Mostly true
- Don't know

Appendix 7. SF-36 Health Survey (continued)

Mostly false
Definitely false

c. I expect my health to get worse
Definitely true
Mostly true
Don't know
Mostly false
Definitely false

d. My health is excellent
Definitely true
Mostly true
Don't know
Mostly false
Definitely false

Appendix 8. GAD-7 Scale

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	Over half the days	Nearly everyday
1. Feel nervous, anxious, or on edge,	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
8. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3