Study Protocol

An 8-Week Prospective Randomized, Controlled, Double-Blind Trial of the Genecept Assay ™ vs. Treatment-as-Usual to Evaluate Efficacy of Assay-Guided Treatment in Adults with Major Depressive Disorder

Protocol ID:	GNM-PROT MDD-01
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Study Sponsor:

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PROTOCOL SUMMARY

Title	An 8-Week Prospective Randomized, Controlled, Double-Blind Trial of the Genecept Assay ™ vs. Treatment-as-Usual to Evaluate Efficacy of Assay Guided Treatment in Adults with Major Depressive Disorder
Sponsor	Genomind Inc.
Study Phase	Phase 3
Indication	Major Depressive Disorder
Primary Objective	To assess efficacy of assay-guided treatment (AGT) versus treatment-as-usual (TAU) in Major Depressive Disorder, as measured by change in Hamilton Depression Rating Scale (SIGH-D-17) at 8 weeks.
Secondary Objectives	-To assess efficacy of assay-guided treatment (AGT) versus treatment-as-usual (TAU) in Major Depressive Disorder, as measured by change in Quick Inventory of Depressive Symptoms (QIDS-SR16) at 8 weeks. -To assess the percentage of responders at Week 8, based on SIGH-D-17, QIDS-SR16, and Clinical Global Impression–Improvement (CGI-I), respectively. Treatment response will be defined in 3 different ways: Blinded Rater Assessment: ≥ 50% reduction from baseline of SIGH-D-17 score ; Subject-Rated Assessment: ≥ 50% reduction from baseline of QIDS-SR16 ; Unblinded Clinician Assessment: ≤ 3 score on the CGI-I; -To assess the percentage of remitters at Week 8, based on the SIGH-D-17 and QIDS-SR16, respectively. Remission is defined for the SIGH-D-17 and the QIDS-SR16: Blinded Rater Assessment: ≤ 7 score on the SIGH-D-17; Subject-Rated Assessment: ≤ 5 score on the QIDS-SR16 -To assess the impact of the Genecept Assay ™ on adverse events, based on Frequency, Intensity and Burden of Side Effects Rating (FIBSER) and Patient-Related Inventory of Side Effects (PRISE), frequency and severity of adverse events and Columbia-Suicide Severity Rating Scale (C-SSRS) outcomes.
Objective of Exploratory Elderly MDD Study	To perform an exploratory, add-on study, in elderly subjects age 65 years and older, to assess the efficacy and safety of AGT vs TAU in Major Depressive Disorder. Primary efficacy will be measured by change in Hamilton Depression Rating Scale (SIGH-D-17) at 8 weeks. This study will provide additional data on this important, Medicare-eligible population, which is sparsely represented in the Main Study (< 8% of subjects). As specified in Protocol Amendment 2, after the Main Study enrollment finishes, 70 subjects, age ≥ 65, will be randomized to the add-on study. Except for change in age of inclusion, all study procedures will be identical to the Main Study.

Study Design	In this randomized clinical trial, subjects will be assigned to either an assay-guided treatment condition (AGT) or a treatment-as-usual condition (TAU). All subjects will provide a DNA sample at the Screening Visit for the Genecept Assay ™. In the AGT condition, assay results will be provided to the treating investigator, who will use the results to guide antidepressant pharmacotherapy. In the TAU condition, the investigator will treat the subjects without the knowledge of the pharmacogenetic testing results. Assay results for all subjects will be provided to the investigator once all Week 8 visit procedures have been completed. Raters of the primary endpoint assessment and subjects will remain blinded to treatment assignment.
Sample Size	Approximately 300 subjects will be randomized according to a 1:1 ratio to AGT or TAU. As specified in Protocol Amendment 2, after Main Study enrollment completes, an additional 70 subjects, age ≥ 65, will be randomized according to a 1:1 ratio, to the Exploratory Elderly MDD Study. The Exploratory Elderly MDD Study will be analyzed as a separate study.
Study Sites Location	Multi-center, with approximately 25 sites in the US. The Exploratory Elderly MDD Study will include approximately 12 US sites.
Key Subject Eligibility Criteria	Inclusion: 1. Main Study: Age 18-75 years Exploratory Elderly MDD Study: Age ≥ 65 years 2. Primary diagnosis of Major Depressive Disorder (without psychosis) based on DSM-5 criteria and MINI 7.0 3. SIGH-D-17 score ≥18 (i.e., moderate depression), at Screening and Baseline 4. Failure of at least 1 prior adequate trial of a standard antidepressant for the current major depressive episode (using ATRQ criteria – i.e., 6 weeks at adequate dose) due to inefficacy, side effects, or intolerability Exclusion: 1. Severe personality traits (based on DSM-5 criteria) that in the opinion of the investigator may interfere with the participation in the study or the evaluation of efficacy and safety and all diagnosed Personality Disorders 2. Current DSM-5 diagnosis of Neurocognitive Disorders, Schizophrenia Spectrum (lifetime diagnosis) and other Psychotic Disorders, Bipolar and related disorders (lifetime diagnosis), Trauma and Stress related Disorders, Obsessive Compulsive Disorder and Related Disorders. Other DSM-5 disorders that in the opinion of the investigator may interfere with the participation in the study or the evaluation of efficacy and safety. 3. DSM-5 diagnosis of Substance Related and Addictive Disorders diagnosed in the last 12 months (other than tobacco and caffeine)

	4. History of Suicidal Behavior within 12 months of screening or presence of Active Suicidal Ideation with Intent in the past 12 months (Items 4 or 5) at Screening or Baseline, as determined by the Columbia Suicide Severity Rating Scale (C-SSRS), or subject is considered to be an acute suicide risk in the clinical judgement of the investigator 5. Four (4) or more failed pharmacologic interventions in the current major depressive episode (one of the four failed interventions must meet ATRQ criteria – i.e., 6 weeks at adequate dose) 6. Electroconvulsive therapy (ECT) or transcranial magnetic stimulation therapy (TMS) started within 90 days of screening or planned during the study 7. Psychotherapy including cognitive behavioral therapy (CBT), or dialectical behavioral therapy (DBT) started within 90 days of screening or planned during the study
Treatment Groups	Utilization of Genecept Assay ™ results to guide treatment decisions (AGT) or treatment-as-usual (TAU).
Safety Parameters	Frequency, Intensity, and Burden of Side Effects Rating (FIBSER), Patient-Rated Inventory of Side Effects (PRISE), Adverse Event (AE) reporting, Columbia-Suicide Severity Rating Scale (C-SSRS).
Study Endpoints	Hamilton Depression Rating Scale (SIGH-D-17), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) and Clinical Global Impression-Improvement (CGI-I) scores.
Statistical Populations (Main Study)	All Randomized Set: All randomized subjects in Main Study (approximately 300 subjects). Full Analysis Set (FAS): All randomized subjects with a post-baseline SIGH-D-17 assessment. Safety Analysis Set (SAF): All randomized subjects who complete the baseline appointment with the treating investigator, i.e., start AGT or TAU treatment. Efficacy will be analyzed on the FAS set, as long as at least 95% of randomized patients have a post-baseline SIGH-D-17. Safety endpoints will be analyzed on the SAF dataset. The All Randomized Set will be listed.
Statistical Populations (Elderly MDD Study)	Same statistical populations applied to the subjects in the Exploratory Elderly MDD Study, e.g.: All Randomized Set: All randomized subjects in Exploratory Elderly MDD Study (approximately 70 subjects).

Statistical Methods (Main Study)	The primary endpoint (change from baseline in SIGH-D-17) analysis will be performed using the MMRM method in the FAS population. The model will include the fixed effect continuous factor baseline SIGH-D-17, and fixed effect categorical factors investigative site, treatment group (AGT and TAU; 2 levels), visit (Weeks 2, 4, 6 and 8; 4 levels), and treatment x visit interaction. AGT and TAU mean change in SIGH-D-17 at Week 8 will be estimated and tested utilizing the least squares (LS) means from the treatment x visit interaction in the MMRM model. The primary analysis will test the difference (contrast) between the Week 8 least squares (LS) means, at two-sided significance 0.05. The test p-value and the 95% CI for the difference in Week 8 means will be presented. Comparisons between the AGT and TAU means at Week 2, Week 4 and Week 6 will also be generated. Key continuous secondary endpoints will be analyzed using the same MMRM model as for the primary endpoint. Key categorical secondary endpoints will be analyzed using the Mantel-Haenszel method, stratified on pooled site. The remaining efficacy and safety data will be summarized by treatment group using descriptive statistics and frequency tables. **Subgroup Analyses:** Consistency of AGT vs TAU treatment effect on SIGH-D-17 will be assessed across various subgroup factors described below, by evaluating the treatment by subgroup interaction in the MMRM model. Subgroup factor — Subgroup categorization Age group — < median age, ≥ median age Gender — Male, Female Race — White, Non-white Baseline SIGH-D-17 — < 24, ≥ 24 Investigative Site — Pooled
Statistical Methods (Exploratory Elderly MDD Study)	The primary efficacy endpoint (change from baseline in SIGH-D-17) analysis will be performed using a Last Observation Carried Forward Analysis of Covariance, in FAS population. Generally, the statistical methods for the Exploratory Elderly MDD Study will follow the outline of the Main Study, but will be primarily descriptive, and statistical analyses will be simpler, as necessitated by the much smaller sample size. The SAP for the Elderly MDD Study, incorporated in the overall SAP (V 3.0), will detail the statistical approaches to be used. The SAP (V 3.0) will be finalized and approved before the Elderly Study database is unblinded.

Sample Size Computations	Main Study: The sample (n=300) size is based on previous study findings comparing SIGH-D-17 improvement in MDD patients whose physician's treatment decision were informed (AGT) or not (TAU) by the results of a targeted suite of genetic assays. The sample size calculation assumed a difference in SIGH-D-17 mean improvement scores = 3.1, the within-subject standard deviation (SD) = 7.2, a dropout rate at Week 8 of 23%, a two-sided 0.05 t-test of treatment means, and 90% power. These assumptions result in a sample size of 150 randomized patients in each treatment group (300 total). Various alternate scenarios are presented in the Section 9 (Statistical Procedures). All calculations were made with Stata version 13 software. Note that all calculations should be somewhat conservative, since the actual primary analysis will be a MMRM analysis. Add-on Exploratory Elderly MDD Study: Sample size (n=70) was not formally calculated for this exploratory study.

SCHEDULE OF VISITS AND PROCEDURES

Study Period	**Screening**	**Day 0 / Baseline**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
Visit Windows	-7 days[a]	0 days	+/- 3 days	+/- 3 days	+/- 3 days	-5/+7 days
Informed Consent	●					
Demographics	●					
Inclusion/Exclusion Criteria (**MINI, ATRQ**)	●					
Columbia Suicide Severity Rating Scale (**C-SSRS**)	●	●	●	●	●	●
Medical/Psychiatric History	●					
Urine Drug Screen Evaluation	●					
Concomitant Medications / MDD Treatment Medications	●	●	●	●	●	●
Adverse Events	●	●	●	●	●	●
Structured Interview Guide for the Hamilton Depression Rating Scale – 17 Item Version (**SIGH-D-17**)[b]	●	●	●	●	●	●
Quick Inventory of Depression Symptoms (**QIDS-SR16**)		●	●	●	●	●
Clinical Global Impression - Severity (**CGI-S**)		●	●	●	●	●
Clinical Global Impression - Improvement (**CGI-I**)			●	●	●	●
Frequency, Intensity, and Burden of Side Effects Rating (**FIBSER**)		●	●	●	●	●
Patient Rated Inventory of Side Effects (**PRISE**)		●	●	●	●	●
DNA Sample Collection[c]	●					
Randomization[e]		●				
Clinical Decision Survey Pre-Result[d,f]		●				
Genecept Assay ™ Results Retrieval[d,f] / Results Review[f,g]		●				
Initiation or Adjustment of MDD Treatment[f]		●				
Clinical Decision Survey Post-Result[d,f]		●				
Disclosure of Treatment Group[c,f]						●

[a] may be extended by up to 5 days
[b] blinded rater
[c] after all visit procedures have been completed
[d] via Investigator Portal
[e] after eligibility has been confirmed by SIGH-D-17 and C-SSRS
[f] unblinded treating investigator
[g] consultation with Genomind as needed

1 BACKGROUND AND CLINICAL RATIONALE

Approximately 30% of US adults will have a mental illness at a given time point in a 12-month period[1], and almost 50% of US adults will develop one within their lifetimes[2]. Depression and other psychiatric illnesses involve substantial costs in human and financial terms, representing several of the main medical causes of disability in established market economies worldwide[3]. Global costs for mental health conditions are projected to be over $6 trillion by 2030[4]. In the U.S., it is estimated that mental health disorders account for 6.2% of the nation's health care spending[5]. A major driver of depression costs is treatment-resistant depression (TRD)[6], which is estimated to occur in 29-46% of depressed patients[7]. Patients diagnosed with TRD have greater medical expenses[8] and poorer overall health[9]. Moreover, comorbid anxiety disorders in patients with depression have an additive effect on indirect health care costs, impacting overall function, quality of life, and absenteeism from work[10].

Treatment-resistant depression is usually defined as failure to achieve symptomatic remission despite at least two adequate treatment trials[11]. Remission rate after a single course of antidepressant pharmacotherapy is only 37%, based on the results of the Star*D study[12].

Treatment of depression and other psychiatric disorders is further complicated by variation in medication response. Pharmacodynamic and pharmacokinetic variations are known to exist among ethnic groups, affecting response to common psychiatric medications[13]. There is abundant evidence that genetic variations influence psychotropic drug, metabolism and transport[14], potentially impacting efficacy and tolerability. An estimated 40% of inter-individual differences in antidepressant response are attributable to common genetic variations[15]. These effects of genetic variations on efficacy, tolerability and possibly on medication compliance may further compound health care costs[16].

A trial-and-error approach to prescribing has traditionally been utilized in psychiatry[17], contributing to the high costs of treatment and treatment failures[18]. Information on a patient's genetic background may help clinicians identify appropriate treatment options by predicting the likelihood of pharmacotherapeutic response or of adverse effects[19]. A number of studies have demonstrated the cost-effectiveness of pharmacogenetic testing in psychiatry[20-24]. One recent report showed a decrease in health care costs in psychiatric patients via the use of genetic testing as well as an increase in medication compliance[25].

1.1 Treatment of MDD

The importance of full symptomatic remission as a treatment goal in MDD is well established[26]. As previously stated, about two-thirds of individuals with MDD fail to remit with an initial antidepressant trial of adequate dose and duration, and roughly half the latter group will not achieve remission despite as many as 3 more pharmacotherapeutic interventions[7,27,28]. The probability of remission, in fact, declines sharply after each failed treatment trial: Remission rates in the STAR*D trial were 36.8%, 30.6%, 13.7%, and 13.0% for each successive treatment, and individuals with 2 or more failed trials were significantly more likely to experience early recurrence, even if they had improved on treatment[29].

MDD is the most frequent factor in years lived with disability in developed countries[30], and Treatment Resistant Depression (TRD) accounts for much of this disability[6,31]. Among outpatients, the annual cost of care for TRD is $10,241, versus $6,512 for outpatients without TRD; these costs become higher when greater rates of hospitalization in TRD patients are factored in[6]. The cost to society in terms of lost productivity is likely to be even greater.

TRD, as mentioned earlier, is usually defined as treatment failure of two or more antidepressant trials of adequate dose and adequate duration[32,33]. As suggested by the STAR*D outcomes cited above, treatment resistance in MDD patients is common and problematic.

The potential benefits of personalized pharmacotherapy for patients with MDD are well recognized in psychiatry. Given the proliferation of treatment options for MDD, patients can spend months or years in and out of various treatment regimens before receiving optimally effective pharmacotherapy. If pharmacogenetic profiles of MDD patients can be defined early in the course of their illness, these patients can receive more targeted interventions to improve likelihood of remission.

1.2 Pharmacogenetic Testing

Pharmacogenetic testing offers the promise of targeting patients more quickly to personalized treatments that are more likely to improve symptomatology and less likely to cause adverse effects. Genomind, Inc. provides a test for genotyping of gene variants (Genecept Assay ™) that are relevant to psychotropic drug response. For example, the short allele of the serotonin transporter gene (*SLC6A4*) is associated with antidepressant efficacy and side effects[16]. This allele is addressed in the Genecept test.

Cytochrome P450 is a family of liver enzymes responsible for metabolizing many drugs and toxins. Known polymorphisms in the genes coding for these enzymes can alter their functions and result in increased or decreased drug metabolism. *CYP2D6*, for example, has more than 100 known mutations. Poor *CYP2D6* metabolizers may have elevated serum concentrations, resulting in adverse effects and drug discontinuation when adverse effects become intolerable. Ultrarapid metabolizers, on the other hand, may have lower serum drug concentrations necessitating higher-than-usual doses to achieve clinical efficacy[34]. The Genecept Assay ™ genotypes many common variants of *CYP2D6*. It also genotypes *CYP2C19 and CYP3A4/5*, which also are involved in the metabolism of a considerable number of psychotropic medications.

1.3 Rationale for Study

A previous study was conducted to examine the effectiveness of genetic testing in a real-world clinical setting and to assess its impact on clinician treatment decisions[35]. This study was a naturalistic, unblinded, prospective investigation in psychiatric patients over 18 years of age and clinicians, in which a commercially available genetic test was utilized (Genecept – Genomind, Inc.). The test analyzed in the naturalistic study (Genecept 1.0) incorporates 10 genes related to the pharmacodynamics and pharmacokinetics of psychiatric medications. Each patient's genetic results were provided to the participating clinicians, who completed a baseline survey of psychotropic medications, number of failed medication trials, psychiatric diagnoses, and severity of psychiatric

disorders. The treating clinicians completed surveys within one week of receiving the genetic results and again 3 months later. The patients, who had provided a saliva sample for DNA analysis at baseline, completed assessments of depression, anxiety, side effects, and quality of life at baseline, 1 month, and 3 months. Data from 685 patients were collected. Approximately 70% of the patients had primary diagnoses of mood disorders, and 29% of the patients had primary diagnoses of anxiety disorders. Clinician-reported data indicated that 87% of patients had clinically measurable improvement, with 62% judged "much improved" or "very much improved", based on the CGI-I scale. Analysis of the patients who had had 2 or more prior treatment failures (69% of the patient population) showed improvement in 91% of this subgroup. Patients reported significant decreases in depression, anxiety, and side effects of medications, and increases in quality of life. This improvement was sustained over a 3-month interval. Moreover, clinicians indicated that the test results influenced their pharmacotherapy decisions in 93% of patients and their confidence in these decisions in 94% of patients. In the absence of a treatment-as-usual control group, however, the degree of improvement attributable to the test could not be precisely estimated[36].

The Genecept Assay™ offers information to guide pharmacotherapeutic decisions personalized to a patient's genetic profile, to maximize improvement in symptomatology and minimize treatment failure and treatment intolerability. While the utility of this assay has been demonstrated in the large naturalistic study as well as in retrospective claims review, it is necessary to confirm these results in a well-controlled clinical trial before such an assay can be widely used in clinical practice. The present study, which uses a prospective randomized single-blind design, is intended to confirm the utility of an enhanced version of the Genecept Assay ™ in the pharmacotherapy of ambulatory patients with Major Depressive Disorder. The enhanced assay includes the 10 genes analyzed in Genecept 1.0 plus 8 additional genes.

Genetic variations will be analyzed using Taqman® SNP genotyping assays. The enhanced Genecept Assay ™ tests for variations in serotonin transporter protein (*SLC6A4*), serotonin receptor subtype 2C (*5HT2C*), melanocortin 4 receptor (*MC4R*), dopamine 2 receptor (*DRD2*), L-type gated calcium channel (*CACNA1C*), ankyrin g (*ANK3*), catechol-o-methyltransferase (*COMT*), alpha-2A adrenergic receptor (*ADRA2A*), methylenetetrahydrofolate reductase (*MTHFR*), brain-derived neurotrophic factor (*BDNF*), μ-opioid receptor (*OPRM1*), glutamate receptor (*GRIK1*) and in 6 cytochrome P450 genes: 1A2 (*CYP1A2*), 2B6 (*CYP2B6*), 2C9 (*CYP2C9*), 2D6 (*CYP2D6*), 2C19 (*CYP2C19*), and 3A4 (*CYP3A4*). In total, 62 SNPs, as well as the copy number of *CYP2D6*, are assessed. These genes appear to be associated with psychiatric symptomatology, treatment efficacy, and liability for adverse effects[21-24].

Similar treatment challenges as described above are found in elderly patients age 65 and older, who are typically covered by Medicare services. This group is of high importance, but is only a very small portion (< 8%) of patients enrolling in Main Study. The add-on Exploratory Elderly MDD Study will provide an exploratory assessment of the utility of the Genecept Assay™ in this older, Medicare-eligible population. The results of this study will be analyzed separately from the Main Study, and will inform possible decisions to implement a large study in this elderly MDD population.

1.4 Study Population

The main study will enroll 300 subjects ranging from ages 18 to 75, who are diagnosed with Major Depressive Disorder (without psychosis).

The add-on Exploratory Elderly MDD Study will randomize 70 subjects age 65 years and older.

Subjects will be recruited from psychiatric outpatient clinics.

Elderly MDD study subjects will begin randomization after enrollment for the primary study has been completed.

1.5 Risk/Benefit Assessment

1. Subjects will have full access to appropriate pharmacotherapy at all times since they will be receiving approved psychotropic drugs with proven efficacy and acceptable safety. It is possible, however, that the test results could cause the treating investigator to choose a less effective treatment regimen than would otherwise have been selected, or that the selected treatment regimen may be associated with problematic adverse effects. This will be clearly explained to all subjects in the informed consent form.

2. Delay in treatment: By participating in this study, subjects are likely to experience a delay in initiation of active treatment during the time needed for completion of genotyping by the study laboratory and review of these results by the treating investigator. This may delay treatment by up to 7 days but no greater than 12 days. During this period, it is possible that the subject's condition could worsen. The following steps, however, will be implemented to minimize risk to the subject:

   A) If needed, the investigational site will give the subject opportunity to maintain contact with the investigator and site throughout the waiting period so that the subject's psychiatric status can be monitored. Subjects will be provided with study-specific contact information and a phone contact to the subject by the site will be made as indicated midway between Screening and Day 0.

   B) Pending results of the genetic test, subjects who are taking psychotropic medications at the time of enrollment will continue to take the same medications, as per the treating investigator's clinical judgment.

   C) Subjects currently taking psychotropic medications or subjects not taking psychotropic medication at screening who are in need of immediate change or addition of pharmacotherapy may receive this from the treating investigator as clinically indicated. These patients will not be eligible for enrollment/randomization at that time but may be eligible (for one time only) for re-screening at a later point during the enrollment period of the study ($\geq$ 6 weeks).

3. During the course of the assessments of the subject, unexpected information on the subject's psychiatric or medical condition may emerge. Should this occur, this information will be discussed with the subject.

4. During the clinical interviews, the subject may become fatigued or distressed from the questions. If this occurs, he/she should communicate this to the interviewer/study personnel and the assessment will be stopped. The subject will be given a break period or rescheduled.

5. Genetic study: Variation in some genes has been associated with risk for various medical or psychiatric illnesses. If confidentiality were to be breached unexpectedly, despite adherence to federal GINA laws, the subject could be jeopardized with respect to insurability or employment, for example. Genetic information from this study will not be disclosed to insurers or other organizations without the written permission from the subject, as applicable by governing laws. Every effort will be made to maintain confidentiality for all subjects, as per federal and institutional requirements.

6. Subjects may experience improvement in psychiatric symptoms, and the study data obtained may provide information about treatment strategies for psychiatric disorders in the future. Depression remains a major clinical problem despite availability of multiple effective treatments. This study may validate a test to facilitate more rapid selection of treatments that may prove optimal with respect to efficacy and safety in a given subject.

7. Subjects may request a copy of the Genecept Assay ™ report at the Week 8 visit after all visit and study assessments have been completed or 8 weeks after randomization for subjects that discontinued early.

2 HYPOTHESIS AND STUDY OBJECTIVE

2.1 Study Objective

To assess the efficacy of assay-guided treatment (AGT) versus treatment-as-usual (TAU) in subjects with MDD at 8 weeks. Additionally, to assess the efficacy and safety of assay-guided treatment (AGT) versus treatment-as-usual (TAU) in subjects with MDD at 8 weeks in subjects age 65 years old and older, a separate analysis will be performed on the approximately 70 subjects in the add-on Elderly MDD Study.

2.2 Clinical Hypothesis

Compared to treatment-as-usual, pharmacological interventions in the treatment of major depressive disorder that are guided by the Genecept Assay ™ will be more effective in reducing depressive severity and medication-induced side effects.

3 STUDY DESIGN

3.1 Overview

In this 8-week double-blind clinical trial, subjects will be randomly assigned to either an assay-guided treatment group (AGT) or a treatment-as-usual group (TAU). All subjects will provide a DNA sample for the Genecept Assay ™. In the AGT group, assay results will be provided to the treating investigator, who will use the results to guide pharmacotherapy of the subject's MDD. The treating investigator will treat subjects of the TAU group without the knowledge of the pharmacogenetic testing results. Up to 150 subjects will be randomized to the AGT group and up to 150 subjects will be randomized to the TAU group. After enrollment completion for the primary analysis, an additional 70 subjects age 65 and older will be enrolled to satisfy requirements for an Exploratory Elderly MDD Study of subjects age 65 years and older. Subjects will be instructed to take their medications as prescribed by the treating investigator. No treatments other than medication interventions should be initiated for the duration of the trial. The investigator may provide assay results to all subjects at their Week 8 visit after the completion of all visit procedures or 8 weeks after randomization if subject discontinued early.

3.2 Safety Monitoring

Investigators will closely monitor the safety of participants throughout the study. Approved drug treatments with known efficacy and adverse effect profiles are recommended. The treatment regimens should be consistent with approved labeling for the respective drugs.

Genomind will closely monitor the progress and conduct of the study. Investigators will be instructed to report issues related to data confidentiality, adherence to protocol, recruitment and retention, study progress and any other relevant issues to the sponsor in a timely manner. Serious adverse events (SAEs) should be reported to Genomind no later than 48 hours after learning of the event (See Section 7.2 for further information on SAEs). Investigators will also report SAEs to the respective IRB according to the IRB's guidelines.

3.3 Blinding

Blinded raters will conduct the administration of the primary endpoint, the SIGH-D-17 scale, on a secure tablet. Rater-specific log-in and password will be required to administer the scale. Rater contact with subjects will be limited to the administration of blinded assessments of the SIGH-D-17 scale. No other type of contact with the subject such as collection of screening data, follow-up assessments, documentation of adverse events, etc. will be conducted by the blinded rater. Blinded raters will not discuss subjects with other study staff. However, the blinded rater should inform the treating investigator of any potential safety concerns. Raters will remain blinded to the treatment arms throughout the study.

Subjects will also be blinded to their treatment assignments. At the completion of all Week 8 procedures or 8 weeks after randomization for subjects that discontinued early, subjects will be

notified of their treatment assignment by the treating investigator. Subjects in the TAU treatment group will be given the opportunity to be treated based on their Genecept Assay ™ results.

Treating investigators will be unblinded and instructed not to mention the results of the Genecept Assay ™ reports in the medication instructions or in any other interactions with the subject at Baseline or at any subsequent study visits. Treating investigators will receive randomization assignments and assay results via a secure portal. Investigator-specific log-in and password will be required to retrieve assay results. No other study personnel will perform this retrieval for the treating investigator. Subject communication tools such as sample language will be provided to the treating investigators to help maintain the blinding.

In addition, investigators will not disclose a subject's treatment assignment to study staff, site monitors or any others for the duration of the subject's participation in the study. A subject's Genecept Assay ™ test results should be kept in a secure location that is accessible only to treating investigators until Week 8 when the results are unblinded.

3.4 Prohibited Medications

No medications are specifically prohibited.

3.5 Prohibited Treatments

Electroconvulsive therapy (ECT) or transcranial magnetic stimulation therapy (TMS) are prohibited for the duration of the study, including ECT and TMS started within 90 days of the screening visit.

Patients with a vagus nerve or deep brain stimulator are prohibited from the trial.

Psychotherapy including cognitive behavioral therapy (CBT), or dialectical behavioral therapy (DBT) are prohibited for the duration of the study, including CBT and DBT started within 90 days of the screening visit. On-going stable psychotherapy started 90 days or more before screening may be continued at the pre-screen level of therapy during study participation.

3.6 Number of Subjects

Approximately 150 subjects will be randomized into each treatment group (AGT and TAU) for a total of 300 study subjects. An additional 35 subjects age $\geq$ 65 will be randomized into each treatment group (AGT and TAU), for an additional total of 70 subjects, for the Exploratory Elderly MDD Study.

3.7 Number of Study Sites

Approximately 25 investigative outpatient psychiatric sites in the US will participate in this study. Approximately 12 sites, who have access to older populations, will participate in the recruitment of additional 70 subjects age ≥65 years, for the Exploratory Elderly MDD Study.

3.8 Estimated Study Duration

Subjects will be participating in this study for about 9 weeks: an approximately 1-week screening period and an 8-week treatment period. The entire study will consist of an estimated 6-month enrollment period for a total study duration of approximately 8.5 months. An additional enrollment period of 6 months will recruit subjects age 65 and older for the add-on Exploratory Elderly MDD Study.

4 SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

The following are requirements for entry into the study:

1. Main Study: Age 18-75 years.

   Exploratory Elderly MDD Study: Age ≥ 65 years (enrolled under Protocol Amendment 2, v12Aug16)

2. Ability to understand and provide informed consent

3. Ability to understand, read and speak English

4. Primary diagnosis of Major Depressive Disorder (without psychosis) based on DSM-5 criteria and

   MINI 7.0

5. SIGH-D-17 score ≥18 (i.e., moderate depression) at Screening and Baseline

6. Failure of at least 1 prior adequate trial of standard antidepressant in the current major depressive episode (using ATRQ criteria – i.e., 6 weeks at adequate dose) due to inefficacy, side effects or intolerability

7. Subject is willing to follow study instructions, complete study assessments and likely to complete all required visits

4.2 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Severe personality traits (based on DSM-5 criteria) that in the opinion of the investigator may interfere with the participation in the study or the evaluation of efficacy and safety and all diagnosed Personality Disorders

2. Current DSM-5 diagnosis of Neurocognitive Disorders, Schizophrenia Spectrum (lifetime diagnosis) and other Psychotic Disorders, Bipolar and Related disorders (lifetime diagnosis*), Trauma and Stress related Disorders, Obsessive Compulsive Disorder and Related Disorders. Other DSM-5 disorders that in the opinion of the investigator may interfere with the participation in the study or the evaluation of efficacy and safety

   PLEASE NOTE: Subjects with a diagnosis of comorbid current Anxiety Disorders (except Panic Disorder) and Adjustment Disorders may be included if the investigator considers MDD to be the primary diagnosis and the other disorders are stable.
   *If in the clinical judgement of the investigator there was a previous misdiagnosis of bipolar disorder, the subject may be enrolled after approval by the sponsor (if other inclusion/exclusion criteria are met).

3. DSM-5 diagnosis of Substance Related and Addictive Disorders diagnosed in the last 12 months (other than tobacco and caffeine)

4. History of Suicidal Behavior within 12 months of screening or presence of Active Suicidal Ideation with Intent in the past 12 months (Items 4 or 5) at Screening or Baseline, as determined by the Columbia Suicide Severity Rating Scale (C-SSRS), or subject is considered to be an acute suicide risk in the clinical judgement of the investigator

5. Previous homicidal behavior or acute homicidal risk at Screening or Baseline, in the clinical judgement of the investigator

6. Four (4) or more failed pharmacologic interventions for depression in the current major depressive episode (One of the four failed interventions must meet ATRQ criteria – i.e., 6 weeks at adequate dose)

   PLEASE NOTE: Treatment with 100 mg or less of trazodone, intended as an aid only for sleep, is not considered a treatment intervention for evaluation of failed interventions. Other low dose psychotropic medications intended for sleep only may also not be considered a treatment intervention (after approval from the sponsor).

7. Subjects who are not willing to take psychotropic medications for treatment of MDD.

8. Electroconvulsive therapy (ECT) or transcranial magnetic stimulation therapy (TMS) started within 90 days of screening or planned during the study

9. Subjects with a vagus nerve or deep brain stimulator are prohibited from the trial

10. Psychotherapy including cognitive behavioral therapy (CBT), or dialectical behavioral therapy (DBT) started within 90 days of screening or planned during the study.

    PLEASE NOTE: on-going psychotherapy started 90 days or more before screening may be continued at the pre-screen level of therapy (no change in type of therapy or frequency of visits).

11. Unstable or active medical condition(s) which in the opinion of the investigator would jeopardize the subject's safety or interfere with participation of the study or confound evaluation of efficacy or safety.
12. Current diagnosis of unstable hypothyroidism
13. Females who are pregnant, nursing, or planning a pregnancy during the study or believe they may be pregnant at Screening or Baseline
14. Participation in another investigative trial within 30 days of screening
15. Subject previously treated with the use of a similar psychotropic genetic testing assay
16. Subject tests positive for illicit drug use on the urine drug screen (UDS) at the screen visit (including Marijuana where legal)*

    *In very exceptional cases, subjects with a positive UDS may be allowed in the study after approval by the sponsor.

5 SUBJECT ENROLLMENT

Investigative sites will recruit the subjects. If a patient agrees to meet with the research team, the study team will speak with the patient and start the informed consent process.

The informed consent process begins with an assessment of the patient's ability to give informed consent. Clinician investigators will use their clinical judgment to make this determination. Family members or caregivers should be encouraged to be involved in the consent process and/or follow-up visits as appropriate. All aspects of the study, including genetic testing, medications, risks and benefits, will be explained to the patient in detail. Patients will have the study thoroughly explained and any questions will be answered. Only when patients are fully informed about the study, will they be asked to sign the informed consent document. Documentation about the subject's capacity to consent for the study and detailed notes about the consenting process will be placed into the subject's research chart.

At the Screening visit, site staff will log on to IWRS to register the subject and obtain a unique subject number that will serve as the subject's identification number on all study documents and case report forms.

After written informed consent and registration in IWRS, subjects will undergo screening procedures to determine eligibility for the study.

Eligible subjects will be randomized in a 1:1 ratio to receive Assay-Guided Treatment (AGT) or Treatment as Usual (TAU). Randomization will be stratified by site, using a variable block size randomization to minimize bias. Randomization will be completed via IWRS during the Baseline visit, after Screening and Baseline inclusion/exclusion criteria have been satisfied, including the SIGH-D-17 and C-SSRS Baseline assessments.

Each subject randomized will continue using the unique study identification number received at Screening which will be used on all study documentation and case report forms. The Genecept Assay ™ results for subjects randomized to the AGT arm will be available via a secure portal to the treating investigator and will be provided upon completion of successful randomization in the IWRS system. Genecept Assay ™ results will be made available to the treating investigator for every subject upon completion of the Week 8 visit.

6 STUDY PROCEDURES

6.1 Genetic Analysis and Results

The Genecept Assay ™ is a commercially available test. At the time of protocol finalization, the assay has been utilized for approximately 40,000 patients in standard care settings. Genomind will distribute a limited number of assay kits to the investigational sites prior to the Site Initiation Visit. Sites will be instructed to account for the assay kit inventory for the duration of the study. Study monitors will periodically review inventory during site visits. The subject chart should clearly indicate which assay kit number was utilized for DNA collection. The Genecept Assay ™ will be used only for subjects in this study, not for non-study patients.

At the Screening visit and after initial eligibility has been established, subjects will provide a buccal sample, which will be used for the Genomind Genecept Assay ™. DNA collection instructions will be provided to sites. Subjects will perform the DNA collection (mouth swab) under the supervision of study staff. DNA samples will be shipped to the laboratory for analysis on the day of collection. In the event of difficulty extracting DNA from the original sample, a second sample may need to be obtained from the subject.

Before the study is initiated, training will be provided to all participating treating investigators on the interpretation of genetic testing results and on the relevance of each genetic variant to pharmacotherapy. The training will include the role of pharmacogenetics and the pharmacodynamic and pharmacokinetic relevance of each gene variation with respect to pharmacotherapy with psychotropic medications. In addition, treating investigators will have access to experts from Genomind regarding interpretation of the pharmacogenetic testing results. Measures will be taken to keep Genomind expert consultations confidential (e.g., consults are not to be discussed, experts have no interactions with study staff). Treatment recommendations will not occur during these consultations.

Upon randomization, after all screening and baseline assessments have been completed and test results have been reviewed by the treating investigator, the Genecept Assay ™ results will be made available if a subject is randomized to the AGT group. The treating investigator will retrieve the randomization assignment and assay result via a secured portal. All treatment decisions and clinically indicated follow-up activities will be the responsibility of the treating investigator. A back-up treating investigator may perform this responsibility if necessary. For the AGT group, the Genecept Assay ™ report will guide treating investigator's treatment decisions. For the TAU group, pharmacotherapy will

be conducted according to usual clinical practice, e.g., continuing the current drug regimen, adjusting dosage, switching to a different drug, or adding a different drug. The treating investigator will complete a questionnaire Clinical Decision Survey prior and after receiving assay results, assessing the pharmacotherapeutic decision-making process for each subject.

Upon completion of Week 8 and registration of the completed visit in IWRS or 8 weeks after randomization for subjects that discontinued early, assay results for subjects in the TAU group will be available via a secure portal. The treating investigator will discuss the Genecept Assay ™ test results with every subject at the completion of study visit Week 8 or 8 weeks after randomization for subjects that discontinued early and are willing to return to the site.

6.2 Study Assessments

The following information will be collected. See **Schedule of Visits and Procedures** for a visit overview. See **Attachments** section for detailed descriptions of assessments.

1. Demographic Data: (age, sex, race, ethnicity, weight, height, BMI, marital status)
2. Psychiatric History: current or previous mental illnesses, number/duration of episodes, number of prior psychiatric admissions, past psychiatric medications.
3. Medical History: current and previous illnesses up to 1 year prior to screening. Investigators may use laboratory evaluations, as judged to be necessary, to evaluate current medical status.
4. Columbia Suicide Severity Rating Scale (C-SSRS)
5. Antidepressant Treatment Response Questionnaire (ATRQ)
6. The M.I.N.I. International Neuropsychiatric Interview 7.0 (MINI)
7. On-site urine drug screen evaluation to test for presence of substances of abuse or dependency
8. Structured Interview Guide for the Hamilton Depression Rating Scale – 17 Item Version (SIGH-D-17) performed by blinded rater (see Section 6.3)
9. Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16)
10. Clinical Global Impression – Severity / Improvement (CGI-S/I)
11. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)
12. Patient Rated Inventory of Side Effects (PRISE)
13. Adverse Events (AE)

14. Concomitant Medications: All current medications for any indication taken by the subject will be recorded. Concomitant medication is defined as any medication taken between Screening and Week 8 visit. All herbal medications, vitamin preparations and other supplements should also be recorded. MDD Treatment Medications: All medications taken for the treatment of MDD and all medication changes during the study should be recorded, including reason for change.

15. DNA Sample Collection

16. Clinical Decision Survey / Pre-Result & Post-Result

6.3 Raters

Rater selection, training and oversight will be implemented to maximize the accuracy of outcome measures for detecting between-group differences on study endpoints. Rater training will be provided to investigators and study staff prior to the completion of any assessments. Investigators and study staff will be trained on the processes and best practices of administering patient reported outcomes.

Blinded rater training for the HAM-D17 will be of particular importance because of its relevance to the primary endpoint (see Section 3.3. Blinding). Structured blinded assessment of the SIGH-D-17 will be conducted by site raters who have undergone a rater pre-qualification, training and certification process by an independent rater-training company. Raters will be trained and certified prior to administering their first screening assessment. Rater's performance will be monitored throughout the study according to pre-determined algorithms. Blinded raters will not be made aware of the subject's treatment assignment for the duration of the study. Blinded raters will administer only the SIGH-D-17 scale. Administration of the SIGH-D-17 will be done utilizing a tablet-based system. All interviews will be audio-recorded. Central rater clinicians will review select audio recordings and electronic source SIGH-D-17 assessments (including scores and source notes). Central rater clinicians will provide collaborative feedback to site raters regarding the general administration of the interview, item score differences between the site rater and the central rater clinician, and a rationale for the clinician scoring. Scoring errors will be addressed with the site rater and corrected as deemed appropriate by the rater. The initial (without central rater review) SIGH-D-17 score obtained at Baseline will be used to determine study eligibility.

6.4 Procedures by Study Visit

6.4.1 Screening (7 days, may be extended by up to 5 days)

1. Informed Consent

2. Demographics, Medical & Psychiatric History

3. Inclusion/Exclusion Criteria

4. The M.I.N.I. International Neuropsychiatric Interview 7.0 (MINI)

5. Antidepressant Treatment Response Questionnaire (ATRQ)
6. Columbia Suicide Severity Rating Scale (C-SSRS)
7. Structured Interview Guide for the Hamilton Depression Rating Scale – 17 Item Version (SIGH-D-17)
8. Adverse Events
9. On-site urine drug screen evaluation
10. Concomitant Medications / MDD Treatment Medications
11. Genecept Assay ™ DNA Collection

6.4.2 Baseline / Day 0

1. Structured Interview Guide for the Hamilton Depression Rating Scale – 17 Item Version (SIGH-D-17)
2. Columbia Suicide Severity Rating Scale (C-SSRS)
3. Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16)
4. Clinical Global Impression – Severity (CGI-S)
5. Concomitant Medications / MDD Treatment Medications
6. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)
7. Patient Rated Inventory of Side Effects (PRISE)
8. Adverse Events
9. Randomization
10. Clinical Decision Survey – Pre-Result
11. Genecept Assay ™ Results Retrieval (AGT Group)
12. Genecept Assay ™ Results Review (consultation with Genomind as needed)
13. MDD Treatment Initiation/Adjustment
14. Clinical Decision Survey – Post-Result

6.4.3 Week 2, 4, 6, and 8 (+/- 3 days, Week 8: -5/+7 days)

1. Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D-17)
2. Columbia Suicide Severity Rating Scale (C-SSRS)
3. Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16)
4. Clinical Global Impression – Severity / Improvement (CGI-S/I)
5. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)
6. Patient Rated Inventory of Side Effects (PRISE)
7. Adverse Events
8. Concomitant Medications / MDD Treatment Medications (if changes)
9. Week 8 only: Disclosure of treatment group & discussion of assay results (investigator-subject)

6.4.4 Unscheduled Visits

Additional visits may be conducted as necessary to ensure the safety and well-being of subjects during the study period. Case report forms should be completed for each unscheduled visit including reason for visit and adverse events (as applicable).

6.4.5 Missing Visits

Investigators should minimize the occurrence of missed study visits. Flexibility of scheduling visits within protocol windows and good communication with subjects (e.g., providing a predicted visit schedule, reminder calls or emails, etc.) are to be implemented. In case of missed visits, reason for the missed visit must be documented in the eCRF.

6.5 Screen Failures

If subjects do not meet inclusion criteria or meet exclusion criteria at any time prior to randomization, they will be considered screen failures. Screen failures must be registered in IWRS; demographic information and reason(s) for screen failure (record all applicable reasons) must be recorded. In select cases, a screen failure subject might be eligible for re-screening at a later point ($\geq$ 6 weeks) during the study, for one time only, after approval by the study sponsor has been obtained.

6.6 Early Discontinuation and Potential Missing Data Remediation

Subjects may voluntarily withdraw from the study at any time. Early discontinuation must be registered in IWRS; reason for early discontinuation must be obtained and recorded in the eCRF. If feasible, the investigator should make his/her best efforts to have the subject return for Week 8 study assessments.

At a minimum, Week 8 SIGH-D-17 assessment, C-SSRS assessment and adverse event collection should be attempted. To maintain blinding, the disclosure of treatment group and discussion of assay results will only occur at the Week 8 visit or 8 weeks after randomization for subjects that discontinued early.

6.7 Early Termination of Study

The study may be terminated by the site investigator at his/her study site at any time. Genomind may terminate the study (and/or the study site) for any reason with appropriate notification.

6.8 Safety Evaluation

Safety measures will include adverse event collection and C-SSRS administration at all visits, and medication side effect reporting collected by FIBSER and PRISE at Baseline (Day 0), Week 2, 4, 6 and 8 visits and at any unscheduled visits or during other contacts with the subject, as applicable.

7 ADVERSE EVENTS

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment (ICH, E2A). Adverse events will be assessed regardless of administration of a pharmaceutical product from time of informed consent signing until completion of study.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH, E2A). Examples of AEs are as follows:

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study
- Any increase in severity or frequency of symptomatology of pre-existing diseases.
- Any clinically relevant abnormality in laboratory values, ECGs or physical findings that occurs during the study.

7.1.1 Documenting Adverse Events

At each visit, subjects are to be queried regarding any AEs that have occurred since the previous visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question. Study site personnel will then record all pertinent information in the subject's eCRF.

At each study visit (and during any communication with a subject or subject representative occurring outside a defined study visit), all AEs reported by the subject or subject's representative or observed or otherwise identified by the treating investigator or other study personnel must be documented. Ongoing adverse events must be followed-up and updated in the eCRF, as appropriate, until the subject completes the study.

For every AE, the investigator must:

- Provide an assessment of the severity, causal relationship to psychotropic medication treatment, and seriousness of the event.
- Document all actions taken in regard to the AE.
- Detail any other treatment measures taken for the AE.

7.1.2 Assessing Severity

The treating investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: The AE was an annoyance to the subject but did not further hinder baseline functioning; the AE may have been intermittent or continuous.

Moderate: The AE caused the subject to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE.

Severe: The AE caused the subject to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE.

7.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that is/causes: (ICH, E2A):

- Life-threatening
- Death

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on 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 seizures that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. However, emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening, other serious [medically important] event).
- Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization are not reportable as serious adverse events. This should be clearly documented in the subject's source document.

7.2.1 Reporting Requirements for Serious Adverse Events

Serious adverse events (SAEs) should be reported to Genomind no later than 48 hours after learning of the event. Genomind should be notified by email using the serious adverse event form. The designated email contact information can be found on the serious adverse event form cover page. All subjects with a serious adverse event must be followed-up and the outcomes reported to the sponsor. The investigator must supply Genomind with any additional requested information. All relevant data and updates will be documented on the appropriate eCRF pages.

7.2.2 Reporting to the IRB

The investigator should promptly report to his/her Institutional Review Board (IRB) all SAEs per governing IRB requirements.

7.3 Pregnancy

Study personnel must report the occurrence of a pregnancy to the sponsor. A pregnancy is not considered an AE or SAE unless complications associated therewith qualify the event as such.

7.4 Investigator Alert Notification

Genomind or its designee will promptly inform all investigators participating in this clinical trial of any new safety information that may be relevant to the utilization of the Genecept Assay ™ results.

7.5 General Safety Monitoring

Genomind will meet periodically as deemed appropriate to review safety data. These data will include but are not limited to:

- AEs that result in an early study withdrawal

- SAEs

Appropriate action, if needed, will be taken based upon this review and in consultation with the clinical team.

8 STATISTICAL CONSIDERATIONS

8.1 General

Note: *The Statistical Considerations which follow generally apply to the Main Study analysis and also the add-on Exploratory Elderly MDD Study analysis. Important exceptions will be noted in the text below. A SAP for the Exploratory Elderly MDD Study, incorporated in the overall SAP (V 3.0), will fully detail the statistical approaches. The SAP (V 3.0) will be finalized, signed, and approved by the Sponsor before the Elderly MDD Study is unblinded.*

Summarizations will be provided in tables and figures. Safety and efficacy variables will be summarized by visit using descriptive statistics. For continuous variables, this will include the number of non-missing values, mean, standard deviation (SD) or standard error of the mean, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

Unless otherwise stated, the significance level for statistical tests will be two-sided, alpha=0.05, with no adjustment for multiple comparisons

The statistical analysis plans (SAPs) for the Main Study and Exploratory Elderly MDD Study will document the technical details of statistical methods, supplementing the key analysis details in this protocol. The Main Study SAP will be finalized (V 2.0), signed, and approved by the Sponsor before the first subject is randomized. If necessary, during the study and before unblinding the Main Study database this SAP may be amended using the same approval process. SAP amendments will clearly document and justify changes, and be completed as early as possible, and in any case prior to unblinding the study database. Revisions in statistical approaches after unblinding (such as performing sensitivity analyses suggested by the data) will be discussed in the CSR Statistical Methods section.

Pooled Investigative Sites: For all statistical analyses, sites with few subjects (< 7 subjects) will be pooled into larger "sites" based on number enrolled. "Investigative site" in all statistical analyses will refer to "sites" as pooled. Details of the pooling algorithm will be in the SAP. Note: the pooling algorithm will be applied separately to the Main Study and the Exploratory Elderly MDD Study.

Missing data: As underscored in Sections 9.4.2 and 9.8, reducing the level of missing data in this trial will allow more interpretable and powerful efficacy analyses, and maximize the sensitivity of the trial with the given sample size. Over recent years there has been growing awareness of the impact of missing data, with resulting improvement of statistical approaches to handling missing data[37-40]. However, it has also become apparent that statistical analyses can patch but not solve the loss of interpretability and credibility from missing data[41]. Most crucial is to first reduce missing data as much as possible. This has spurred development of straightforward changes in trial conduct with potential to

dramatically reduce the dropout rate[42-44]. The influential report of the 2010 National Research Council Missing Data Panel[45], superbly summarized expert consensus on handling missing data, including measures to reduce dropouts and missing data:

1) Select investigators who have a good track record with respect to enrolling and following participants and collecting complete data in previous trials.
2) Set acceptable target rates for missing data and monitor the progress of the trial with respect to these targets.
3) Provide monetary and nonmonetary incentives to investigators and participants for completeness of data collection, as long as they meet rigorous ethical requirements.
4) Limit the burden and inconvenience of data collection on the participants, and make the study experience as positive as possible.
5) Train investigators and study staff that keeping participants in the trial until the end is important, regardless of whether they continue to receive the assigned treatment. Convey this information to study participants.
6) Collect information from participants regarding the likelihood that they will drop out, and use this information to attempt to reduce the incidence of dropout.
7) Keep contact information for participants up to date.

These recommendations have been endorsed by clinical trialists, editorial staff of major medical journals, and regulatory agencies[46-48]. Trials managed consistent with the NRC recommendations have indeed shown important reduction in dropout rate.

This trial will incorporate as many of these recommendations as possible. All analyses will be implemented using SAS software, version 9.3 or later.

8.2 Efficacy Analysis Estimands

This trial is a comparison of outcomes between two treatment strategies, evaluated at 8 weeks. For practical interpretation, this implies the statistical analyses should estimate and test the difference in Week 8 outcomes for all subjects, irrespective of attrition or compliance. [This may also be described as following the Intent to Treat (ITT) principle, but there is confusion about the use of this term when there is missing data, and ITT terminology will not be used further here.]. Specifying the "estimands") (what is being estimated), aligned with the study purpose, is the basis for the formal statistical methods which follow.

8.2.1 Primary Efficacy: AGT vs TAU

-Difference at Week 8 in SIGH-D-17 mean change from baseline, for all randomized subjects.

8.2.1 Secondary Efficacy: AGT vs TAU

-Difference at Week 8 in QIDS-SR16 mean change from baseline, for all randomized subjects.

-Difference at Week 8 in mean % improvement from baseline in SIGH-D-17 scores, for all randomized subjects.

-Difference at Week 8 in mean % improvement from baseline in QIDS-SR16 scores, for all randomized subjects.

-Difference in % treatment responders at Week 8, for all randomized subjects. Treatment response will be defined in 3 different ways:

≥ 50% reduction of SIGH-D-17 from baseline for blinded rater assessment

≥ 50% reduction of QIDS-SR16 from baseline for subject-rated assessment

Score of ≤ 3 on the CGI-I from baseline for the unblinded clinician assessment

-Difference in % treatment remitters at Week 8, for all randomized subjects. Remission is defined for the SIGH-D-17 and the QIDS-SR16:

Score of ≤ 7 on the SIGH-D-17 from baseline for blinded rater assessment

Score of ≤ 5 on the QIDS-SR16 from baseline for subject-rated assessment.

-Difference at Week 8 in Clinical Global Impression – Improvement (CGI-I), % scores, for all randomized subjects.

8.3 Safety Endpoints

Treatment Emergent Adverse Events (TEAEs)

Frequency and severity of medication-induced side effects based on collection of FIBSER, PRISE and Adverse Events

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

8.4 Other Endpoints

Clinical Decision Survey Findings

Pre-Result: Clinician intended treatment prior to receiving assay results

Post-Result (AGT only): Clinician rating of confidence in making treatment decisions, treatment plan and gene results which influenced treatment plan after results are received.

8.5 Analysis Datasets

All Randomized Set: All randomized subjects.

Full Analysis Set (FAS): All randomized subjects with a post-baseline SIGH-D-17 assessment.

Safety Analysis Set (SAF): All randomized subjects who complete the (post-randomization) baseline appointment with the treating investigator, i.e., start AGT or TAU treatment.

The **FAS** will be the primary dataset for all efficacy analyses. Note that, as described above, the desired estimands are based on all randomized patients. It is anticipated the percent of patients missing post-baseline SIGH-D-17 will be small, and thus the FAS analyses are valid, and may be done with fewer statistical assumptions.

The **All Randomized Set** data will be listed, and the reason for dropout of patients without post-baseline, will particularly be reviewed. If the number of FAS subjects is less than 95% of the All Randomized Set, the primary and secondary analyses will be conducted on this dataset as sensitivity analyses.

9 STATISTICAL PROCEDURES

Note: *The Statistical Procedures given here are for to the Main Study. The Statistical Procedures for the MDD the add-on Exploratory Elderly MDD Study will follow the same outline, but statistical methods will be primarily descriptive, and statistical analyses will be simpler, as is appropriate in light of the much smaller sample size.*

Important changes in Elderly Study statistical procedures (from the Main Study) will be noted in this document. A SAP for the Exploratory Elderly MDD Study, incorporated in the overall SAP (V 3.0), will fully detail the statistical procedures. The SAP (V 3.0) will be finalized, signed, and approved by the Sponsor before the Elderly MDD Study is unblinded.

9.1 Subject Disposition

The number of subjects will be summarized by treatment group, country, and study center for the three analysis datasets. Randomized subjects excluded from the SAF and FAS populations will be listed. The number and percentage of subjects per treatment group who prematurely discontinued treatment will be presented by visit and overall, by treatment group, for SAF population. The number and percentage of subjects per treatment group who prematurely discontinued from the study will be presented by visit and overall, for the SAF and FAS populations. The coded Reason for premature discontinuation of treatment and discontinuation from the study will be summarized (number and percentage) by treatment group for the SAF Population. The verbatim Reason for Disposition and Further Info fields will be listed. The coded and verbatim Reason for Discontinuation may be used in sensitivity analyses for the primary efficacy analysis.

9.2 Demographic and Pretreatment Characteristics

Demographics (age, race, sex, weight, height, and BMI), disease severity [including SIGH-D-17, QIDS-SR16], previous depression treatment, and other screening/baseline visit assessments will be summarized by visit (Screening, Baseline) and treatment group using descriptive statistics.

9.3 Depression Treatment and Concomitant Medications

9.3.1 Depression Drug Treatment

On-study depression drugs (taken between Day 0 and Week 8 visit) will be summarized by the number and proportion of subjects in each treatment group receiving each medication within each therapeutic class, for the Safety Population. Multiple medication use by a subject will only be counted once. Treatment Exposure (days) to on-study depression drugs (days) from Day 0 to Week 8 will be summarized for the Safety Population by treatment group and drug class. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented. For each drug, overall mean daily dose and final daily dose will be listed and summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum).

9.3.2 Concomitant Medications

Non-study depression drugs and all other concomitant medications (medication taken between Day 0 and Week 8 visit) use will be summarized by the number and proportion of subjects in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a subject will only be counted once.

9.4 Efficacy Analyses

9.4.1 Primary Endpoint Analyses

A Mixed Model Repeated Measures (MMRM) analysis will test whether AGT shows greater improvement in SIGH-D-17 at Week 8 than TAU. Formally, the analysis tests for a difference in mean change from baseline to Week 8 between the treatment groups, in the FAS population. Compared to analyzing All Randomized subjects, this excludes subjects who don't return after the Baseline Visit, which is generally acceptable if this excluded group is small.

In the MMRM model, the dependent variable is the change in SIGH-D-17 from baseline at each of the scheduled visits Week 2, Week 4, Week 6 and Week 8. The model will include the fixed effect continuous factor baseline SIGH-D-17, and fixed effect categorical factors (pooled) investigative site, treatment group (AGT and TAU; 2 levels), visit (Weeks 2, 4, 6 and 8; 4 levels), and treatment x visit interaction. The interaction term will remain in the model regardless of statistical significance. An unstructured covariance pattern will be used to estimate the variance-covariance matrix of the within-subject repeated measures (i.e., model within-subject errors). The variance-covariance matrix will be estimated across both treatment arms. The fixed effects will be estimated by the method of restricted maximum likelihood estimation using the Newton-Raphson algorithm, based on all available data. The denominator degrees of freedom and adjustment of standard errors will use the Kenward-Roger method.

AGT and TAU mean change in SIGH-D-17 at Week 8 will be estimated and tested utilizing the least squares (LS) means from the treatment x visit interaction in the MMRM model. The primary analysis

will test the difference (contrast) between the Week 8 LS means, at two-sided significance 0.05. The test p-value and the 95% CI for the difference in Week 8 means will be presented. Comparisons between the AGT and TAU means at Week 2, Week 4 and Week 6 will also be generated. Diagnostics for outliers, non-normality and other model assumptions will be run. Significant findings will be followed up with appropriate sensitivity analyses.

To allow comparison with previous SIGH-D-17 studies, two supportive analyses of the primary endpoint will be produced. Each will be an Analysis of Covariance (ANCOVA):

1) Last Observation Carried Forward (LOCF) analysis, and

2) Observed Cases (OC) analysis.

Each ANCOVA will include baseline SIGH-D-17, Pooled Investigative Site and Treatment Group as the independent variables in the model. The dependent variable for the LOCF analysis will be last available SIGH-D-17 change from baseline. The dependent variable for the OC analysis will be the Week 8 SIGH-D-17 score, with no imputation of missing Week 8 scores.

Note: *The Exploratory Elderly MDD Study primary analysis will test the Difference at Week 8 in mean SIGH-D-17 change from baseline in a Last Observation Carried Forward ANCOVA, adjusting for baseline SIGH-D-17 and pooled site, in the FAS set. Descriptive statistics and confidence intervals will also be calculated. The Treatment x Pooled Site and Treatment x Baseline SIGH-D-17 interaction tests, as well as diagnostics for outliers, non-normality and other model assumptions will be run, and followed up, as appropriate.*

9.4.2 Missing Data

The MMRM analysis may be biased unless the missing Week 8 SIGH-D-17 values are Missing at Random (MAR). This is because the MMRM, as well as LOCF and OC ANCOVA analyses assume the unobserved missing data has the same behavior as the observed data for the same treatment group and covariates. [For example, if a computer failure causes loss of some Week 8 SIGH-D-17 scores, this missing data should be MAR: the missing data is not informative about the actual Week 8 SIGH-D-17 scores, and the missing scores may be predicted from available SIGH-D-17 scores. Contrarily, if scores are missing due to subject dropout resulting from , (un-measured) worsening depression, then these missing scores would likely be Not Missing at Random (NMAR)].

To address this issue, if there is more than 10% missing Week 8 SIGH-D-17 scores, sensitivity analyses using alternate approaches to handling missing data will be explored. The sensitivity analyses will incorporate a range of plausible NMAR assumptions. Further technical detail will be given in the SAP.

9.4.3 Subgroup Analyses

Consistency of AGT vs TAU treatment effect on SIGH-D-17 will be assessed across various subgroup factors described below, by evaluating the treatment by subgroup interaction in the MMRM model. If

there is evidence of inconsistency of treatment effect (i.e., p-value <0.10 for interaction test), further analyses may be performed.

Subgroup factor	Subgroup categorization
Age group	< median age, ≥ median age
Gender	Male, Female
Race	White, Non-white
Baseline SIGH-D-17*	< 24, ≥ 24 Moderate, Severe MDD
Previous failed drug treatments	1, 2, 3 Previous failed, adequate trials of antidepressants in the current depressive episode
Investigative Site	Pooled sites.

Graphical presentations of the primary efficacy subgroup results will also be provided.

Note: *For the Exploratory Elderly MDD Study, subgroup analyses will utilize the Treatment x Subgroup interaction in the ANCOVA LOCF model. Subgroups will include Gender, Baseline SIGH-D-17 and Pooled Site.*

9.4.4 Analyses of Key Secondary Efficacy Variables

The test for the following secondary continuous variables will use the same MMRM model in the FAS population, outlined for the primary analysis:

- Difference at Week 8 in QIDS-SR16 mean change from baseline.
- Difference at Week 8 in mean % improvement from baseline in SIGH-D-17 scores.
- Difference at Week 8 in mean % improvement from baseline in QIDS-SR16 scores.
- Difference at Week 8 in mean change of CGI-S.

Note: *For the Exploratory Elderly MDD Study, the QIDS-SR16 mean change from baseline will be tested and summarized using the ANCOVA methodology described for the primary analysis. The remaining secondary efficacy variables will be descriptively summarized.*

The Mantel-Haenszel method, stratified by investigative site, in the FAS population, will test AGT vs TAU estimates based on categorical variables:

- Difference in % treatment responders at Week 8, done separately for SIGH-D-17, QIDS-SR16 and CGI-I. Treatment response is defined as ≥ 50% reduction of SIGH-D-17 from baseline to Week 8 for blinded rater assessment, ≥ 50% reduction of QIDS-SR16 from baseline to Week 8 for subject-

rated assessment, score of ≤ 3 on the CGI-I from baseline to Week 8 for the unblinded clinician assessment. If Treatment Response is missing at Week 8, the subject will be considered a Week 8 treatment non-responder. The two-sided p-value, estimated odds ratio and 95% CI for the odds ratio will be computed.

- Difference in % treatment remitters, done separately for SIGH-D-17 and QIDS-SR16, at Week 8. Remission is defined as score of ≤ 7 on the SIGH-D-17 from baseline to Week 8 for blinded rater assessment, score of ≤ 5 on the QIDS-SR16 from baseline to Week 8 for subject-rated assessment. If Treatment Remission is missing at Week 8, the subject will considered a Week 8 treatment non-responder. The two-sided p-value, estimated odds ratio and 95% CI for the odds ratio will be computed

- Difference at Week 8 in Clinical Global Impression – Improvement (CGI-I)

9.5 Safety Analyses

All safety analyses will be performed on the SAF dataset.

- Adverse events

The analysis will focus on the TEAEs. TEAEs will be summarized and tabulated according to body system and frequency for each treatment group. Separate tabulations of AEs depending on seriousness, severity, possible relationship to study medication, and outcome ”death” will be given.

- FIBSER, PRISE

The results from the FIBSER and PRISE scales will be summarized descriptively.

Note: *Safety data for the MDD Elderly MDD Study will be descriptively summarized in the SAF.*

9.6 Other Analyses

All other endpoints will be descriptively summarized, including the Pre-Result and Post-Result Clinical Decision Survey Findings.

9.7 Interim Analysis

No interim analysis is planned for this study.

9.8 Sample Size Justification

Sample size is calculated for the primary endpoint, improvement from baseline to eight weeks in the SIGH-D-17 of subjects with Major Depressive Disease.

As there are few studies comparing MDD AGT vs TAU, information to guide sample size is limited.

Nevertheless, three controlled MDD trials of AGT vs TAU[49-51]provide some quantitative basis for sample size. All are single center, 8-10 weeks in duration, measured SIGH-D-17, and utilized the AssureRx assay battery. For each study an approximate SIGH-D-17 Delta and SD were approximated from tables and figures in the report publication. Delta is the between group difference in mean SIGH-D-17 change and SD is the assumed constant standard deviation of the individual subject's change in HAMD). Cohen's d = Delta/SD was further calculated. Brief summaries of the three studies follow:

1) Hall-Flavin DK et al 2012, *Using a pharmacogenomic algorithm to guide the treatment of depression*[49]. This was the pilot study for next trial in this list: non-randomized, open, single center, comparison of pharmacogenomic guided treatment vs usual treatment for 8 weeks. N=51, 44 analyzed. Dropout rate = 14%. Approximate Delta and SD = 3.5 and 6.0. Approximate delta/SD ratio= 0.58

2) Hall-Flavin DK et al 2013.Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting[50]. Non-randomized, open, single center, comparison of pharmacogenomic guided treatment vs usual treatment for 8 weeks. N=227, 165 analyzed. The dropout rate = (27%) with 37% AGT vs 18% TAU dropout. The approximate delta and SD are 3.1 and 7.2. Approximate delta/SD ratio= 0.43

3) Winner JG et al 2013.A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder[51]. Pilot study, randomized, single center, blinded subject and rater, comparison of pharmacogenomic guided treatment vs usual treatment for 10 weeks. (Although described as double-blind, the Winner study does not meet the minimum conventional double-blind standard – blinded investigator and subject) N=51, 49 analyzed. The approximate Week 8 delta/SD ratio=0.47. This ratio was extrapolated from the % SIGH-D-17 improvement results, and is likely an overestimate of the mean SIGH-D-17 improvement ratio.

The three studies are consistent with one another. The small pilot studies show evidence of efficacy, but are too small for reliable inference. Study 1 greatest observed efficacy (Cohen's d =0.58). The second pilot study (Study 3), is more rigorous, adding randomization and rater/subject blinding, with extrapolated Cohen's d = 0.47, not statistically significant.

The largest study (Study 2) shows a somewhat lower Cohen's d (0.43), a more reliable result due to the much larger sample size and the added sensitivity analyses to assess robustness. Accepting that there remains potential bias due to the non-randomized, open design, this study result was used as the best available basis for sample size calculation.

The sample size is calculated for the two-sided alpha=0.05, 90% power test of two independent means of improvement in SIGH-D-17. In this case the sample size depends only on the postulated Cohen's d, and the % dropouts. Note this should be a conservative estimation of sample size, as the actual analysis will use a more efficient MMRM method. However, this conservatism is balanced by the potential underestimation of needed sample size due to design bias in the reference study.

Using the Trial 2 observed difference in SIGH-D-17 improvement and variability, with resulting Cohen's d=0.43, the resulting sample size is 115 per group, with no dropouts. If we assume the dropout rate somewhat less than the reference (23% vs 27% reference), then with the conventional dropout correction, the needed sample size per group is 150, or 300 total randomized subjects. The table below summarizes the design properties of this size study, under varying assumptions for delta, power and % missing Week 8 SIGH-D-17 assessment. The statistical testing significance level is two-sided alpha < 0.05, and the SD is assumed to be the same (7.2).

Detectible* Delta for Varying Power and Missing Data Assumptions

Total Sample Size	Subject SD	Delta	Power	% Missing Week 8
300	7.2	3.09	90%	23%
300	7.2	2.67	80%	23%
300	7.2	2.94	90%	15%
300	7.2	2.54	80%	15%
300	7.2	2.85	90%	10%
300	7.2	2.46	80%	10%
300	7.2	2.70	90%	0%
300	7.2	2.34	80%	0%

*Detectible delta is the smallest postulated "true" difference between means for which 80% (or 90%) of trials would be statistically significant with the given % missing Week 8 data.

All sample size calculations used Stata Version 13 software.

As reiterated above, the reference study is not a definitive foundation for sample size calculation. However, it may be expected the following would hold:

1) The base planning SIGH-D-17 delta, at 3.1, is a high bar for an active vs active treatment depression trial. Commonly, the planning delta for placebo controlled depression trials is 3.0 (SIGH-D-17 units) and active vs active studies can expect delta of 1.5 or less and may often designed as non-inferiority studies. It could be argued that a planning delta should be 2.5 or less.
2) We expect the SD for this study should be less than the reference study. SIGH-D-17 will be assessed by blinded, trained SIGH-D-17 raters, centrally monitored by an independent group.

This reduces bias and improves precision, and should result in the primary endpoint being more accurate, with a smaller SD. A reduction of the SD by 15% seems reasonable (SD=6.12).

3) We expect the 8-week dropout rate will be considerably less than the reference, as well as the nominal 23% used in the base sample size calculation. As discussed in Section 8.1, as this trial will institute measures to reduce missing data, consistent with the recommendations by the 2010 NRC Missing Data panel. This, combined with the observed lower dropout rate in active vs active trials, suggests a target of 10% dropouts is realistic.

Assuming the improved rigor of the trial conduct reduces the SD by 15% and the dropout rate to 10%, then with 300 randomized subjects and a 0.05 2-sided test, the "detectable delta" is more realistic: 2.42 with 90% power, and 2.09 with 80% power.

Note: *For the Exploratory Elderly MDD Study, the sample size (n=70) was not formally calculated, as it is an exploratory study.*

10 STORAGE OF ASSAY KITS

The Genecept Assay ™ kits will be stored securely at sites and will be accessible to authorized study personnel only. Kits should be stored at room temperature. Each kit will be labeled with a serial number, which upon utilization, will be recorded in the subject's study chart. Investigators are responsible to keep account of all used and unused assay kits. Routine accountability of assays will be performed by the site monitor. Upon completion of the study, the sponsor will advise sites regarding the disposal of assay kits.

11 STUDY DOCUMENTATION

11.1 Electronic Case Report Form (eCRF)

11.1.1 eCRF Documents

Study data obtained in the course of the clinical trial will be recorded in eCRF. Access for data entry to the eCRF for study staff members will be provided by the sponsor or its designee. The eCRF will contain information identifying the protocol number, study site, and subject identification number.

11.1.2 Recording Data in eCRF

eCRFs are used to record clinical trial data and as such are a key component of the trial and are the basis from which the study results are tabulated and final reports are written. Data recorded in the eCRFs must be supported by information captured on a source document. eCRFs should be completed within 72 hours of the subject's study visit.

11.1.3 Source Documents and the Study Data File

Regulations (21 CFR 312.62(b)) require "an investigator … to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case

histories include the case report forms and supporting data including, for example, progress notes of the physician, the individual's hospital charts, and nurses' notes. The case history for each individual will document that informed consent was obtained prior to participation in the study." Such case histories, as well as original copies of laboratory data, test reports, instrument- or computer-generated data, and working copies (if used) of the eCRFs, and narrative reports or progress notes of subject study visits, subject correspondence, and records of interim (unscheduled) subject contacts are collectively referred to as "source documents."

Source documents must be kept on file by the investigator together with the remainder of the study files because of the potential for errors and inaccuracies to occur in data entry into the eCRFs, as well as potential inaccessibility of medical records. Availability of source documentation is required by the sponsor to confirm the integrity of the study data. The study data file must contain documentation that informed consent was obtained prior to participation in the study. The eCRFs must be retained in the appropriate electronic medium for record retention. Review of source documentation is an integral part of study monitoring visits. eCRFs and source documents must be available at all times for review by authorized representatives of the sponsor or potentially regulatory agencies.

11.1.4 Certification of Accuracy of Data

Final electronic signatures of the investigator must be affixed to all eCRFs upon completion of all data entry and prior to the eCRF being "locked" by data management.

11.1.5 Monitoring of Study Sites

Prior to any screening efforts, sponsor monitors or designee will conduct protocol training at each site during a Site Initiation Visit. Following the screening or enrollment of the first few subjects at each site, site monitoring visits will commence and be conducted periodically throughout the study. The purpose of site visits is to: 1) verify qualifications of site personnel and train on protocol requirements, 2) verify subject eligibility and informed consent process documentation, 3) complete source document verification and review eCRF completion, 4) review the investigator study file, 5) to review accountability of assay kits, 6) complete other monitoring tasks as applicable.

11.1.6 Retention of Records

The investigator must retain all records, including source documents and investigator copies of eCRFs, for a minimum of 2 years. In the event that the clinical research program is terminated by the sponsor, records must be retained for 2 years beyond the completion of the entire research program or its termination. Investigators should consult with the sponsor before discarding or destroying records. After destruction has been authorized by the sponsor, records must be destroyed in a manner to ensure confidentiality.

12 ETHICAL AND LEGAL ISSUES

12.1 GCP Statement

The study will be carried out according to the provision of Good Clinical Practices (GCP), the Declaration of Helsinki (2013) and the Code of Federal Regulations (CFR) as applicable.

12.1.1 Institutional Review Board

This clinical trial must be reviewed and approved by the IRB representing each participating institution prior to enrolling subjects and annually thereafter. Such IRBs must be appropriately constituted and meet all requirements as described in Part 56, Title 21 of the Code of Federal Regulations. The review must include both the protocol and the informed consent document for the trial. A copy of the Letter or Notice of Approval from the IRB must be received by the sponsor prior to the commencement of enrollment. The IRB membership list must be submitted to the sponsor or designee with the written IRB approval and updated lists, if applicable.

12.1.2 Protocol Adherence - Amendments

This protocol must be read thoroughly and the instructions must be followed exactly. Changes in the design or operation of the protocol, whether initiated at the study site or by the sponsor, must be incorporated into a Protocol Amendment. Such amendments will be reviewed and approved by the sponsor. All amendments that affect the conduct of the study or potentially affect subject welfare must also be reviewed and approved by the IRB at each applicable study site. Notice of such review and approval must be provided to the sponsor.

12.1.3 Required Documents

The investigator must provide to the sponsor or its representative the following documents before any subjects can be consented and screened (copies should be kept by the investigator in the investigator's regulatory document binder). Approval of the sponsor must be obtained before screening can commence.

1. Signed copy of Investigator Agreement (Section 17)
2. Executed Clinical Study Agreement (CSA)
3. Curriculum vitae of investigator and sub-investigators
4. Financial disclosure information for investigator and sub-investigators
5. Medical licenses for investigator and sub-investigators (as applicable)
6. IRB letter stating site approval, approval of informed consent document and approval of study materials, IRB Roster

7. Copy of the IRB-approved site-specific written informed consent document
8. Site Signature and Responsibility Log
9. Site Training Log

12.1.4 IRB Record Keeping

Records of the IRB review and approval of all documents pertaining to this trial (including annual IRB approval of ongoing studies) must be kept on file by the investigator. These records may be open to inspection by representatives of the sponsor or regular authorities at any time during and after the trial. As detailed in 21 CFR Part 56, the investigator must submit annual reports and a final report to the IRB, or more often if applicable. The investigator must keep an accurate and complete record of all submissions to the IRB and IRB approvals to facilitate their retrieval.

12.2 Informed Consent

A copy of the informed consent document to be used for the study, together with documentation of its review and approval by the appropriate IRB, must be provided to the sponsor or designee. The IRB-approved consent document must be included in the regulatory document package provided to the sponsor and will be reviewed and approved before enrollment can begin. Each subject's study data file must include documentation that informed consent was obtained prior to performance of study-related procedures.

12.2.1 Updating and Revising Informed Consent Documents

During the study it may be necessary to revise the information presented to subjects in the informed consent document. Examples of such instances include protocol amendments or extension of the study beyond its original approved term. At such times, the sponsor or the IRB will require that subjects sign an updated and revised informed consent document. Documentation that a subject has signed a revised informed consent document will be maintained in the study data file.

12.2.2 Administering / Obtaining Informed Consent

The written informed consent document should be signed and dated by subject and by the investigator or designee responsible for administering and obtaining the informed consent from the subject prior to any study procedures. The original informed consent document will then be retained by the investigator as part of each subject's individual study record. If revised consent forms are issued, any active subject must be re-consented and re-sign the consent form. Informed consent forms must be available at any time during an inspection by representatives of the sponsor or regulatory agencies. A copy of each version of the signed informed consent document must be given to the subject.

12.3 Subject's Rights

In accordance with the current revision of the Declaration of Helsinki, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and/or sponsor also have the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a subject (or a subject's legally authorized representative) decide to withdraw consent, all efforts will be made to report reasons as thoroughly as possible on the appropriate case report form.

12.4 Subject Confidentiality

Subject information will be stored in a secure location and kept confidential. Identifiers will be separated from medical information and other data and will be replaced with a unique study identification number. Access to Protected health information (PHI) contained within the database will be restricted to study investigators, their authorized research staff and study monitors.

Written authorizations and other documentations in accordance with local privacy requirements are to be obtained from each subject prior to screening for the study (e.g., Health Insurance Portability and Accountability Act - Standards for Privacy of Individually Identifiable Health Information [HIPAA]).

A report of the results of this study may be published or sent to the appropriate health authorities but subject's name will not be disclosed in these documents. The subject's name may be disclosed to the sponsor of the study, Genomind and its representatives, or governing health authorities. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

DNA Banking: DNA samples from the study will be banked into the Genomind Bank in a de-identified manner.

The investigator must ensure that the subject's anonymity is maintained. Subjects will be identified by their initials and a subject identification number only on eCRFs or other documents submitted to the sponsor or its designee. Documents that will not be submitted to the sponsor or its designee (e.g., the signed informed consent document) should be kept in strict confidence by the investigator.

The investigator will permit representatives of the sponsor or regulatory agencies to inspect the subject's medical records; however, the confidentiality of the records will be maintained.

13 AUDITS

All documentation pertaining to this clinical trial may be subject to a quality assurance audit by the sponsor or regulatory agencies. Upon request, the auditor will have access for inspection, copying, review, and audit of all source documentation, eCRFs, medical records, correspondence, and informed consent documents pertaining to the participants in the trial. The investigator agrees to promptly take any reasonable steps that are requested by the sponsor as a result of an audit to cure deficiencies in the

study documentation and eCRFs. Other documentation subject to quality assurance audit includes the investigator's IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the trial maintained in any supporting pharmacy facilities. Conditions of storage of study materials may also be subject to inspection. Representatives of the sponsor may observe conduct of any aspect of the clinical trial or its supporting activities both within and outside of the investigator's institution.

14 LANGUAGE

All written information and other material to be used by subjects and clinical staff must use a vocabulary and language that are clearly understandable to the study participant.

15 INVESTIGATOR RESPONSIBILITIES

- Conflict of Interest: No study personnel may possess an undue financial conflict of interest; however, if one arises, this should be declared in the informed consent form and reported to the sponsor.

- Compensation: Subjects will receive nominal compensation for their time and travel as approved by the governing IRB at Baseline visit and follow-up visits Week 2, 4, 6 and 8.

- Costs to the Subject: The subject will not be billed for the cost of the genetic testing. Subjects will NOT have to pay any additional copays or deductibles or any other costs for this test. Subjects will be responsible for costs/copays and deductibles for visits and medication and other visit related expenses during the study.

The investigator agrees to:

- Conduct the study in accordance with the protocol and only make changes after receiving approval from the sponsor, except to protect the safety, rights, or welfare of subjects.

- Personally conduct or supervise the study.

- Ensure that requirements related to obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56, and local laws.

- Report to the sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64 and local laws.

- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection if applicable.

- Ensure that IRB complies with requirements of ICH, 21 CFR Part 56, and local laws and will be responsible for initial and continuing review and approval of the clinical study.

- Promptly report to the IRB and the sponsor all changes in research activity and unanticipated problems involving risks to subjects.

16 STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, the sponsor or designee will activate the study site for commencement of screening. Subject consenting and screening should not begin until after the required essential documents are confirmed as received and the site initiation visit has occurred. All personnel expected to be involved in the conduct of the study will undergo training to include review of study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including test kit accountability and study file maintenance.

If the study is discontinued, sponsor instructions for discontinuing subjects should be followed.

17 INVESTIGATOR'S AGREEMENT

I have read the attached protocol, dated version in the footer of this page, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonization Guideline for Good Clinical Practice (GCP) and all applicable federal, state, and local laws, rules, regulations, and guidelines relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency or treating clinicians without medical license will not be allowed to conduct or work on studies for Genomind. I will immediately inform the sponsor in-writing if any changes to this effect occur during the study.

_____ _____

(Signature of Principal Investigator) (Date)

_____

(Printed Name)

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19 ATTACHMENTS

19.1 Description of Scales/Surveys

1. Columbia-Suicide Severity Rating Scale (C-SSRS): An assessment tool used to identify and evaluate the frequency and severity of a range of suicidal thoughts and behaviors. Two versions of the scale will be used in this protocol – a) the Baseline/Screening version which assesses the subject for lifetime thoughts and behaviors as well as those specific to the past 12 months, and b) the Since Last Visit version which assess the subject for any suicidality that may have emerged since the last study visit. Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.) (Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J. © 2008 The Research Foundation for Mental Hygiene, Inc.). The C-SSRS is to be administered by an individual with relevant clinical and suicidality assessment experience.

2. Antidepressant Treatment Response Questionnaire (ATRQ): A scale examining the efficacy and adequacy (adequate duration and dose) of antidepressant treatment taken by subjects during the current episode of depression (Fava, M, Davidson, K.G. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996; 19:179–200). The ATRQ is to be administered by a trained study physician.

3. The M.I.N.I. International Neuropsychiatric Interview 7.0 (MINI): A clinician-administered brief diagnostic tool using a structured interview guide to assess for and track psychiatric disorders found in the DSM-5 (Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry. 1997; 12:232-241; Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997; 12: 224-231; Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 1998;59(suppl 20):22-33; Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. European Psychiatry. 1998; 13:26-34.) The MINI is to be administered by a trained study physician.

4. Structured Interview Guide of the Hamilton Depression Rating Scale (SIGH-D-17): A structured interview guide developed to standardize the administration of the Hamilton Depression Rating Scale (Hamilton, M. A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960). The 17-item guide assists clinician in assessing the frequency, severity, and impact of depressive symptomatology reported by subjects in the seven days prior to a given study visit. The anchor point descriptions, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). A reliability study of the SIGH-D has been reported (Williams JBW: A structured interview guide for the Hamilton Depression Rating Scale. Archives of General Psychiatry 45:742-747, 1988). The SIGH-D-17 is to be administered by an individual with relevant clinical and rating experience who will remain blinded to all other subject-specific study data.

5. Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16): A 16-item patient self-report measure of depression symptoms experienced in the seven days prior to a given study visit focusing on the nine DSM-IV diagnostic domains of the condition (Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self-Report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. Biological Psychiatry, 54:573-583, 2003.).

6. Clinical Global Impression – Severity scale (CGI-S): A clinician-rated scale that evaluates the severity of depression reported in the last seven days prior to the interview. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (Guy, W. ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). The CGI-S must be administered by a trained study physician in the presence of the patient or after having been in the presence of the patient.

7. Clinical Global Impression – Improvement scale (CGI-I): A scale clinician-rated instrument that measures the improvement or worsening of the patient's symptoms presented at a study visit compared to those endorsed at the baseline visit. It is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) (Guy, W. ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). The CGI-I must be administered by a trained study physician in the presence of the patient or after having been in the presence of the patient.

8. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale: A 3-question patient-rated scale for assessing frequency, intensity, and burden of medication side effects for patients receiving treatment for depression (Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA: Self-rated global measure of the frequency, intensity, and burden of side effects. Journal of Psychiatric Practice. 2006; 12:71-79).

9. Patient Rated Inventory of Side Effects (PRISE): A patient self-rated questionnaire aimed at identifying potential side effects of antidepressant treatment and evaluating the tolerability of symptoms experienced in the following domains: Gastrointestinal, Heart, Skin, Nervous System, Eyes/Ears, Genital/Urinary, Sleep, Sexual Functioning, and Other.

10. Clinical Decision Survey / Pre-Result: Records the treating investigator's intended medication treatment decisions without the guidance of the genetic assay results. Post-Result: Treating investigator verifies that treatment discussion with subject was conducted (AGT & TAU group). Treating investigator records the impact of the assay result on his/her medication treatment decisions and which individual gene results affected treatment plan (AGT group only).

19.2 Glossary of Abbreviations

AGT	Assay Guided Treatment
ANCOVA	Analysis of Covariance
ATRQ	Antidepressant Treatment Response Questionnaire
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CSA	Clinical Study Agreement
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DBT	Dialectical Behavioral Therapy
DNA	Deoxyribonucleic Acid
DSM IV/5	Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association 4th and 5th edition
ECT	Electroconvulsive Therapy
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FIBSER	Frequency, Intensity, and Burden of Side Effects Ratings
GCP	Good Clinical Practices
SIGH-D-17	Structured Interview Guide for the Hamilton Depression Rating Scale – 17 Item Version
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IWRS	Interactive Web Response System
HIPAA	Health Insurance Portability and Accountability Act
LOCF	Last Observation Carried Forward
LS	Least Squares
MAR	Missing at Random
MDD	Major Depressive Disorder
MINI	M.I.N.I. International Neuropsychiatric Interview

MMRM	Mixed Model Repeated Measures
NMAR	Not Missing at Random
OC	Observed Cases Analysis Set
PRISE	Patient Rated Inventory of Side Effects
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 item)
SD	Standard Deviation
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
STAR*D	Sequenced Treatment Alternatives to Relieve Depression Study
TAU	Treatment as Usual
TEAE	Treatment Emergent Adverse Event
TMS	Transcranial Magnetic Stimulation
TRD	Treatment Resistant Depression
UDS	Urine Drug Screen