Official Protocol Title:	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Efficacy and Safety of MK-8189 using Risperidone as an Active Control in Subjects Experiencing an Acute Episode of Schizophrenia
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TITLE:

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Efficacy and Safety of MK-8189 using Risperidone as an Active Control in Subjects Experiencing an Acute Episode of Schizophrenia

IND NUMBER: 118,986

EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.5	Concomitant Medications/Vaccinations (Allowed & Prohibited), Table 2	Prohibited medications added	These changes were made to enhance the usefulness of the table.
5.5	Concomitant Medications/Vaccinations (Allowed & Prohibited), Table 3	Dosage of lorazepam or lorazepam equivalents decreased. Added text instructing sites to avoid using "PRN" when entering dosage in the CRF	These changes were made to reduce the dosage of benzodiazepine permitted during the clinical trial, and to promote reporting of daily dosage administered.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.2	Subject Inclusion Criterion 8	Minor wording change	Clarification
5.1.2	Subject Inclusion Criterion 10	Deleted sentence	Text did not apply to this protocol
5.1.3	Subject Exclusion Criterion 5	"Or" changed to "and"	Clarification
5.1.3	Subject Exclusion Criterion 19	"Known" inserted before "serological evidence"	Clarification
5.8.1	Discontinuation of Treatment	Delete "confirmed" from text "the subject has a confirmed positive serum pregnancy test."	Clarification

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow chart assessments, footnotes	Changes in assessments and some assessment wording.	Revisions better encapsulate actions needed at these assessments; footnotes revised for clarity
7.1.1.5.1	Psychiatric Intake Evaluation and MINI	Delete "vendor" from phrase external vendor's SDME	To make consistent with the rest of the protocol.
7.1.3.1	Laboratory Tests (Table 4)	Addition of creatinine phosphokinase total analyte, and other clarifications	Clarification
7.1.3.2	Pregnancy Testing	Section revised to provide clarity on use of urine pregnancy tests and results confirmation through serum pregnancy testing	Consistent with rest of protocol
7.1.3.3	Urine Alcohol Drug Screen	Added text to align with other protocol sections	Consistency
7.1.4.4	Calibration of Critical Equipment	Added text regarding ECG equipment calibration documentation.	Minor correction
7.1.5.1	Screening	Added sentence regarding re-screens	Clarification
7.1.5.1.1	Hospitalization During the Trial	Added text regarding in-patient period	Clarification

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
12.4	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	Deleted Visit 4 prolactin collection.	Consistency with Trial Flow Chart
12.4	Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types	"At the discretion of the investigator" added to HIV/ hepatitis screen.	Clarification, alignment with flow chart update
12.5	Abbreviations	Expanded one abbreviation, added another.	
Global		Minor spelling, grammar, and/or style changes throughout document	

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8189 vs. placebo with active control in adults with acute schizophrenia
Trial Phase	Phase IIa
Clinical Indication	Treatment of Acute Episode of Schizophrenia
Trial Type	Interventional
Type of control	Placebo, active comparator
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Randomized to MK-8189, placebo, or risperidone
Number of trial subjects	Approximately 215 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 14 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 7 weeks, from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a Screening visit and tapering of prohibited medications of 3 (+4) days, each subject will be receiving assigned treatment for approximately 4 weeks. After the end of treatment, each subject will be followed for 14 days.

Randomization Ratio	2:2:1 (MK-8189:placebo:risperidone)

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of MK-8189 with placebo using risperidone as an active control in adult subjects experiencing an acute episode of schizophrenia, according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 ™), and to be conducted in conformance with Good Clinical Practices.

This trial will be up to 7 weeks in duration, with up to 7 site visits for each subject. The study will consist of a Screening/tapering period (up to 1 week long), a 4-week treatment period, and a 14-day follow-up period. Subjects could be admitted to the hospital/inpatient unit as early as the day of consent signing but no later than the evening of Screening visit assessment collection completion. Subjects may continue as an inpatient in this trial throughout the active treatment period.

At Baseline (Visit 2/Day 1), subject eligibility will be reassessed and subjects found to be eligible to participate in the study will be randomly assigned to an investigational product (IP) treatment group: MK-8189, placebo, or risperidone in a 2:2:1 distribution, respectively.

This is a double-dummy design. The initial IP dose of MK-8189 will start [redacted] The initial dose of risperidone will start at 2 mg QD and titrate up to 6 mg QD. Initial dosing and titration of IP over the 7 day titration period are described in Section 5.2.1.2 (Dose Modification [Escalation/Titration/Other]).

Subjects who discontinue or complete the treatment period will have 2 follow-up phone call visits (post treatment Days 3 and 14) and a follow-up clinic visit (post treatment Day 7) after their last dose of IP.

The primary endpoint will be the assessment of symptoms of schizophrenia, as measured by the Positive and Negative Syndrome Scale (PANSS) at 4 weeks, as well as safety and tolerability. The secondary endpoint will assess the severity of schizophrenia at 4 weeks, as measured by the Clinical Global Impression-Severity of Illness (CGI-S) score. Exploratory endpoints will include the proportion of PANSS total responders (≥30% reduction in PANSS total score), as well as the mean change from baseline to 4 weeks in the PANSS negative and positive subscale scores.

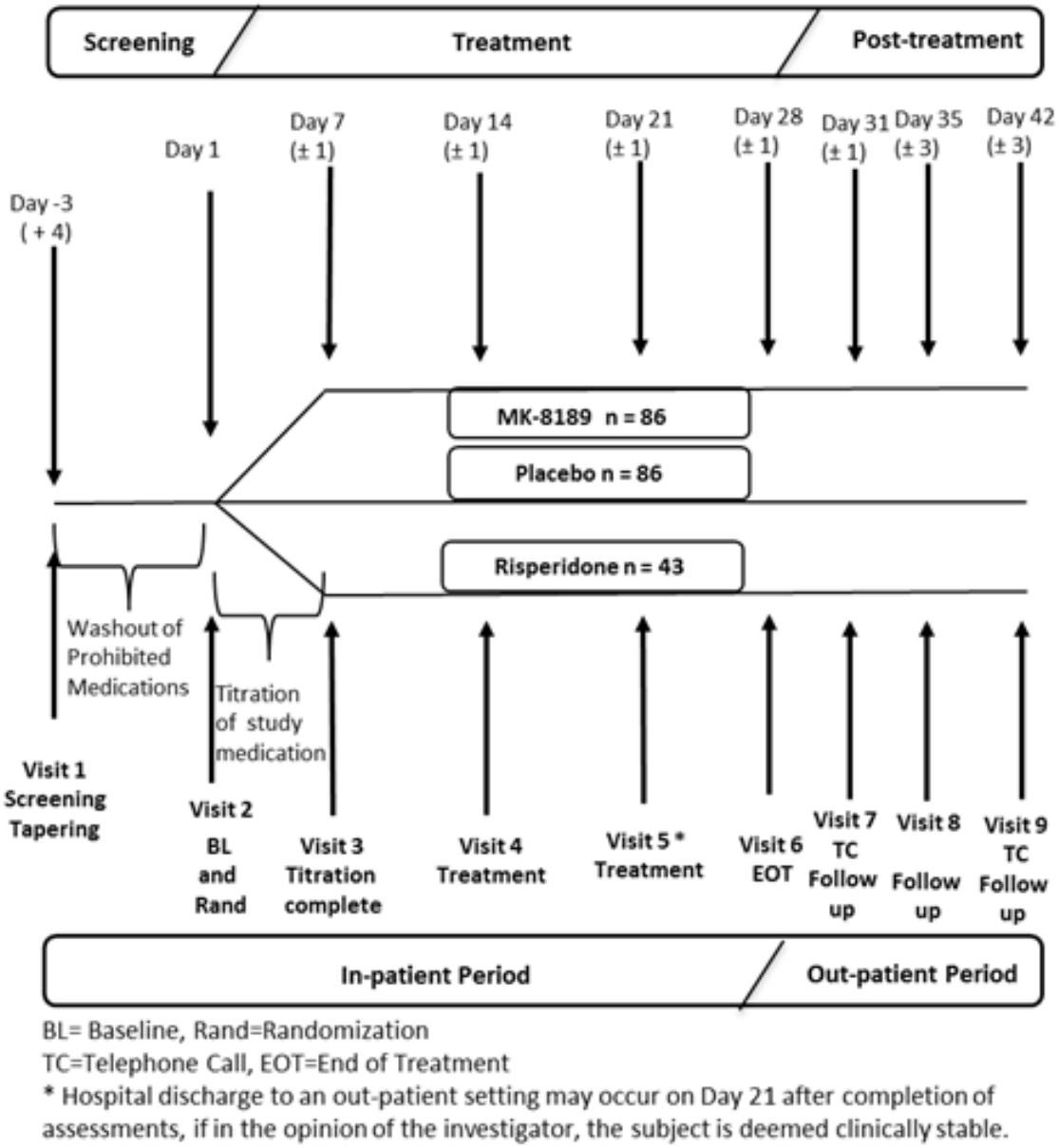
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

A standing internal Data Monitoring Committee (siDMC), which is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial, will evaluate the unblinded safety and efficacy data to assess the overall risk and benefit to trial participants when approximately 25%, 50% and 75% of the subjects have had the opportunity to complete the study.

An interim unblinded efficacy (futility) analysis will be considered unless more than 50% of the subjects have been enrolled 4 months after the first subject was randomized into the study. The interim analysis, which would be performed by an internal statistician not affiliated with the project, would occur when 50% of the subjects have completed or discontinued IP treatment and include all data collected (including partial data from subjects who were randomized, but did not yet have the opportunity to complete the study). The siDMC would review the analysis results and recommend whether the study should continue.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



BL= Baseline, Rand=Randomization
TC=Telephone Call, EOT=End of Treatment
* Hospital discharge to an out-patient setting may occur on Day 21 after completion of assessments, if in the opinion of the investigator, the subject is deemed clinically stable.

Figure 1 Diagram of PN-005 Study Structure

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In male or female subjects with schizophrenia according to the DSM-5™ criteria who are ≥18 to ≤50 years of age, and currently experiencing an acute episode of schizophrenia:

(1) **Objective:** To evaluate the efficacy of MK-8189 compared to placebo after 4 weeks of treatment as measured by the PANSS total score.

Hypothesis: MK-8189 is superior to placebo in reducing the overall symptoms of schizophrenia as assessed by the mean change from baseline in PANSS total score after 4 weeks of treatment.

(2) **Objective:** To evaluate the safety and tolerability of MK-8189.

3.2 Secondary Objective(s) & Hypothesis(es)

In male or female subjects with schizophrenia according to the DSM-5™ criteria who are ≥18 to ≤50 years of age, and currently experiencing an acute episode of schizophrenia:

(1) **Objective:** To evaluate the efficacy of MK-8189 compared to placebo after 4 weeks of treatment as measured by the CGI-S score.

Hypothesis: MK-8189 is superior to placebo in improving global functioning as assessed by the mean change from baseline in CGI-S score after 4 weeks of treatment.

3.3 Other Objectives (e.g., Tertiary, Exploratory, etc.)

In male or female subjects with schizophrenia according to the DSM-5™ criteria who are ≥18 to ≤50 years of age, and currently experiencing an acute episode of schizophrenia:

(1) **Objective:** To evaluate the efficacy of MK-8189 compared to placebo after 4 weeks of treatment as measured by the proportion of PANSS total responders (≥30% reduction in PANSS total score).

(2) **Objective:** To evaluate the efficacy of MK-8189 compared to placebo after 4 weeks of treatment as measured by the PANSS negative subscale score.

(3) **Objective:** To evaluate the efficacy of MK-8189 compared to placebo after 4 weeks of treatment as measured by the PANSS positive subscale score.

(4) **Objective:** To evaluate the efficacy of risperidone compared to placebo (for assay sensitivity) after 4 weeks of treatment as measured by the PANSS total score.

(5) **Objective:** To assess the plasma pharmacokinetics of multiple doses of MK-8189 administered as monotherapy.

(6) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8189.

4.1.1 Pharmaceutical and Therapeutic Background

MK-8189 is a potent and selective [redacted] that is being developed as a novel therapeutic for the treatment of schizophrenia. [redacted]

4.1.2 Information on Other Trial-Related Therapy

Risperidone is indicated for the treatment of schizophrenia. Efficacy was established in 4 short-term trials in adults, 2 short-term trials in adolescents (ages 13 to 17 years), and 1 long-term maintenance trial in adults. See Appendix 12.6 for label information. The goal of the current trial is to detect the clinical efficacy of MK-8189 for the treatment of acute schizophrenia in comparison to placebo. Risperidone will act as the active control in this setting to provide validation of the trial design.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study will evaluate the efficacy and safety of MK-8189 in subjects experiencing an acute episode of schizophrenia according to the DSM-5 ™ criteria.

Schizophrenia is a chronic debilitating disorder consisting of 3 symptom domains, including positive symptoms (eg, psychosis, hallucinations and delusions), negative symptoms (e.g., apathy and amotivation), and cognitive impairment (e.g., impaired memory and planning). The prevalence of schizophrenia is low but the disease burden is high. Schizophrenia affects about 1% of the population globally. It is believed that disruption of corticostriatal signaling, stemming from increased dopamine and decreased glutamate neurotransmission, results in the positive symptoms of schizophrenia, and may also contribute to cognitive impairment. Atypical antipsychotics are the current "gold standard" medications used for the treatment of schizophrenia. However, a substantial portion of patients with schizophrenia are not adequately treated by these medications and ~70% of patients switch medications within a year due to either a dissatisfaction with efficacy or a general lack of tolerability due to a wide

array of adverse events. The major adverse events associated with these medications include weight gain/metabolic effects, extrapyramidal effects, increased prolactin secretion and sedation.

MK-8189 was shown to be fully efficacious in 3 well-defined preclinical assays predictive of antipsychotic activity. [redacted]

Overall, the preclinical toxicity profile of MK-8189 via the oral route of administration supports the conduct of clinical trials up to 6 weeks in duration. In the nonclinical toxicology program, there were no target organ toxicities identified in the 6-week toxicity studies in rats or monkeys. MK-8189 was well-tolerated in adults with schizophrenia for up to 14 days (both mono and add-on therapy) at doses up to 16 mg.

The results of this study will be used to determine if MK-8189 is efficacious in the treatment of schizophrenia and has a safety profile supportive of continued clinical development.

In order to assess the efficacy and safety of MK-8189 in schizophrenia, subjects with schizophrenia who are currently experiencing an acute episode of the illness will be eligible.

The Positive and Negative Syndrome Scale (PANSS) is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and will be used as the primary efficacy endpoint measure. The scale was developed to assess positive and negative symptoms of schizophrenia as well as general psychopathology. The PANSS is a well-characterized, standardized measurement technique used for measuring symptom severity of patients with schizophrenia and is widely used in the study of antipsychotic therapy.

4.2.2 Rationale for Dose Selection/Regimen/Modification

[redacted]

[redacted]

[redacted]

4.2.2.1 Rationale for the Use of Comparator/Placebo

Despite the seriousness of the indication, a placebo treatment arm is necessary to evaluate efficacy and safety. Without the use of placebo, false assumptions regarding the true efficacy of new drugs may be made. In the absence of a placebo control, it is nearly impossible to distinguish true drug effects from placebo effects in this study population.

Risperidone is an antipsychotic drug mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, and the mixed and manic states of bipolar disorder. Risperidone is a second-generation atypical antipsychotic. It is a dopamine antagonist possessing anti-serotonergic, anti-adrenergic and anti-histaminergic properties. The recommended starting dose of risperidone approved by the Food and Drug Administration (FDA) for schizophrenia in adults is 2 mg (QD). Further dosage adjustments in 1 to 2 mg QD increments are recommended if necessary, to the recommended dose of 4 to 8 mg QD. Efficacy with risperidone in schizophrenia was demonstrated in a dose range of 4 to 16 mg QD in clinical trials according to the US approved label. However, doses above 6 mg per day for twice daily dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are generally not recommended. The current trial will use a target dose of risperidone 6 mg QD as the active control to provide validation of the trial design.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The Positive and Negative Syndrome Scale (PANSS), is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia and will be used as the primary efficacy endpoint measure. The positive scale consists of 7 items which measure delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, and hostility . The negative subscale consists of 7 items which measure blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general psychopathology scale consists of 16 items which measure somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The change from baseline in the PANSS total score at 4 weeks is the primary efficacy endpoint.

The Clinical Global Impression Severity of Illness (CGI-S) is a 7-point clinician-rated scale for assessing the global severity of the illness. The change in CGI-S score from baseline to 4 weeks will be used as a secondary efficacy endpoint.

Exploratory endpoints will consist of the proportion of PANSS total responders (≥30% reduction in PANSS total score), as well as the mean change from baseline to 4 weeks in the PANSS negative and positive subscale scores.

4.2.3.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring subjects for clinical adverse experiences. Physical examinations, vital signs, 12-lead ECGs and laboratory safety tests will be performed routinely to detect any medically meaningful effects of the MK-8189 on physiology.

Prospective assessment of suicidal ideation and behavior will be performed in this trial using the Columbia-Suicide Severity Rating Scale (C-SSRS). This assessment is being conducted in compliance with the 2012 FDA guidance requiring prospective assessment in clinical trials conducted under investigational new drug (IND) applications and trials that are intended for submission in a new drug application (NDA) to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in trials that fall within the guidance for other reasons (e.g., Central Nervous System [CNS] active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

Extrapyramidal symptoms will be documented with the Extrapyramidal Symptom Rating Scale–abbreviated (ESRS-A).

Pre-specified events of clinical interest (ECIs) (Section 7.2.3.2) in this study will include the following:

1. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
2. Suicidal ideation and/or behaviors reported in C-SSRS scores, Treatment Emergent Adverse Events (TEAEs) or any self-injurious behavior.
3. Dystonia
4. Tardive dyskinesia
5. QT corrected Fridericia (QTcF) interval of ≥500 msec (The average of the 3 QTcFs will be used)

4.2.3.3 Pharmacokinetic Endpoints

Blood will be drawn at time points specified in the Study Flow Chart for MK-8189 pharmacokinetic (PK) measurements. The plasma samples will be used to evaluate the pharmacokinetics of MK-8189 in a subject population, and to enable the characterization of the pharmacokinetic/pharmacodynamic (PK/PD) and pharmacokinetic/adverse event (PK/AE) relationships. Additional metabolites based on ongoing metabolites in safety

testing (MIST) analysis, may also be evaluated. These data will be used in pharmacokinetic model development and analysis.

The final decision as to which plasma samples will be assayed will be made by the Sponsor's Department of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism (PPDM) and the Clinical Monitor. Information regarding the collection and shipping of plasma samples will be provided in the administrative binder.

4.2.3.4 Pharmacodynamic Endpoints

An exposure-response analysis of PANSS total score data will be performed to substantiate the efficacious dose range of MK-8189 for the treatment of schizophrenia and to assess the impact of factors such as exposure, patient population and drop-out on outcomes with MK-8189.

4.2.3.5 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects

receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead ECG, laboratory safety tests, C-SSRS assessments, and adverse events monitoring) are adequate to protect the subjects' safety and should detect all adverse events.

There may be no direct health benefit for study participants from receipt of study medication, since it is still to be determined if treatment will improve, worsen or have no effect on the symptoms of schizophrenia. We may learn more about this drug from this study that might benefit people in the future.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) for MK-8189, the label for risperidone and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

The eligibility criteria are designed to select subjects for whom treatment according to this protocol is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the DSM-5 ™ criteria by a qualified psychiatrist (Doctor of Medicine [MD]) or psychologist (Doctor of Philosophy [PhD]) or other equivalent degree. The diagnosis will be confirmed using the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders (MINI; Version 7). Male or female subjects with schizophrenia according to the DSM-5 ™ criteria (295.90) who are ≥18 to ≤50 years of age, currently experiencing an acute episode of schizophrenia (worsening of active symptoms as listed in DSM-5 ™ Criterion A) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research. Note: the subject must have a level of decision-making capacity needed to make a meaningful choice about whether

or not to participate in the study (i.e, if lack of decisional capacity is evident, the subject shall be excluded from the study).

2. Be fluent in the language of the investigator, trial staff (including raters), and the informed consent.

3. Be ≥18 to ≤50 years of age at Screening and of minimal legal age for signing the consent form.

4. Meet one of the following categories:

   a) The subject is a male (there are no requirements pertaining to reproductive potential or contraceptive method).

   b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to Screening; OR (3) has a congenital or acquired condition that prevents childbearing.

   c) The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 30 days after the last dose of study drug by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

      Combination method (requires use of two of the following):

      - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
      - cervical cap with spermicide (nulliparous women only)
      - contraceptive sponge (nulliparous women only)
      - male condom or female condom (cannot be used together)

   [†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

   [‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5. Currently meet the diagnostic criteria for schizophrenia according to the DSM-5™ criteria (295.90); have a past diagnosis of schizophrenia with the onset of the first episode being ≥1 year prior to study entry; and illness duration of ≤ 20 years.

6. Be confirmed (documented in the psychiatric intake evaluation form by the investigator, and reviewed / approved by the external sponsor designated medical

expert [SDME] prior to randomization) to be experiencing an acute episode of schizophrenia, as evidenced by ALL of the following:

a) Onset of the current acute episode is ≤ 4 weeks prior to Screening,

b) the subject's current symptoms represent a marked and substantial change compared with the subject's symptomatic state prior to the emergence of the current episode,

c) the subject is in need of increased medical attention to treat worsening acute episode symptoms.

7. Have a minimum PANSS total score of ≥ 80 at Screening (note the Screening minimum PANSS total score must be independently verified by an external expert rater designated by the Sponsor).

8. Have a score of ≥ 4 (moderate) in three or more of the following items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution) in the positive subscale of the PANSS at Screening (note the Screening minimum scores in at least three PANSS positive items must be independently verified by an external expert rater designated by the Sponsor).

9. Have a CGI-S score of ≥ 4 (moderately ill) at Screening.

10. Be able to taper off psychotropic medications (including antipsychotics, antidepressants and mood stabilizers) without significant destabilization or increased suicidality in the opinion of the investigator (see Section 5.5) with the last dose taken no later than the evening prior to the Baseline visit (Visit 2 / Day 1) (the dosing cycle of depot neuroleptics must end no later than the day prior to Baseline). For subjects who can skip the tapering period, last dose is to be taken no later than the day of Screening (the dosing cycle of depot neuroleptics must end no later than the day of Screening).

11. Have responded positively to an antipsychotic medication other than clozapine (Clozaril®) in a prior psychotic episode. Subjects who have responded to another antipsychotic only when paired with clozapine would not qualify.

12. Be willing and considered able by the investigator to participate in protocol assessments, including recordings of interviews, adhere to dose and visit schedules, study procedures and restrictions.

13. Subject must have an identified responsible person (e.g., family member, social worker, case worker, case manager, or nurse), referred to as the "external contact person" in the protocol, who has agreed to provide information about the subject's location if needed during outpatient portion of the trial. The site personnel must consider this identified responsible person a reliable contact person and somebody who has regular contact with the subject (the external contact person must have regular contact no less than once per week with the subject, and this frequency of contact is anticipated to continue (either in person or via telephone) during the follow-up period as well as the outpatient treatment period if the subject is discharged on Day 21. If the subject does not have an external contact person that is considered reliable by the site, the site may designate a site representative to act as the subject's external contact person, with the same responsibilities as described above.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating in or has participated in an interventional clinical research study ≤ 6 months prior to the Screening visit of this current trial.
2. Is currently under involuntary commitment because the subject is considered a danger to themselves or others.
3. Is unwilling to remain hospitalized for the duration of the trial treatment.
4. Has participated in more than one interventional clinical trial research study within 12 months prior to Screening based on site experience or patient self-report.
5. Is unwilling to allow audio/video taping of the MINI and/or PANSS interview at Screening and Baseline.
6. Has a history of malignancy ≤ five years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
7. Has a body mass index (BMI) <18.5 or >40.0 kg/m^2.
8. Has a history of treatment resistance exhibited by any of the following:
   a) no or minimal response to at least two periods of treatment in the past with antipsychotic agents (from at least two different chemical classes) at the maximally tolerated dose in treatments lasting six weeks or more.
   b) history of Electroconvulsive Therapy (ECT) treatment for treatment resistant schizophrenia within the past 5 years.
   c) past or current use of clozapine as single or adjunctive therapy within the past 5 years.
9. Is currently being treated with and benefiting from medications with a moderate or strong inhibiting or inducing effect on CYP3A and/or CYP2C9 and/or sensitive substrates of CYP2B6 or in the opinion of the investigator, cannot be safely tapered off these medications prior to Randomization.
10. Has laboratory and/or clinical evidence of clinically significant hepatic conditions such as:
    a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2x upper limit of normal (ULN) and total bilirubin >1.5x ULN.
    b) ALT or AST >3x ULN
    c) A history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the six months prior to Screening.
11. Has a prolactin laboratory value of ≥ 5 X ULN at Screening.
12. Has known cardiovascular disease (history of angina, myocardial infarction or ischemia, heart failure, or conduction abnormalities) or cerebrovascular disease.
13. Has a risk factor for QTc prolongation as defined by:

a) a known history or current evidence of QTc interval >450 msec for males or > 470 msec for females

b) a known history of risk factors for Torsades de Pointes (e.g., heart failure/cardiomyopathy or family history of long QT Syndrome)

c) hypokalemia or hypomagnesemia

(Note: Determination of QTc interval at Screening as a pretreatment reference will be based on the average of three measurements, using the Fridericia formula [QTcF] for correction. The average will be calculated by the site.)

14. Has known renal disease or is experiencing renal insufficiency as defined by:

    a) Estimated glomerular filtration rate (eGFR) of <70 mL/min/1.73m^2 [as measured by Modification of Diet in Renal Disease (MDRD) formula]

15. Has adverse events or clinically significant abnormal laboratory, vital sign, or physical examination, or ECG finding during Screening phase indicative of emerging or unstable medical conditions that potentially interfere with the ability to evaluate the safety, tolerability and the efficacy of the trial medication, according to the judgment of the investigator.

16. As a female, has a positive serum pregnancy test at Screening or is nursing or plans to nurse children.

17. Has a known history of untreated narrow angle glaucoma.

18. Has ever been diagnosed with epilepsy or had any seizure disorder beyond one childhood febrile seizure.

19. Has known serological evidence of human immunodeficiency virus (HIV) antibody.

20. Has a history of neuroleptic malignant syndrome.

21. Has a primary current diagnosis other than schizophrenia or a comorbid diagnosis that is primarily responsible for the current symptoms and functional impairment.

22. Has a known history of the following

    a) borderline personality disorder, antisocial personality disorder, or bipolar disorder.

    b) traumatic brain injury causing ongoing cognitive difficulties, Alzheimer's disease or another form of dementia, or any chronic organic disease of the central nervous system

    c) intellectual disability of a severity that would impact the ability of the subject to participate in the trial

23. Currently (within the past 6 months prior to screening) meets the DSM-5™ criteria for substance use disorder (excluding nicotine dependence) or alcohol use disorder.

24. Has a positive urine alcohol/drug screen at the Screening visit (subjects with positive psychotropic medication results for drugs permitted at time of screening may be included provided the finding can be accounted for by documented prescription use and the subject is able and willing to comply with protocol requirements regarding excluded

medications). Subjects with positive alcohol or cannabis results on the urine alcohol/drug screen may be included at the investigator's discretion, provided the investigator does not feel the subject is a compliance risk and the subject does not fulfill the criteria for substance abuse or dependence.

25. Has a current diagnosis of a psychotic disorder (other than schizophrenia) or a behavioral disturbance thought to be substance-induced or due to substance abuse.

26. Is at imminent risk of self-harm or harm to others, in the investigator's opinion based on clinical interview, MINI, or responses provided on the C-SSRS. Note that subjects must be excluded if they report suicidal ideation ***meeting the description of C-SSRS*** Type 4 or 5 (i.e., suicidal ideation with intent, with or without a plan) within the past two months or suicidal behavior ***(as described by the C-SSRS)*** within the past six months ***at Screening.*** Subjects must be excluded at Baseline if they report suicidal ideation of Type 4 or 5 or suicidal behavior, as measured by the C-SSRS between Screening and Baseline.

27. Committed an act of violence (assaultive behavior) ≤ 2 years prior to the Screening visit. Note: history of assaultive behavior which resulted in commitment or incarceration is not necessarily exclusionary if the behavior was verbal abuse only or if the investigator has a full understanding of the nature of the assaultive behavior in question and judges the past assaultive behavior as not indicative of a risk to personal or public safety. The investigator should exclude enrollment of subjects who may be at risk for future assaultive behavior.

28. Is known to be repeatedly medically noncompliant in the management of their disease as assessed by the investigator.

29. Has a history of significant multiple and/or severe allergies (e.g., food, drugs, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.

30. Has a known allergy or sensitivity to risperidone, active ingredients or other inert ingredients.

31. Has hypothyroidism, diabetes, high blood pressure, or chronic respiratory condition or other chronic medical conditions unless the condition is stable and the prescribed dose and regimen of medication are stable for ≥ 3 months prior to Screening and there are no expected changes in co-medication during the study.

32. Presents any concern which in the opinion of the investigator may render the subject inappropriate for participation in the study.

33. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 1.

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-8189 (4 mg)	4 mg controlled release (CR) formulation	QD	Oral	1 tablet/day, Visit 2 /Day 1 (3 [+1] days)	Experimental treatment
Placebo for 4-mg MK-8189	0 mg	QD	Oral	1 tablet/day, Visit 2/Day 1 (3 [+ 1] days)	Placebo to experimental treatment
Risperidone 2 mg	2 mg	QD	Oral	1 capsule/day Visit 2 /Day 1 (3[+1] days)	Comparator
Placebo for 2-mg risperidone	0 mg	QD	Oral	1 capsule/day Visit 2 /Day 1 (3[+1] days)	Placebo to comparator
MK-8189 (8 mg)	4 mg controlled release (CR) formulation	QD	Oral	2 tablets/day, Day 4 (3[+1] days)	Experimental treatment
Placebo for 8-mg MK-8189	0 mg	QD	Oral	2 tablets/day, Day 4 (3[+1]days)	Placebo to experimental treatment
Risperidone (4 mg)	2 mg	QD	Oral	2 capsules/day, Day 4 (3[+1] days)	Comparator
Placebo for 4-mg risperidone	0 mg	QD	Oral	2 capsules/day, Day 4 (3[+1] days)	Placebo to comparator
MK-8189 (12 mg)*	4 mg controlled release (CR) formulation	QD	Oral	3 tablets/day, Visits 3-6	Experimental treatment
Placebo for 12-mg MK-8189*	4 mg controlled release (CR) formulation	QD	Oral	3 tablets/day, Visits 3-6	Placebo to experimental treatment
Risperidone 6 mg *	2 mg	QD	Oral	3 capsules/day, Visits 3-6	Comparator
Placebo for 6-mg risperidone*	0 mg	QD	Oral	3 capsules/day, Visits 3-6	Placebo to comparator
* Subjects may decrease dose to 8 mg MK-8189 / 4 mg risperidone QD if 12 mg MK-8189 / 6 mg risperidone QD is not tolerated. Subjects will be discontinued from IP if they cannot tolerate the 8 mg MK-8189 / 4 mg risperidone QD dose.					

Each subject will be randomized to study treatment MK-8189, placebo, or risperidone and receive a randomization number at Visit 2 (baseline visit). Randomization should not occur until all eligibility criteria have been assessed (i.e., the site has received and evaluated all pending reports from central ECG, central laboratory, and external SDME's approval of eligibility based on the information provided in the psychiatric intake evaluation form).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Subjects who are found to be eligible to participate in the study will, at the Baseline (Visit 2/Day 1) visit, be randomly assigned to MK-8189, placebo, or risperidone treatment groups in a 2:2:1 distribution, respectively. Each dose per treatment group will be given in a double-dummy and QD fashion. Subjects randomized to the MK-8189 treatment group will receive, per dose, equal numbers of 4-mg MK-8189 active tablets and risperidone matching placebo capsules; subjects randomized to the risperidone treatment group will receive, per dose, equal numbers of 2-mg risperidone active capsules and MK-8189 matching placebo tablets; subjects randomized to the placebo treatment group will receive, per dose, equal numbers of risperidone matching placebo capsules and MK-8189 matching placebo tablets.

Initial doses per treatment group will be given as 1 tablet and 1 capsule: the combination of 1 tablet and 1 capsule will therefore result in the initial QD dose [redacted] 2-mg risperidone for subjects randomized to MK-8189 and risperidone treatments groups, respectively, and placebo only for subjects randomized to placebo.

For subjects in each randomized group, titration [redacted]

- [redacted]
- Subjects assigned to the placebo group will be titrated to a final target of 3 MK-8189 matching placebo tablets and 3 risperidone matching placebo capsules using the following titration steps: on Day 4, the IP dose will be increased to 2 MK-8189 matching placebo tablets and 2 risperidone matching placebo capsules; on Day 7, the dose will again be increased to 3 MK-8189 matching placebo tablets and 3 risperidone matching placebo capsules for the remainder of the trial, as tolerated.
- Subjects assigned to the risperidone group will be titrated to a final targeted dose of 6-mg risperidone (3 capsules) and 3 MK-8189 matching placebo tablets using the

following titration steps: on Day 4, the IP dose will be increased to 2 risperidone 2-mg capsules and 2 MK-8189 matching placebo tablets for a total of a 4-mg dose of risperidone; on Day 7, the dose will again be increased to 3 risperidone 2-mg capsules and 3 MK-8189 matching placebo tablets for a total of a 6-mg risperidone dose for the remainder of the trial, as tolerated.

[redacted]

Subjects will be discontinued from IP in the event that subjects cannot tolerate the dose of [redacted] / 4-mg risperidone QD.

All dosing should occur in the morning. The dose titration schedule in the current trial is based on previous clinical pharmacology trial data for the MK-8189 compound and the label for risperidone. Decisions to change the dose are to be made by the primary investigator based on the subject's symptomatology and tolerability.

Once a subject has completed participation in the treatment phase at Day 28, the IP will no longer be available to the subject.

5.2.2 Timing of Dose Administration

Subjects will receive double-blind IP on Visit 2 (Day 1) in the inpatient setting if they meet all eligibility criteria. The first dose will be administered after all baseline visit safety assessments and efficacy assessments are completed (including the collection of blood samples and pre-dose PK sample) and subsequent randomization. Note: randomization and first dose must be done on the same day. While in the inpatient setting, subjects should be administered their IP at approximately the same time each morning. The IP dose can be taken without regard to food intake. If a dose is missed in the morning, it can be taken any time up to 1 PM. Subjects will be monitored for compliance.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-8189 and risperidone will be packaged identically relative to their respective matching placebo so that blinding/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 treatment arms.

Subjects will be assigned randomly in a 2:2:1 ratio to MK-8189, placebo, or risperidone for the duration of the 4 weeks of treatment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Listed below are specific restrictions for concomitant therapy during the course of the trial:

Medications specifically prohibited in the exclusion criteria are not allowed during the treatment period. Medications with a moderate or strong inhibiting or inducing effect on cytochrome P450 (CYP) 3A and/or CYP2C9 and/or the use of medications that are sensitive substrates of CYP2B6 are prohibited during the treatment period. In addition, all psychotropic medications (including antipsychotics, antidepressants, mood stabilizers, other psychotropics) are prohibited during the treatment period, except as described in Table 3. The subject must be able to discontinue or, in the opinion of the investigator, safely taper off, of any prohibited treatment listed in Table 2 over 3 (+4) days prior to the Baseline visit (Visit 2) without significant destabilization or increased suicidality.

The following list is not to be considered an exhaustive list of the aforesaid medications. All current and recent medications taken by a potential subject should be reviewed to ensure they are not exclusionary to recruitment or screening. The Investigator should seek guidance from the Sponsor when needed.

Table 2 Prohibited Medications during the Treatment Period

CYP inducers, inhibitors and sensitive substrates [a]	
CYP3A known inhibitors:	Strong: Boceprevir, clarithromycin, conivaptan, indinavir, traconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, tipranavir, cobicistat Moderate: Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil, idelalisib, danoprevir, delavirdine
CYP3A known inducers	Strong: Carbamazepine, phenytoin, rifampin, mitotane, avasimibe, enzalutamide, St John's Wort extract, rifabutin, phenobarbital Moderate: Bosentan, efavirenz, etravirine, modafinil, nafcillin; ritonavir and St. John's Wort, tipranavir and ritonavir, genistein, thioridazine, talviraline, lopinavir, lersivirine
CYP2C9 known inhibitors	Strong: Piperine, miconazole, phenylbutazone, tienilic acid, azapropazone, bucolome, sulfaphenazole, benzbromarone Moderate: Amiodarone, fluconazole, oxandrolone
CYP2C9 known inducers	Moderate: Carbamazepine, rifampin, enzalutamide, ritonavir
CYP2B6 known substrates with sensitive therapeutic range	Bupropion, efavirenz
Medications Supplements, Other Substances and Procedures	
Antipsychotics (other than trial medication)	
Antidepressants	
Mood stabilizers	
Stimulants such as Ritalin and amphetamines	
MAO inhibitors [b]	
Herbal drugs/dietary supplements, including and not limited to St John's Wort, ginkgo, goldenseal[c]	
Antiemetics containing dopamine agonist	
Illicit drugs	
Medium and long-acting benzodiazepines[d]	
ECT	
Individual therapy	

MAO = Monoamine oxidase
ECT = Electroconvulsive Therapy

a Sources include the FDA website http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency

b The last dose of a MAO inhibitor must be 1 month prior to Screening.

c Dietary supplements that are specifically marketed for psychiatric symptoms (e.g., valerian, Bach's flower remedies) are prohibited. Supplements with broader applications for general health (such as omega-3-fatty acids, magnesium) are not prohibited

d For countries where no short-acting benzodiazepine is approved, diazepam (up to 30 mg/day during the taper period and first 14 days of active treatment, up to 15 mg/day thereafter) is permitted to be used for the control of agitation, anxiety, and insomnia, if available. In the event diazepam is not available in countries where no short-acting benzodiazepine is approved, use of other benzodiazepines must first be discussed with and approved by SDME prior to use.

Table 3 Medications and Procedures Permitted during the Treatment Period

Permitted medications post Baseline[a]	
As-needed use non-psychotropic medications	Aspirin, Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophens
Chronic use medication	Chronic use of certain medications are allowed if the history of its use and subject's condition meets specifications of the eligibility criteria
Approved extrapyramidal symptoms (EPS) medications	Anticholinergic or any other medications to treat EPS ongoing at the time of screening should be maintained through the treatment phase. If EPS worsens, doses should be adjusted to treat symptoms during the trial as needed
Lorazepam up to 6 mg/day during the taper period and the first 14 days of active treatment or the equivalent dose of short-acting benzodiazepines for the treatment of agitation, anxiety Remainder of days on active treatment: lorazepam up to 4 mg/day or an equivalent dose of short-acting benzodiazepine on a daily basis. [b,c]	To be used only on as-needed basis. For recording in the CRF, enter total daily dose for each day when recording benzodiazepine use. If a daily dose is the same for greater than a single day over consecutive days, recording of the consecutive date range for the same daily dose is acceptable.
Partial benzodiazepine agonists for the treatment of insomnia at recommended dose ranges[c,d] Suvorexant[e]	Zolpidem (2.5 to 10 mg/day), zaleplon (5 to 20 mg/day), zopiclone (7.5 to 15 mg/day), or any equivalent short half-life non-benzodiazepine hypnotic may also be used for insomnia/sleep disturbance if zolpidem, zaleplon, or zopiclone are not available in specific countries. To be used only on an as-needed basis: Suvorexant (10 mg-20 mg)

a Chronic use of certain medications are allowed if the subject's condition is stable, and the dose was stabilized prior to the first dose on Day 1 and they are not strong or moderate CYP3A known inhibitors and inducers, strong or moderate CYP2C9 known inhibitors and inducers, and CYP2B6 known substrates with sensitive therapeutic range.
b To be used on as-needed basis. For countries where no short-acting benzodiazepine is approved, diazepam (up to 30 mg/day during the taper period and first 14 days of active treatment, up to 15mg/day thereafter) is permitted to be used for the control of agitation, anxiety, and insomnia. In the event diazepam is not available in countries where no short-acting benzodiazepine is approved, use of other benzodiazepines must first be discussed with and approved by SDME prior to use.
c The use of drugs to treat agitation, anxiety, or insomnia or with known sedative effects have the potential to impact efficacy assessments. The sites should consider avoiding their use within the 4 to 8 hours prior to efficacy assessments.
d Any equivalent short half-life non-benzodiazepine hypnotic may also be used for insomnia/sleep disturbance if zolpidem, zaleplon, or zopiclone are not available in specific countries.
e In countries where approved (USA, Japan).

All medications used in the last 3 months prior to screening should be recorded. Reasons for use for each medication (prior and concomitant) should also be recorded.

5.6 Rescue Medications & Supportive Care

See Section 5.5 regarding the use of EPS medications and permitted medications for treating insomnia, agitation and anxiety during the trial. After last day of IP treatment and after all

assessments have been completed the subject may begin standard of care treatment for the disease under study.

5.7 Diet/Activity/Other Considerations

Subjects should refrain from the consumption of more than 1 grapefruit or 1 glass (8 ounces) of grapefruit juice a day, throughout the entire study period. Otherwise, subjects are allowed to consume their usual diet throughout the study period.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1. – Withdrawal/Discontinuation.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition, or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk or does not allow the subject to adhere to the requirements of the protocol.
- The subject experiences a further increase of psychotic symptoms or suicidal ideation/behavior during the study which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk or does not allow the subject to adhere to the requirements of the protocol.
- The subject has a positive serum pregnancy test.
- The subject has a positive urine alcohol/drug screen (excluding allowed concomitant medications) with the exception of the screening visit urine alcohol/drug screen, as described in Section 7.1.3.3.

- The subject experiences one of the following elevated liver enzyme conditions, which is confirmed by repeat testing:
    - ALT or AST >3x ULN and total bilirubin >2x ULN,
    - ALT or AST >5x UNL
    - ALT or AST >3x ULN for more than 2 weeks
    - ALT or AST >3x ULN with the appearance of jaundice, worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
- The subject has an absolute neutrophil count of <1000 per mm^3, and after repeat testing within 48 hours, the values are not normalized or increased.
- Subjects who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior may meet discontinuation criteria. Please refer to Section 7.1.2.2.3 and the ECI guidance document for details.
- The subject has eGFR of < 60 mL/min/1.73m^2.
- The subject has a QTcF interval of ≥500 msec (The average of the three QTcFs will be used).
- The subject cannot tolerate a dose of 8-mg MK-8189 QD/4-mg risperidone QD.

In the event of any reason for discontinuation from treatment, all procedures for the study discontinuation visit (V6) should be performed. The subject should be followed-up per the Study Flow Chart Post-Treatment period to assess for safety.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.4.1 – Withdrawal/Discontinuation for those procedures to be completed at each specified visit.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Trial Period:	Screening	Treatment					Post-treatment		
	Inpatient								
Visit Number/Title:	1 Screening Tapering[a]	2 Baseline[b] Rand	3 Treatment	4 Treatment	5 Treatment[c]	6 End of Treatment[d]/DC[e]	7 TC[f]	8 Follow-up	9 TC[f]
Scheduled Days:	-3	1	7	14	21	28	Post 3 days	Post 7 days	Post 14 days
Scheduling Window, Days:	+4		±1	±1	±1	±1	±1	±3	±3
Administrative Procedures									
Informed Consent	X								
Informed Consent for Future Biomedical Research (FBR)	X								
Inclusion/Exclusion Criteria	X	X							
Subject Identification Card[g]	X								
Medical and Psychiatric History	X								
Substance, Alcohol /Smoking History	X								
Social History	X								
Psychiatric Intake Evaluation[h]	X								
MINI[i]	X								
Identify external contact person[j]	X								
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Treatment Allocation/Randomization		X							
Call/log into IVRS/IWRS	X	X	X	X	X	X			
IP Dispensing via IVRS/IWRS		X	X	X	X				
Clinical Procedures/Assessments									
Physical Examination	X					X			
Height	X								
Weight, Waist Circumference	X	X				X			
12-Lead Electrocardiogram[k]	X			X		X			
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	X			
PANSS[i,l]	X	X	X	X	X	X			
CGI-S	X	X	X	X	X	X			
C-SSRS[m]	X	X	X	X	X	X[n]			
ESRS-A	X	X	X	X	X	X			
Monitor compliance with Trial Medication		X	X	X	X	X			
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X

Trial Period:	Screening	Treatment					Post-treatment		
	Inpatient								
Visit Number/Title:	1 Screening Tapering[a]	2 Baseline[b] Rand	3 Treatment	4 Treatment	5 Treatment[c]	6 End of Treatment[d]/DC[e]	7 TC[f]	8 Follow-up	9 TC[f]
Scheduled Days:	-3	1	7	14	21	28	Post 3 days	Post 7 days	Post 14 days
Scheduling Window, Days:	+4		±1	±1	±1	±1	±1	±3	±3
Laboratory Procedures/Assessments									
Blood Draw[o]	X	X		X		X			
Insulin	X	X				X			
Lipid Panel	X	X				X			
Prolactin	X	X				X			
Serum β-Human Chorionic Gonadotropin (β-hCG) – if applicable[p]	X								
Serum Follicle Stimulating Hormone (FSH) - if applicable[p]	X								
HIV Screen (Per site SOPs and at the discretion of the investigator	X								
Hepatitis Screen (Per site SOPs and at the discretion of the investigator	X								
Blood for Genetic Analysis[q]		X							
Thyroid Stimulating Hormone (TSH)	X	X				X			
Urine Specimen Collection[r]	X	X		X		X			
Additional Urine Specimen Collection –if applicable[r]			X		X				
Urine Alcohol/Drug Screen[p, r]	X					X			
Urine Pregnancy Test – if applicable[p, r]	X	X	X	X	X	X			
Urinalysis	X	X		X		X			
Residual urine[s]		X				X			
PK Sample[b,t]		X		X		X[u]			

TC = Telephone contact, DC = discontinuation, MINI = Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders, PANSS = Positive and Negative Syndrome Scale, CGI-S = Clinical Global Impression Scale-Severity, C-SSRS = Columbia Suicide Severity Rating Scale, ESRS-A = Extrapyramidal Symptoms Rating Scale-Abbreviated, PK = Pharmacokinetics

a) During this tapering period, any psychotropic medications prohibited in Section 5.5 of the protocol (antipsychotics, antidepressants, and mood stabilizers) should be tapered under the direct supervision of the investigator (last dose to be taken no later than the evening prior to baseline) (Visit 2). If it is the clinical judgment of the investigator that the -3(+4) day tapering period may be skipped for an individual subject, trial medication may begin as early as the morning after the Screening procedures, provided all of the eligibility criteria have been met.

b) For subjects who skip the tapering period, the Baseline PK assessments must be completed on the screening day. Screening assessments that are normally repeated at Baseline need not be repeated for subjects who skip the tapering period with the following exceptions: blood draw should be repeated on the morning of Day 1, prior to the first dose of trial medication, if the Screening blood draw was not taken in a fasting state (no food or drink other than water ≥10 hours).

c) Hospital discharge may occur on Day 21 if the subject is ready for discharge according to the specifications of the protocol. Subjects that are discharged on Day 21 will be discharged after completion of assessments and may continue in the treatment phase as outpatients. The day after discharge and approximately mid-week after discharge, the subject should be telephoned to ensure that he or she has understood dosing instructions, to assess adverse events, and to remind the subject of the Day 28 visit. Subjects who are discharged on Day 21 will have their end of treatment assessments on Day 28.
d) Subjects that are discharged on Day 28 will be discharged after completion of assessments. Subjects who are not ready to be discharged on Day 28 will have their end of treatment assessments on Day 28. Approval is required to extend the hospitalization past Day 28.
e) In the event of premature discontinuation from treatment, end of treatment assessments (V6) are administered at the time of treatment discontinuation and all post-treatment follow-up phone contacts and site visit will be conducted unless there is withdrawal of consent.
f) Virtual phone visits will be conducted 3 and 14 days post-treatment after the subject completes or discontinues from treatment.
g) Subject will receive a subject identification card at Screening. If the subject is randomized, the card will be updated with the subject's randomization number.
h) The Psychiatric Intake Evaluation must be reviewed/approved by the external SDME prior to randomization.
i) PANSS and MINI interview process will include video and/or audio technology which must be reviewed/approved by the external SDME prior to randomization.
j) Subjects must have an identified responsible person (e.g., family member, social worker, case worker, case manager, or nurse), referred to as the "external contact person" in this protocol, to be considered eligible for enrollment. Site personnel must assure that the external contact person will be available to help the site locate the trial subject when a phone contact or visit is missed.
k) Determination of QTc interval at Screening and QTc prolongation will be based on the average of three measurements, using the Fridericia formula for correction.
l) To avoid the influence of subject fatigue on the diagnostic and primary outcome data, the PANSS interviews should be conducted early in each applicable visit.
m) During the Screening visit, the subject's symptoms and actions over the past 6 months should be evaluated with the C-SSRS (C-SSRS Screening Version). For all other visits, the subject's symptoms and actions since the last assessment should be evaluated (C-SSRS Since Last Visit Version).
n) The investigator should be aware of the C-SSRS scores upon discontinuation from treatment. Subjects with scores showing suicidality (e.g., any suicidal ideation of Type 4 or 5 and/or any suicidal behavior) should be thoroughly evaluated by the investigator.
o) Blood collected at all time points for "blood draw" is used for analysis of Chemistry and Hematology (as specified in Table 4). Insulin, TSH, Lipid Panel, Prolactin, Serum β-hCG, FSH, and Genetic Analysis are analyzed at time points specified in this Flow Chart. HIV screening and/or viral hepatitis panel screen may be performed (at discretion of investigator). Fasting blood draws at Screening are encouraged. During the inpatient phase, including Baseline, blood samples (for clinical laboratory evaluations and pre-dose PK) are drawn with subjects in the fasting state before breakfast prior to the morning dose. It is anticipated that blood samples for laboratory and pre-dose PK evaluations are drawn at the same time.
p) In addition to the testing at the required times specified in the table, urine/alcohol/drug tests, urine pregnancy tests, and serum pregnancy tests may be performed at the investigator's discretion throughout the course of the trial. Urine and serum pregnancy tests will be performed for only women of child-bearing potential. Note that local urine alcohol drug screen can be done for determining eligibility if the central laboratory results are pending.
q) This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the institutional review board/ethics committees (IRB/IEC) does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
r) Urine is collected for all subjects at every visit except visits 3 and 5, when urine is collected only for women of child bearing potential. Collected urine will be used for urine alcohol/drug tests, urine pregnancy tests, and urinalysis (as specified in Table 4) at time points specified in the Flow Chart. Residual urine at time points specified in the Flow Chart will also be sent to the central laboratory.
s) Leftover residual urine will be stored for future biomedical research, if the subject consents to future biomedical research.
t) PK samples are collected at time points relative to dosing as follows: Day 1 pre-dose (baseline); Day 14 pre-dose, 4 hr and 10 hr post-dose; and Day 28 pre-dose.
u) PK sample will not be collected if the subject discontinues from treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Visit 1 and Visit 2 by the investigator or qualified designee to ensure that the subject qualifies for the trial. For assessments that require reviewing by a central reader or vendor for eligibility qualification, please refer to the specific guidance documents relating to that particular assessment.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history (including any pre-existing clinically significant medical conditions) will be obtained by the investigator or qualified designee. Clinically significant findings in physical examination, laboratory tests, ECGs, and other physical evaluations during Screening are to be noted in the medical history page of the electronic case report form (eCRF). Clinically significant changes from the Screening evaluation during the trial should be captured on the AE page of the eCRF. Psychiatric conditions and symptoms including those captured in the MINI evaluation should be recorded in the medical history form.

7.1.1.4.1 Substance/Alcohol/Smoking History/ Social History

Personal and social history such as living/employment/arrest and substance/alcohol/smoking will be reviewed. Arrest history will also be assessed. Note: history of assaultive behavior which resulted in commitment or incarceration which was verbal abuse only (not violent, aggressive or physical in nature) is not necessarily exclusionary. The investigator should exclude enrollment of subjects who may be at risk for future assaultive behavior.

7.1.1.5 Psychiatric History

Diagnostic eligibility will be assessed based on a psychiatric evaluation of the subject by reviewing the subject's psychiatric history including other information sources (e.g., medical

charts, health care provider or paraprofessional), and confirmation of the diagnosis of schizophrenia using the MINI Version 7. All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the DSM-5™.

7.1.1.5.1 Psychiatric Intake Evaluation and MINI

The subject's history of the presenting problem, a detailed description of the current acute exacerbation (onset, duration, precipitants, differentiation from symptom status prior to the current episode, functional impairment, and corroboration of a current acute exacerbation by available sources [e.g., medical charts, health care provider, or paraprofessional]), psychiatric and treatment history (response/nonresponse to previous antipsychotics as described in the inclusion criteria), medical history, mental status, diagnosis and treatment plan must be documented in the source documents. Identification of the source of this information must be included; if this information was obtained from a verbal account by a healthcare professional or paraprofessional, the relationship and duration of the relationship between the professional and the subject must be included in the description. A family member may be considered as the sole source for corroboration only in the event that corroboration cannot be provided through medical records or through a health professional, and the subject lives with a family member who is considered a reliable informant by the investigator.

Diagnostic eligibility will be assessed based on interview with the subject, review of the subject's history including other information sources (listed above) and documented during psychiatric intake evaluation.

All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the DSM-5 ™ criteria. The diagnosis will be confirmed using the MINI Version 7.

The eligibility criteria require an illness duration of ≤ 20 years. The PI will use his/her best estimate, based on available resources (including medical charts, patient self-report, family member, health or paraprofessional report) to determine illness duration.

A psychiatric intake evaluation form containing key elements of the psychiatric evaluation must be forwarded to the external SDME for review, to ensure that the subject meets diagnostic eligibility criteria prior to randomization. Additionally, the external SDME will take into account the independent PANSS ratings of the central rater for the final determination of the subject's eligibility.

The completed psychiatric intake evaluation form should be sent no more than 2 days after the screening visit to ensure a timely review by the external SDME. Subjects cannot be randomized without the approval of the external SDME.

For subjects who skip the taper period, the investigator must contact the external SDME by telephone to review critical elements of the psychiatric intake evaluation form and must receive verbal agreement that the subject's acute exacerbation and diagnostic status meet entry criteria. This telephone review must be documented and a copy kept in the subject's source documents.

7.1.1.6 Identify External Contact Person

Subjects must have an identified responsible person (e.g., family member, social worker, case worker, case manager, or nurse) to be considered eligible for enrollment. The subject must provide the name and contact information of his/her external contact person. Site personnel must confirm that this person (referred to as the "external contact person") will be available to locate the subject in the event that the subject cannot be contacted. The site must interview the potential external contact person and consider the external contact person to be reliable; the external contact person must confirm that they anticipate to have contact no less than once per week with the subject as an outpatient during the trial; either in person or via telephone. The source documents must record the external contact person's agreement to act as the subject's contact person. If the subject does not have an external contact person that is considered reliable by the site, the site may designate a site representative to act as the subject's external contact person, with the same responsibilities as described above. The investigator may not act as the external contact person. In the event the designated external contact person has been designated for more than 1 subject, the investigator is responsible for documenting in the source that the external contact person will have the time to devote to each subject as defined by the protocol requirements.

7.1.1.7 Prior and Concomitant Medications Review

7.1.1.7.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified tapering requirement, and record prior medication taken by the subject within 3 months before Visit 2.

The subject must be able to discontinue or, in the opinion of the investigator, safely taper off, of any prohibited treatment listed in Table 2 prior to the Baseline visit (Visit 2) without significant destabilization or increased suicidality.

7.1.1.7.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial and reasons for medication use. If the subject reports taking any prohibited medications during the screening or treatment period, this should be recorded as a study deviation. Concomitant medications should preferably not be changed during the course of treatment period, without first consulting the investigator, except in cases of medical emergencies or other obvious exceptions.

7.1.1.8 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

7.1.1.9 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.10 Interactive Voice Response System/Integrated Web Response System

The investigator or designee will call/log into IVRS/IWRS as specified in the Trial Flow Chart. Upon confirmation of a subject's eligibility at Visit 2, the investigator or designee will call IVRS or log into IWRS to randomize the subject. Subjects who do not meet eligibility criteria at Visit 2 will be screen-failed in IVRS/IWRS. For all randomized subjects, the investigator or designee will continue to call/log into IVRS/IWRS as per the Trial Flow Chart. For completed or discontinued subjects, the investigator or designee will make the final call/web action into IVRS/IWRS at their last treatment visit.

7.1.1.11 Trial Medication Dispensing

At the visits specified in the Trial Flow Chart, the site will dispense trial medication using the IVRS/IWRS system.

7.1.1.12 Trial Compliance (Medication/Diet/Activity/Other)

Medication compliance during the trial will be monitored and determined by IP count (total IP count as well as separate tablet/capsule counts). For all subjects who are eligible for outpatient status, IP count will be monitored and determined by subject interview, entries into the dosing diary, and by tablet/capsule count at Visit 6. Instances of trial medication non-compliance should be documented as follows:

- Less trial medication was taken than prescribed: Instances where a subject failed to take trial medication as prescribed and missed a dose should be documented. A missed IP dose is defined as taking less of either IP type (less tablets and/or less capsules of IP) than required in a single 24 hour period (see Table 1 for the number of IP tablets and capsules taken per QD dose).
- More trial medication was taken than prescribed: Taking more medication of either IP type (more tablets and/or more capsules of IP) than prescribed for a subject is considered an AE of "*overdose*". See Section 7.2.1 for details regarding reporting of overdoses. An overdose of IP is defined as taking more than the maximum number of either IP type (capsules and/or tablets) specified for a single dose in one day.

Note that a subject is counted as an overdose and also as a missed dose if the subject takes more than either IP type and less of the other (tablets or capsules) specified in a dose.

- For subjects who are discharged as outpatients at Day 21, overdose or under-dose may need to take into account the investigator's best judgment if IP tablets/capsules were lost or taken in the event that the drug return, entries into the dosing diary, and/or subject contact recollection does not match.

Interruptions from the protocol specified dosing for ≥ 3 consecutive days at any time point during the active treatment phase require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

All individuals who dispense trial medication to the subject should monitor the subject to ensure doses are taken as directed, and record relevant dosing information (including number of tablets/capsules and exact time taken) in source documents.

If the subject is discharged from the hospital at Day 21, they will continue as outpatients for the remainder of the active treatment period (to Day 28). See Section 7.1.4.5 (Administer Trial Medication) for additional instructions pertaining to outpatient training.

In addition to routine surveillance of IP count (tablets and capsules), outpatient subjects will be given an IP dosing diary to help subjects record the number of tablets and capsules taken from each bottle and the time that each dose was taken.

When the outpatient returns to the clinical site at Visit 6, the outpatient should return their completed dosing diary and trial medication, including empty bottles. The site will perform an IP (tablet and capsule) count and also review the entries in the dosing diary to verify IP count and any possible missed or extra doses taken. If there is a discrepancy between the bottle and the dosing diary, the subject verbal account and site judgment will be used to determine the final decision on documenting IP count in the eCRF.

Discrepancies and the reasoning for what was ultimately recorded in the eCRF should be documented in the site's source documents. For outpatient subjects who discontinue trial medication early, site personnel should ensure the subject returns all trial medication.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Assessments/Examinations

7.1.2.1.1 Physical Examination/Neurological Examination

A physical examination (PE) will be performed at Screening, Endpoint or in the event of early discontinuation by a primary investigator or sub-investigator (M.D., Doctor of Osteopathic Medicine [D.O.]) or by a Physician's Assistant (P.A.) or Nurse Practitioner (N.P.) in areas where P.A.s and N.P.s are licensed to perform PEs.

If a physical or neurological abnormality is noted post-treatment, the investigator will indicate whether or not the result is clinically significant and if it constitutes an adverse experience.

7.1.2.1.2 Body Height/Weight/Waist Circumference

Height (inches/centimeter [in/cm]), body weight (pounds/kilograms [lbs/kg]) and waist circumference (in/cm) will be collected and recorded. Measurements should be recorded to the nearest inch/centimeter and pound/kilogram. Body weight data will be collected without shoes and with heavy clothing (such as coats) removed. It is recommended that body weight measurement should be performed on the same scale for the same individual throughout the study (this may not be possible if weight is measured in an inpatient versus outpatient setting). Abdominal waist circumference should be measured by encircling the subject's body at the navel with a cloth measuring tape or similar pliable measuring device.

7.1.2.1.3 12-Lead Electrocardiogram

A 12-lead electrocardiogram will be performed according to the instructions in a separate ECG Instruction Manual by the central ECG vendor which will also provide a cardiologist read of each ECG. Triplicate measurements of ECG will be required at the Screening Visit. *See exclusion criteria* pertaining to the three Screening QTcFs. A single ECG is required at post-screening visits unless there is an observation of a QTc prolongation (QTcF interval of ≥500 msec). An additional 2 ECGs will be required and an average taken to determine the QTc interval for that visit. The subject's ECGs are to be repeated ideally at 2-5 minute intervals.

For subjects who skip the taper period, the triplicate screening ECGs must be printed and reviewed by a qualified cardiologist and can be used as a guide to determine subject eligibility.

7.1.2.1.4 Vital Signs

Heart Rate and Blood Pressure: Subjects should be resting in a semi recumbent position for at least 5 minutes prior to having vital sign measurements obtained. For blood pressure readings, the correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements.

The same method for measuring heart rate and blood pressure (e.g., manual or automated) is recommended for all measurements for each individual subject and should be the same for all subjects throughout the study.

7.1.2.2 Clinical Assessment

The efficacy assessments PANSS and CGI-S as well as the safety assessments C-SSRS and ESRS-A will be performed at each center by qualified raters. The required qualifications of the raters are specified in an external manual. Prior to the start of rating subjects in the trial, candidate raters will participate in rating scale training. Certification is required for the PANSS raters. The Sponsor or an appointed representative, prior to the start of the trial, will implement the training and certification process. Quality monitoring of the MINI and PANSS will include video and/or audio technology.

Additional detailed information concerning administration, scoring and recording of the aforesaid assessments will be provided in an external manual.

Some or all of the PANSS recorded interviews will be reviewed and scored by an external vendor's rater (referred to in this protocol as the central rater). Site raters will be provided feedback on the quality of their interviews and ratings by the central rater to help develop and maintain good inter-rater reliability. Additionally, the site rater's consideration of the central rater's feedback may be used to refine the PANSSs scores entered by the site for an individual rating.

For the screening visit, the external SDME will review the diagnostic decisions of the site as determined through the MINI (see Section 7.1.1.5.1).

While concerns have been raised that recording assessments via audiotaping or videotaping could theoretically compromise subjects' privacy, this issue must be balanced with the need to conduct methodologically adequate and scientifically rigorous trials that are capable of testing key hypotheses. Given that the key endpoints in this trial involve subjective judgments, monitoring the adequacy of subject interviews and ratings is essential and part of strong research methodology. Prior studies suggest that the failure to adequately monitor such ratings can substantially increase the risk of failed trials [5]. Recorded interviews will be encrypted using state of the art methods to ensure privacy. Additional steps will be taken to ensure anonymity of specific private health information. Recordings will be reviewed only by approved trial personnel for quality control purposes and will be destroyed in accordance with current retention requirements.

Each assessment scale may require different raters, but it is strongly encouraged that the same rater evaluates the same subject throughout his/her participation in the trial for a particular scale.

7.1.2.2.1 Positive and Negative Symptom Scale (PANSS)

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (Sci-PANSS), a 30-item clinician-rated instrument for assessing the symptoms of Schizophrenia [6], will be used.

To avoid the influence of subject fatigue on the diagnostic and primary outcome data, it is recommended that the PANSS interviews be conducted early in each applicable visit.

7.1.2.2.2 Clinical Global Impression Scale-Severity (CGI-S)

The Clinical Global Impressions Scale Severity, a 7-point clinician-rated scale for assessing the global severity of the illness, will be used.

7.1.2.2.3 C-SSRS

The C-SSRS is an instrument designed to systematically assess and track suicidal AEs (behavior and ideation). The C-SSRS will be administered at each visit (as indicated in the

Trial Flow Chart, as well as at unscheduled visits as clinically indicated) by a qualified, trained individual who has been approved by the Sponsor to administer the instrument.

During the Screening visit, the subject's symptoms and actions over the past 6 months should be evaluated with the C-SSRS. The C-SSRS is not explicit about whether the subject specifically has ideation at the time of screening. If a subject reports a prior history of ideation/behavior, the assessor should also inquire and document if this is also present at the time of the screening visit.

For all other assessments, the subject's symptoms and actions since the last assessment should be evaluated. Subjects must be excluded if they report suicidal ideation ***meeting the description of C-SSRS*** Type 4 or 5 (i.e., suicidal ideation with intent with or without a plan) within the past 2 months or suicidal behavior within the past 6 months at ***Screening. Subjects must be excluded at Baseline if they report suicidal ideation of Type 4 or 5 or suicidal behavior, as measured by the C-SSRS between Screening and Baseline.***

If during the trial the subject demonstrates emerging or increasing suicidal ideation and/or behavior, in the investigator's opinion or based on responses provided on the C-SSRS (e.g., any suicidal ideation of Type 4 or 5 and/or any suicidal behavior), he or she should be thoroughly evaluated by the investigator and should be considered for treatment discontinuation. Subjects should continue treatment only if their suicidal ideation is passive, they expressly deny any intent to act, and who, after evaluation, the investigator feels it is safe and in the subject's best interest. In case subjects are discontinued from treatment, sites should ensure adequate clinical supervision to ensure subject's well-being. In case subject withdraws consent it is recommended that clinical supervision continues outside the scope of the trial.

Prior to discharge from the hospital at Day 21 or Day 28, the investigator should be aware of the C-SSRS score. For subjects with scores showing suicidality (e.g., any suicidal ideation of Type 4 or 5 and/or any suicidal behavior), the investigator should discuss discharge readiness with the SDME prior to discharge.

In the event an AE related to suicidality occurs during treatment, an additional C-SSRS should be performed and external sources (e.g., family members, external contact) may be used if patient is not available. In addition, all adverse events of suicidal ideation or behavior must be recorded as an Event of Clinical Interest (See Section 7.2.3.2).

7.1.2.2.4 Monitoring of Extrapyramidal Symptoms

Extrapyramidal symptoms include parkinsonism, dyskinesia, akathisia, and dystonia. Extrapyramidal symptoms will be documented with the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A).

It is strongly encouraged that the same rater evaluates the same subject throughout his/her participation in the trial for the scale.

Extrapyramidal symptoms present at Screening must be recorded in the medical history. In addition, if a) clinically significant movement disorder side effects are observed by trial staff or volunteered by the subject during the study, or b) a clinically significant movement disorder already present at Screening increases in severity during the study, or c) concomitant therapy for increasing or emerging EPS symptoms is initiated, increased, or reinstated while the subject is participating in the trial, these symptoms must be recorded as an AE.

Tardive dyskinesia and dystonia are considered events of clinical interest (ECI) (Section 7.2.3.2).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Appendix 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 4.

Fasting blood draws/urine collection at Screening are encouraged.

It is anticipated that blood samples (laboratory and pre-dose PK) should be obtained fasting and pre-dose. For subjects who are discharged from the hospital at Day 21, as outpatients they will be instructed to fast overnight if possible and withhold their dose of IP prior to clinical laboratory sample collection at Day 28. The self-reported fasting/non-fasting state of the subject will be noted on the laboratory requisition form (no food or drink other than water ≥10 hours is considered fasting).

Subjects who skip the tapering period will have duplicate laboratory specimens collected, with 1 specimen being sent to the local laboratory for immediate analysis of all Screening parameters and the other processed at the central laboratory. The local laboratory results will be used as a guide to determine subject eligibility. If the Screening laboratory samples were not taken in a fasting state (no food or drink other than water ≥10 hours), clinical laboratory assessments should be repeated on the morning of Day 1, prior to the first dose of trial medication.

At any time during the trial, if the investigator determines that immediate local laboratory results for protocol-specified parameters are needed to further evaluate the subject's condition, a duplicate set of sample(s) should be collected and sent to the central laboratory.

The site and Sponsor will remain blinded to the prolactin levels of the blood samples taken after the Baseline visit until database lock. Local laboratories will not analyze prolactin levels after the Baseline visit.

Table 4 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Appearance (macroscopic exam)	Follicle Stimulating Hormone (FSH) female only, if applicable
Hemoglobin	Alkaline phosphatase	Bacteria	Serum β-human chorionic gonadotropin (β-hCG female only, if applicable)
Platelet count	Alanine aminotransferase (ALT)	Bilirubin	Free Thyroxine (T4) (TSH Reflex to Free T4 if TSH abnormal)
White Blood Cells (WBC) (total and differential)	Aspartate aminotransferase (AST)	Blood	
	Bicarbonate	Color	Viral hepatitis panel (at the discretion of the investigator)
	Calcium	Glucose	HIV (at the discretion of the investigator)
	Chloride	Ketone	Urine Alcohol Drug Screen (Amphetamine Barbiturates Cannabinoids Cocaine metabolites Ethyl Alcohol Methadone Opiates Phencyclidine Propoxyphene Cocaine Metabolites)
	Creatinine phosphokinase, total	Microscopic exam, if abnormal appearance results are noted (RBC, WBC and bacteria)	
	Creatinine	pH	
	eGFR (estimated glomerular filtration rate (eGFR) [as measured by Modification of Diet in Renal Disease (MDRD) formula]	Protein	
	Glucose	Red Blood Cells (RBC) count	
	Lactate Dehydrogenase	Specific gravity	
	Phosphorus	WBC count	
	Potassium	Nitrate	
	Sodium	Leukocyte esterase	
	Total Bilirubin		
	Direct Bilirubin and indirect Bilirubin if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Special		**Lipid Panel**
	Thyroid Stimulating Hormone		Total cholesterol
	Insulin		High Density Lipoproteins (HDL)
	Prolactin		Low Density Lipoproteins (LDL)
			Triglycerides

Laboratory safety tests will be performed after at least a 10-hour fast.

7.1.3.2 Pregnancy Testing

For women of childbearing potential, blood samples for β-human chorionic gonadotropin (β-hCG) will be obtained at Screening. Urine pregnancy tests will be done at all visits. A positive urine pregnancy test must be confirmed with a serum pregnancy test. A blood sample for serum pregnancy testing is to be collected for central laboratory testing; a duplicate sample for local laboratory testing is recommended if local test results would be made available sooner. Dosing should be interrupted until serum pregnancy test results from either local or central laboratory results are available, and if the serum pregnancy test result is negative, subject may resume dosing. See Section 7.1.4.5 for information on missed doses. If the serum pregnancy test result is positive, note the criteria for discontinuation of treatment has been met (see Section 5.8.1). A female may forego pregnancy testing if she is not of reproductive potential according to the criteria specified in Section 5.1.2. In addition, pregnancy tests may be performed at the investigator's discretion throughout the course of the trial. See **Section 7.2.2** for procedures that must be followed regarding pregnancy reporting and follow-up. Any female subject who has a positive serum pregnancy test result during treatment should be discontinued from trial medication.

7.1.3.3 Urine Alcohol Drug Screen

A urine alcohol/drug test will be done at Screening. The urine sample will be collected along with the other laboratory specimens and will be analyzed and reported by the central laboratory. Any positive finding will require confirmation by the central laboratory prior to reporting final drug screen results. At any time during the trial, if the investigator determines that immediate local urine alcohol/drug screening results are needed to evaluate eligibility or further evaluate the subject's condition, a duplicate set of sample(s) should be collected and sent to the central laboratory. Provided there is no exclusionary evidence of substance use disorder in the past 6 months (Section 5.1.3), a positive Screening finding of alcohol, cannabinoid drugs, or prohibited psychotropic medications will not necessarily exclude the subject from participation. However, the investigator should interview the subject and ensure the subject understands that he/she must refrain from using cannabinoid drugs and prohibited psychotropic medications throughout his/her participation in the trial. Alcohol use during the trial should also be discouraged. This discussion must be noted in the source documents or on the laboratory report. The investigator may enroll the subject if he/she feels confident that the subject will comply with instructions. Additional tests may be scheduled post-Screening at the discretion of the investigator. If a subject is considered to be under the influence of illegal drugs or is believed to have taken a prohibited psychoactive drug, or if he or she meets the DSM-5™ criteria for substance use disorder (excluding nicotine) within a 1-week period, the investigator may consider the subject for discontinuation.

7.1.3.4 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.4.1 Blood Collection for Plasma MK-8189

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.5 Planned Genetic Analysis Sample Collection

Sample collection, storage, and shipment instructions for Planned Genetic Analysis samples will be provided in the laboratory manual provided by the central laboratory.

7.1.3.6 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover DNA for future research

  See Appendix 12.2 for the Collection and Management of Specimens for Future Biomedical Research.

- Leftover residual urine will be stored for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final treatment visit (Visit 6) should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. In addition, subjects who discontinue from treatment should have 2 follow-up phone call visits (post treatment Days 3 and 14) and a follow-up clinic visit (post treatment Day 7) after their last dose of IP.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 Domiciling

Not applicable

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

The central ECG vendor will provide documentation of calibration from the ECG manufacturer.

7.1.4.5 Administer Trial Medication

Trial medication is administered by the trial or inpatient staff during the inpatient phase. All personnel who will administer trial medication must receive training 1) at the investigator meeting, 2) on-site from a Sponsor representative, or 3) on-site from trial staff or lead inpatient personnel who received training at the Investigator meeting or previously from a Sponsor representative.

All individuals who dispense trial medication to the inpatient subject should monitor the subject to ensure doses are taken as directed, and record relevant dosing information (including number of tablets and exact time taken) in source documents. For subjects who are discharged at Day 21, trial medication will be self-administered starting the day after discharge from the hospital. Prior to discharge, the subject will be educated by a member of the trial staff on dosing requirements and self-administration. Subjects will be provided with a dosing diary. The day after discharge from the hospital at Day 21 and approximately mid-week after discharge, the outpatient subject should be telephoned to ensure that he or she has understood dosing instructions, to assess adverse events and to remind the subject of site visit on Day 28.

Interruption from protocol specified dosing for ≥ 3 consecutive days at any time point during the active treatment period requires consultation between the investigator and the Sponsor and written documentation of the collaboration decision on the subject management. Failure to take prescribed capsules and/or tablets per IP dosing as listed in Table 1 constitutes a missed dose.

All IP dose units (tablets and capsules) will be administered by the study staff / inpatient staff QD (approximately 8:00 AM) to the inpatient.

If a subject misses an IP morning dose or does not take the full IP morning dose he/she should not complete that day's dose after 1 PM or attempt to double that dose the next day. The subject will miss that day's dose, and will resume IP dosing the next morning with one IP dose.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 3 (+4) days prior to treatment allocation/randomization, potential subjects will be evaluated to determine if they fulfill the entry requirements as described in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Informed consent should be obtained on the day of the Screening visit prior to the start of any study-specific procedures. The Screening/tapering period will begin after the consent form is completed. During the Screening visit, a psychiatric diagnostic assessment will be performed and recorded using the Mini International Neuropsychiatric Interview for Schizophrenia and

Psychotic Disorders (MINI, Version 7). All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the DSM-5 ™ criteria by a qualified psychiatrist (MD) or psychologist (PhD) or other equivalent degree. The subject's medical history, prior medications, and demographic information will also be obtained to determine eligibility as well as additional assessments of psychiatric symptoms [Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity of Illness (CGI-S) score, and Columbia-Suicide Severity Rating Scale (C-SSRS)]. If the subject meets the Screening eligibility criteria for which results are available, the subject will begin the tapering period. Note: laboratory results, final electrocardiogram [ECG] results, corroboration of acuity and prior antipsychotic treatment response by available sources as documented in the psychiatric intake evaluation form with subsequent documented review and approval by the external sponsor designated medical expert [SDME] may still be pending at the start of the tapering period. If the subject is deemed ineligible based upon review and corroboration of the Screening eligibility criteria, the subject will be considered a screen failure prior to the Baseline visit (Visit 2).

The tapering period will begin after the Screening visit is completed and provides a period of time in which the subject will taper off prohibited medication. All subjects must be safely tapered off prohibited medications (antipsychotics, antidepressants and mood-stabilizers, See Section 5.5) during the Screening/tapering period in a manner consistent with local medical practices. If it is the investigator's clinical judgment that the tapering period can be skipped for an individual subject, Investigational Product (IP) dosing may begin as early as the morning following the Screening procedures, provided all of the eligibility criteria have been met. For assessments that are not repeated at Baseline, for those subjects skipping the tapering period, the Screening assessments will serve as the pre-treatment reference level.

The subject will identify an external contact person at the time of Screening who may be contacted in the event that the subject cannot be reached between Day 21 and Day 28 (if the subject is an outpatient) and during the 14-day follow-up period. (See inclusion criterion 13).

Note that subjects who are screen failures may not repeat screening.

7.1.5.1.1 Hospitalization During the Trial

For those subjects who were already hospitalized when approached for recruitment into this trial, the start of hospitalization under this trial is the day of the signing of the consent form. For subjects who are outpatients when approached for recruitment into this trial, subjects could be admitted to the hospital as early as the day of consent signing but no later than the evening of Screening visit assessment collection completion. Subjects will remain hospitalized throughout the tapering and treatment period.

Hospital discharge will occur on Day 28 after end of treatment assessments (V6 are completed). Exceptions to a 28-day inpatient stay may occur on Day 21 only if, after completion of Day 21 assessments, the following conditions are met: the subject's current clinical symptoms and functioning are much improved and thus continued treatment can occur safely (subject is not at risk to self or others) in a less restrictive environment; the subject can self-administer the study drug correctly, and can abide by all study procedures as

an outpatient as described in the protocol. Subjects who meet these conditions may continue in the treatment phase as outpatients. On the day of discharge, the outpatient subject will be given visit schedule, dosing instructions, a dosing diary and site will ensure the subject has their patient ID card. The day after discharge and approximately mid-week after discharge on Day 21, the subject should be telephoned by study staff to ensure that he or she has understood dosing instructions, to assess adverse events, and to remind the subject of the Day 28 visit.

During the inpatient phase of the trial, subject will not be treated as an outpatient (i.e., visits are not to be performed in a setting that requires the subject to leave the hospital or other research unit in which the inpatient unit is located). During the inpatient stay, an occasion may arise which requires the subject to leave the inpatient unit for social or personal reasons. In that event, subjects may be permitted to temporarily leave the unit during the day at any time during the inpatient phase of the study, provided they are escorted at all times during that leave by site personnel, at the discretion of the investigator and as per hospital regulations. If the subject was not discharged at Day 21, the subject will be discharged from the inpatient unit at Day 28 (±1). At Day 28 (±1), all final study assessments (End of treatment visit assessments) will be performed for all subjects, whether the subject was discharged at Day 21 or Day 28 as per the Study Flow Chart.

The Sponsor is to be contacted if it is anticipated that the subject will not be ready to be discharged from the hospital after screen fail, treatment discontinuation, or after V6 assessments are completed on Day 28. Subjects will begin their follow-up period after the treatment period termination or completion.

If the subject is hospitalized during the follow-up period of the trial, it is anticipated that these specified contacts will still take place, but may be conducted between the site personnel and subject in person.

7.1.5.2 Treatment Period Visit 2 through Visit 6

Each visit should be performed as noted in the Trial Flow Chart. For visits that require additional explanations, please see those specific visits below.

Visit 2

Subjects will be assessed for final eligibility per Inclusion/Exclusion criteria as described in Section 5.1. The subject may be randomized into the trial and will be assigned a randomization number (via IVRS/IWRS) only after ensuring that the subject meets all criteria. For trial IP titration, please refer to Section 5.2.1.2.

Visit 5

At Visit 5, assessments will be conducted as stated in the Trial Flow Chart. For details on subject eligibility for outpatient status and subject requirements, please refer to Section 7.1.5.1.1.

Visit 6

Subjects that were outpatients for the last week of treatment will return for their final site visit, Visit 6. Subjects should refrain from eating and should not take that morning dose of IP. Subjects will be instructed to arrive at the site in the morning. Subjects should be instructed to bring all trial supplies (e.g., dosing diary, IP) to the site for final compliance and accountability.

7.1.5.3 Telephone Contact Procedures

The principal investigator is responsible for ensuring that all phone contacts are performed by a site staff member, who is a healthcare professional qualified to elicit a discussion with the subject that will lead to a clinically meaningful disclosure on the subject's well-being. Phone contacts must be documented immediately in a contact log for review by the PI within 24 hours of log entry. In the event of worsening symptoms reported by either the subject or the external contact person, the site's ensuing action steps must be recorded. The site must follow-up on any report of worsening symptoms by contacting the subject to schedule an immediate visit. In the event that the subject cannot be reached by phone at the regularly scheduled time or misses a visit, the site should make at least three attempts (in addition to the initial phone call) to contact the subject within 48 hours of the missed scheduled time. The last contact attempt should represent stronger action by the site to contact the subject (i.e., a visit to the subject's residence, an attempt to reach the external contact person identified at the time of Screening) in the event that the subject cannot be reached on the third attempt. All phone contacts, attempted contacts, and home visits should be recorded in source documents.

7.1.5.4 Post-Treatment Contact (phone and visit)

Subjects will have 2 phone calls (at 3 and 14 days post dose) and one clinic visit at Visit 7 (7 days post dose) after the last dose of trial drug (regardless of the date of the Discontinuation Visit, if applicable) to determine if any AEs have occurred during the post-trial clinic contacts. See Section 7.2 for further detail on collection of AEs post-treatment.

Refer to Section 7.1.5.3 regarding phone contact procedures.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than the maximum number of either IP type (capsules and/or tablets) specified for a single dose in 1 calendar day (accidental or intentional).

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization [Notable exceptions a) any admission solely for social reasons, b)any extended hospitalization past last day of study drug treatment for subjects not clinically ready to be discharged is not in itself an SAE. The PI instead should consider whether the events associated with extended hospitalization meet the definition of an SAE. Extended hospitalization must be discussed with the Sponsor Designated Medical Expert (SDME) and the reasons for extended hospitalizations must be documented in the medical record daily until discharge.];
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 5 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the

upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. Suicidal ideation and/or behavior as reported in C-SSRS scores, TEAEs or any self-injurious behavior
3. Dystonia
4. Tardive dyskinesia
5. QTcF interval of ≥500 msec (the average of the three QTcFs will be used)

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 5. The investigator's assessment of causality is required for each adverse event. Refer to Table 5 for instructions in evaluating adverse events.

Table 5 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the standing internal Data Monitoring Committee (siDMC) regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will monitor the interim data from this trial. The siDMC comprises members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial. The siDMC will monitor the trial at an appropriate frequency (see Section 8.7 - Interim Analyses) for evidence of adverse effects of trial treatment and efficacy/futility, as described in the detailed monitoring guidelines. The siDMC will determine whether the trial should continue (or other modifications, pre-specified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to trial participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Efficacy and Safety of MK-8189 in the Treatment of Adult Subjects with Schizophrenia
Treatment Assignment	Subjects will be randomly assigned to MK-8189, placebo or risperidone in a 2:2:1 distribution, and will receive MK-8189 [redacted] placebo (3 tablets/capsules QD) or risperidone (6 mg QD) for the remainder of the trial, as tolerated.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint	1) Positive and Negative Syndrome Scale (PANSS) total score – Change from baseline at Week 4
Key Secondary Endpoints	1) Clinical Global Impression Severity of Illness (CGI-S) score – Change from baseline at Week 4
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary efficacy hypothesis will be evaluated by comparing MK-8189 to placebo with respect to the mean change from baseline in PANSS total score after 4 weeks of treatment using a longitudinal analysis of covariance (ANCOVA) method.
Statistical Methods for Key Safety Analyses	The count and percentage of adverse events will be provided. 95% confidence intervals for between-group comparisons will be calculated using the unstratified Miettinen and Nurminen method [7].
Interim Analyses	An internal data monitoring committee will evaluate the unblinded safety and efficacy data to assess the overall risk and benefit to trial participants when approximately 25%, 50%, and 75% of the subjects have had the opportunity to complete the study. One interim unblinded efficacy (futility) analysis may also be performed in this study. Results would be reviewed by the internal data monitoring committee. This interim analysis is summarized below. Details are provided in Section 8.7. • Trigger: Interim analysis will be considered unless more than 50% of the subjects have been enrolled 4 months after the first subject was randomized into the study. • Timing: To be performed when 50% of the subjects have completed or discontinued IP treatment. • Testing: Inferential analyses for the change from baseline in the PANSS total score at 4 weeks will be provided.
Multiplicity	A small amount of alpha (α=0.0001) will be allocated to each of the 3 interim analyses. The effect of the alpha spending for the interim analyses on the alpha to be used at the time of the final analysis is negligible. If the test of the primary efficacy hypothesis is statistically significant (i.e., p-value is less than or equal to 0.05), then the secondary hypothesis will be tested to control the overall type-I error at the 5% level (two-sided). That is, MK-8189 would be compared to placebo with respect to the mean change from baseline in CGI-S score after 4 weeks of treatment using α=0.05 (two-sided).

Sample Size and Power	The planned number of subjects to be randomized is 215 (86, 86 and 43 in the MK-8189, placebo and risperidone groups, respectively). For the PANSS total score change from baseline at Week 4, the trial has 72% power (if no futility analysis is performed) or 65% power (if the planned futility analysis is performed) to demonstrate that MK-8189 is superior to placebo at an overall two-sided 5% alpha level, if the underlying treatment difference (MK-8189 minus placebo) is -8.0. For assay sensitivity, the trial has 67% power to demonstrate that risperidone is superior to placebo at an overall one-sided 5% alpha level, if the underlying treatment difference (risperidone minus placebo) is -8.0.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

The planned interim analyses are described in Section 8.7. Study enrollment is likely to be ongoing at the time of the interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of the interim analyses will not be shared with the investigators prior to the completion of the study. Subject-level unblinding will be restricted to an internal unblinded statistician and scientific programmer performing the interim analyses, who will have no other responsibilities associated with the study.

Treatment-level results and/or subject-level data of the interim analyses will be provided by the unblinded statistician to the standing internal Data Monitoring Committee (siDMC) which consists of Sponsor personnel. Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of the interim analyses will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the Sponsor. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Efficacy Endpoints

The Positive and Negative Syndrome Scale (PANSS) is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia. Increases in the PANSS total score represent a worsening of symptoms. The change from baseline in the PANSS total score at 4 weeks is the primary efficacy endpoint.

The Clinical Global Impression Severity of Illness (CGI-S) is a 7-point clinician-rated scale for assessing the global severity of the illness. Increases in the CGI-S score represent a worsening of symptoms. The change from baseline in the CGI-S score at 4 weeks is a key secondary efficacy endpoint.

Exploratory endpoints will consist of the proportion of PANSS total responders (≥30% reduction in PANSS total score), as well as the mean change from baseline to 4 weeks in the PANSS negative and positive subscale scores.

8.4.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring subjects for clinical adverse experiences. Physical/neurological examinations, vital signs, 12-lead ECGs and laboratory safety tests will be performed periodically to detect any medically meaningful effects of MK-8189 on physiology.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to systematically and prospectively ascertain and document the occurrence of suicidal events (i.e., ideation and behavior). Responses on the C-SSRS are classified according to 11 prespecified categories as described in Appendix 12.7. The most severe treatment-emergent ideation and behavior event reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it newly emerged or is more severe compared to recent history (i.e., protocol-defined recent history prior to entering the trial as stated in the inclusion/exclusion criteria for suicidal ideation/behavior, up to and including the randomization visit).

Extrapyramidal symptoms will be documented with the Extrapyramidal Symptom Rating Scale–abbreviated (ESRS-A).

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who:

- receive at least 1 dose of study treatment

- have at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of study treatment

- have baseline data for those analyses that require baseline data

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data. Details on the approach to handling missing data are provided in Section 8.6, Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects, this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6, Statistical Methods.

8.6 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (two-sided) level.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

The primary efficacy hypothesis will be evaluated by comparing MK-8189 to placebo with respect to the mean change from baseline in PANSS total score after 4 weeks of treatment using a longitudinal analysis of covariance (ANCOVA) model. The analysis model will include terms for treatment, baseline PANSS total score, age, duration of illness, week, and the interaction of week by treatment (Table 6). The treatment difference in terms of the mean change from baseline to a given time point will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among

repeated measurements. The criterion for declaring MK-8189 superior to placebo in terms of PANSS total score change from baseline is that the p-value is less than or equal to 0.05.

An additional sensitivity analysis using the tipping-point approach will be used to assess the robustness of the primary analysis approach. The Variant 3 of the tipping point as described in Ratitch, et al. (2013) [8] will be applied. In that approach, missing data are first imputed for all visits under the missing-at-random (MAR) assumption, and then a worsening/shift is applied. This is repeated until the result is no longer statistically significant (i.e., p>0.05). This tipping point (smallest worsening/shift in which the significant result turns non-significant) provides a measure of robustness of the primary result.

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Primary Hypothesis				
Positive and Negative Syndrome Scale (PANSS) total score – Change from baseline at Week 4	P	Longitudinal analysis of covariance (ANCOVA) model§	FAS	Model-based
Positive and Negative Syndrome Scale (PANSS) total score – Change from baseline at Week 4	S	Longitudinal analysis of covariance (ANCOVA) model§	FAS	Tipping-point Analysis
Secondary Hypothesis				
Clinical Global Impression Severity of Illness (CGI-S) score – Change from baseline at Week 4	P	Longitudinal ANCOVA model‖	FAS	Model-based

† P=Primary approach; S=Supportive approach.
‡ Statistical model is described in further detail below:
§ Longitudinal ANCOVA model includes terms for treatment, baseline PANSS total score, age, duration of illness, week, and the interaction of week by treatment.
‖ Longitudinal ANCOVA model includes terms for treatment, baseline CGI-S score, age, duration of illness, week, and the interaction of week by treatment.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints is described in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier-1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier-2 parameters will be assessed via point estimates with 95%

confidence intervals provided for between-group comparisons; only point estimates by treatment group will be provided for Tier-3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.

Continuous measures, such as changes from baseline in laboratory, vital signs, and ECG parameters, will be considered Tier-3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, there are no pre-specified events of interest, i.e., no Tier-1 events. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, who discontinued due to an AE, and who discontinued due to a drug-related AE will be considered Tier-2 endpoints. For these endpoints, 95% confidence intervals will be provided for between-treatment differences (MK-8189 minus placebo) in the percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method [7], an unconditional, asymptotic method.

The percentage of subjects with any treatment-emergent suicidal ideation, with any treatment-emergent suicidal behavior, or with any treatment-emergent self-injurious behavior, no suicidal intent, will be analyzed per the tiered analysis strategy outlined above, and will be considered as either Tier-2 or Tier-3 events, depending on the number of subjects with an event observed within each treatment group. Additionally, the 11 pre-specified categories of suicidal ideation and behavior will be summarized. Subject counts (and cumulative counts) for each category will be based upon the most severe treatment-emergent event observed during the assessment period.

The percentage of subjects having their dose up-titrated (per protocol), maintained or reduced will also be considered as Tier-3 events.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any drug-related AE		X	X
	Any serious AE		X	X
	Any serious and drug-related AE		X	X
	Discontinuation due to an AE		X	X
	Discontinuation due to a drug-related AE		X	X
	Specific AEs, SOCs or C-SSRS treatment-emergent events[‡] (incidence ≥4 subjects in at least 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or C-SSRS treatment-emergent events[§] (incidence <4 subjects in each of the treatment groups)			X
	Change from baseline results (labs, vital signs, ECGs, ESRS-A)			X
	Dose up-titrated (per protocol), maintained or reduced			X

[†] Adverse Experience references refer to both clinical and laboratory AEs.

[‡] Any ideation, any behavior, or any self-injurious behavior, no suicidal intent.

[§] Includes only those endpoints not already pre-specified as Tier-2 endpoints.

Note: SOC = System Organ Class;
C-SSRS = Columbia-Suicide Severity Rating Scale;
ESRS-A = Extrapyramidal Symptoms Rating Scale-Abbreviated;
X = results will be provided.

8.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

A standing internal Data Monitoring Committee (siDMC), which will consist of Sponsor personnel not affiliated with the project, will evaluate the unblinded safety and efficacy data to assess the overall risk and benefit to trial participants when approximately 25%, 50% and 75% of the subjects have had the opportunity to complete the study.

An interim unblinded efficacy (futility) analysis will be considered unless more than 50% of the subjects have been enrolled 4 months after the first subject was randomized into the study. The interim analysis, which would be performed by an internal statistician not

affiliated with the project, would occur when 50% of the subjects have completed or discontinued IP treatment and include all data collected (including partial data from subjects who were randomized, but did not yet have the opportunity to complete the study). The siDMC would review the analysis results and recommend whether the study should continue.

If the study is stopped early, the CSR will comprise all available data up to and including the close-out visits, which include the data used to draw the conclusion in the decisive interim analysis plus the remaining data obtained afterwards (from additional visits and close-out visits). This approach to include all available information is in line with the International Council for Harmonisation (ICH)-E9 guideline, the intent-to-treat (ITT) principle and the Committee for Medicinal Products for Human Use (CHMP) guideline on adaptive designs.

8.7.1 Futility of Primary Outcome

The futility analysis would be performed to assess whether it would be highly unlikely for MK-8189 to be declared superior to placebo with respect to the change from baseline in the PANSS total score at 4 weeks. The primary efficacy analysis will be performed on the Full Analysis Set. The siDMC will review the analysis results and recommend whether the study should continue. The stopping boundaries for the futility analysis will be based on the Gamma spending function [9] with parameter 1. The study may be stopped with early rejection of the alternative hypothesis (i.e., MK-8189 will not be considered superior to placebo with respect to the change from baseline in the PANSS total score at 4 weeks) if the test statistic crosses the pre-specified stopping boundaries (i.e., the value of the test statistic is greater than the value of the Gamma stopping boundary at the time of the futility analysis, suggesting that MK-8189 is not superior to placebo).

Table 8 displays the operating characteristics of the futility analysis. Assuming that the futility analysis is performed when 108 subjects have completed or discontinued IP treatment and an observed standard deviation of the change from baseline in the PANSS total score of 17.0, the study may be stopped if the mean change in PANSS total score is <4.6 better than that observed in the placebo group. This corresponds to the conditional power of the study being <26% at the time of the futility analysis (i.e., at the time of the futility analysis, if the observed difference in the mean change in PANSS total score between the MK-8189 and placebo groups (MK-8189 minus placebo) is -4.6, then there would be a 26% chance that MK-8189 would be declared superior to placebo at the time of the final analysis).

Table 8 Operating Characteristics of the Futility Analysis†

Number of randomized subjects at the time of the futility analysis	108
Observed difference between groups that would stop the study (futility analysis)	> -4.6
P-value (two-sided) for stopping the study	> 0.30
Conditional power‡ for stopping the study	< 26%
Probability that the study will be stopped (MK-8189 is ineffective; difference§ = 0)	70%
Probability that the study will be stopped (MK-8189 is effective; difference = -8)	22%
Observed difference between groups that would result in superiority (final analysis)	≤ -6.2

† Sample size is the total number of subjects randomized (2:2:1 ratio in MK-8189, placebo and risperidone groups, respectively); Expected drop-out rate = 30%; Differences and probabilities are based on the primary treatment comparison (i.e., MK-8189 vs. placebo). The futility boundary is non-binding.
‡ Calculated under the assumption that the observed data trend at the time of the futility analysis will continue to the end of the trial.
§ Difference = MK-8189 – placebo.

8.8 Multiplicity

A small amount of alpha (α=0.0001) will be allocated to each of the 3 interim analyses. The effect of the alpha spending for the interim analyses on the alpha to be used at the time of the final analysis is negligible.

The secondary hypothesis will only be formally tested if the test of the primary efficacy hypothesis is statistically significant (i.e., p-value is less than or equal to 0.05), thus controlling the overall type-I error over the primary and secondary hypotheses at the 5% level (two-sided). That is, MK-8189 would be compared to placebo with respect to the mean change from baseline in CGI-S score after 4 weeks of treatment using α=0.05 (two-sided).

If the primary efficacy hypothesis test is not statistically significant, then a nominal p-value would be displayed for the secondary hypothesis test, but statistical significance (i.e., superiority to placebo) would not be concluded for this test.

8.9 Sample Size and Power Calculations

The planned number of subjects to be randomized is 215 (86, 86, and 43 in the MK-8189, placebo and risperidone groups, respectively). For the PANSS total score change from baseline at Week 4, the trial has 72% power (if no futility analysis is performed) or 65% power (if the planned futility analysis is performed) to demonstrate that MK-8189 is superior to placebo.

The power and sample size are based on the following assumptions:

- $\alpha = 0.05$ (two-sided)
- True treatment difference (MK-8189 minus placebo) = −8.0
- Standard deviation = 17.0
- Drop-out rate = 30%

The criterion for success is that the p-value for the between-treatment difference in the mean PANSS total score change from baseline (MK-8189 minus placebo) will be less than or equal to 0.05. Given the above assumptions, this may occur when the observed difference between treatment groups is approximately ≤ -6.2. The power calculations for the primary comparison are summarized under various assumptions in Table 9 (assuming that a futility analysis is not performed) and Table 10 (assuming that a futility analysis is performed).

Table 9 Power† (%) Under Various Assumptions With 215 Subjects Randomized if Futility Analysis is Not Performed

True Standard Deviation of Change from Baseline	True Difference‡ in Change from Baseline in PANSS§ Total Score								
	-10.0	**-9.5**	**-9.0**	**-8.5**	**-8.0**	**-7.5**	**-7.0**	**-6.5**	**-6.0**
15.0	95	93	90	87	83	78	72	65	58
16.0	92	90	86	82	78	72	66	60	53
17.0	89	86	82	78	**72**	67	61	55	48
18.0	86	82	78	73	68	62	56	50	44

† Assumptions: $\alpha = 0.05$ (two-sided); drop-out rate = 30%;
60 subjects per treatment group (MK-8189 and placebo) expected to be included in the analysis.
‡ Difference = MK-8189 − placebo.
§ PANSS = Positive and Negative Syndrome Scale.

Table 10 Power† (%) Under Various Assumptions With 215 Subjects Randomized if Futility Analysis is Performed

True Standard Deviation of Change from Baseline	True Difference‡ in Change from Baseline in PANSS§ Total Score								
	-10.0	**-9.5**	**-9.0**	**-8.5**	**-8.0**	**-7.5**	**-7.0**	**-6.5**	**-6.0**
15.0	92	89	86	81	76	71	65	58	51
16.0	88	85	81	76	71	65	59	53	46
17.0	84	80	76	71	**65**	60	54	48	42
18.0	80	75	71	66	60	55	49	44	38

† Assumptions: $\alpha = 0.05$ (two-sided); drop-out rate = 30%;
60 subjects per treatment group (MK-8189 and placebo) expected to be included in the analysis.
‡ Difference = MK-8189 − placebo.
§ PANSS = Positive and Negative Syndrome Scale.

For assay sensitivity, the trial has 67% power to demonstrate that risperidone is superior to placebo at an overall one-sided 5% alpha level, if the underlying treatment difference (risperidone minus placebo) is -8.0.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated within each category of the following classification variables:

- Age category (≤ 35 years, > 35 years)
- Gender (female, male)
- Race (white, Asian, other)
- Duration of illness (≤ 10 years, > 10 years)
- Baseline PANSS total score (≤ 95, > 95)

8.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each subject, the number of tablets and capsules remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

A day within the study will be considered an "On-Therapy" day if the subject takes the required number of IP tablets and capsules, as noted in Section 5.2.

For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study

permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the date the subject discontinued from the study.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

8.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (N, mean, range) and frequencies (number of subjects exposed to study treatment for various durations, e.g., within 1-week intervals over the course of the study) for the "Number of Days on Therapy" by treatment group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
MK-8189 4 mg	tablet
Placebo to MK-8189 4 mg	tablet
Risperidone 2 mg	capsule
Placebo to risperidone 2 mg	capsule

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

For the tablet of capsule formulation, subjects will receive blinded bottles (each containing a 1 week supply of the study therapy). No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. 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 trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures,

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

[1] Bender AT, Beavo JA. Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. Pharmacol Rev 2006;58:488-520.

[2] Seeger TF, Bartlett B, Coskran TM, Culp JS, James LC, Krull DL, et al. Immunohistochemical localization of PDE10A in the rat brain. Brain Res 2003;985:113-26.

[3] Grauer SM, Pulito VL, Navarra RL, Kelly MP, Kelley C, Graf R, et al. Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. J Pharmacol Exp Ther 2009;331(2):574-90.

[4] Schmidt CJ, Chapin DS, Cianfrogna J, Corman ML, Hajos M, Harms JF, et al. Preclinical characterization of selective phosphodiesterase 10A inhibitors: a new therapeutic approach to the treatment of schizophrenia. J Pharmacol Exp Ther 2008;325(2):681-90.

[5] Khan A, Yavorsky WC, Liechti S, DiClemente G, Rothman B, Opler M. et al. Assessing the sources of unreliability (rater, subject, time-point) in a failed clinical trial using items of the Positive and Negative Syndrome Scale (PANSS). J Clin Psychopharmacol. 2013 Feb;33(1):109-17.

[6] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-76.

[7] Miettinen O, Nurminen M. Comparative analysis of two rates. Statist Med 1985;4:213-26.

[8] Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat. 2013 Nov-Dec;12(6):337-47.

[9] Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9:1439-45.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.6 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed,

present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research

specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in

international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e. only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

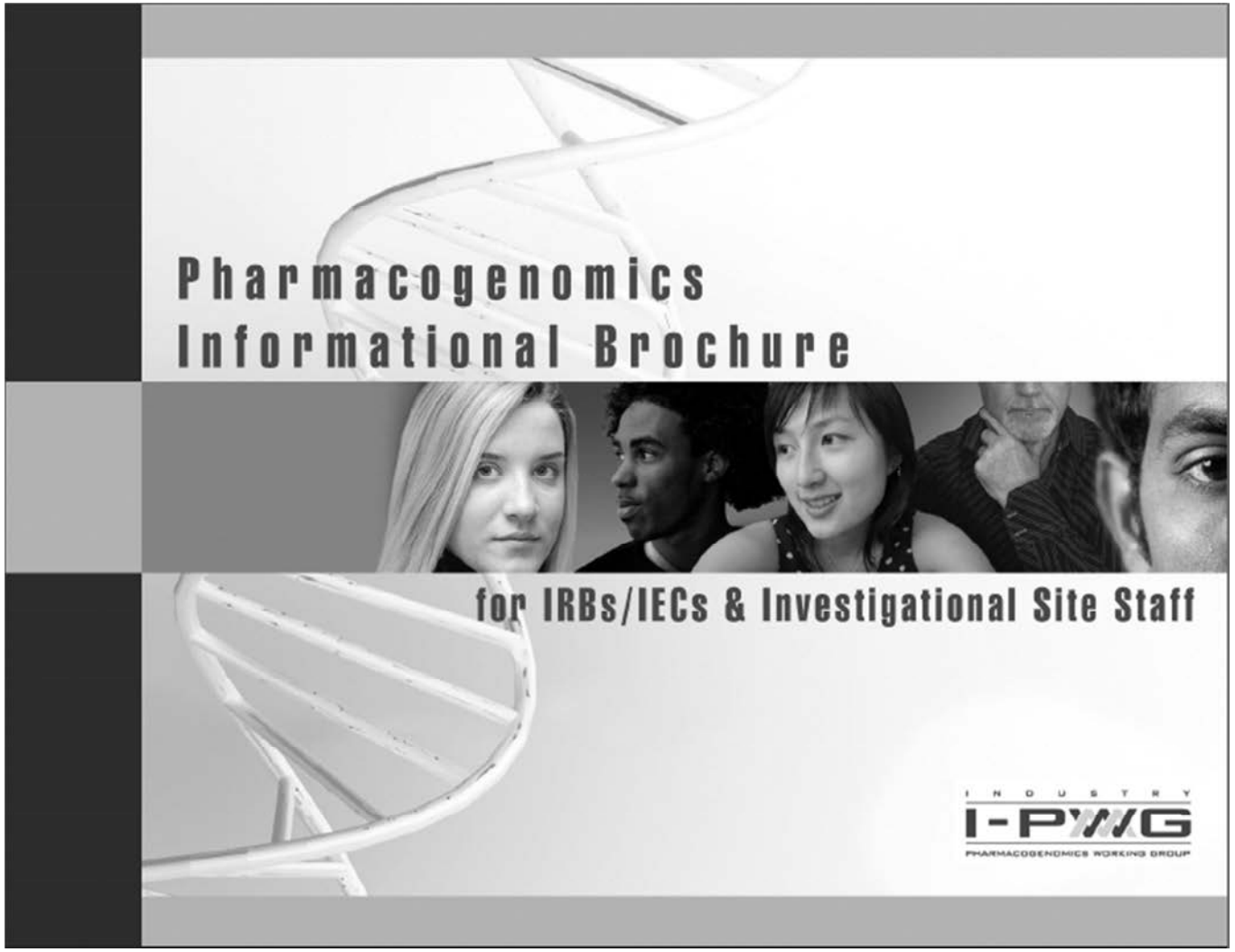
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



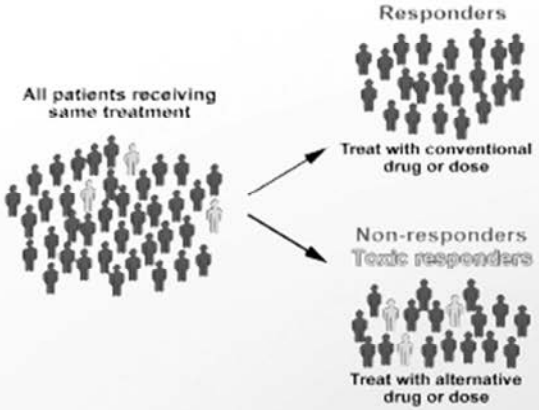
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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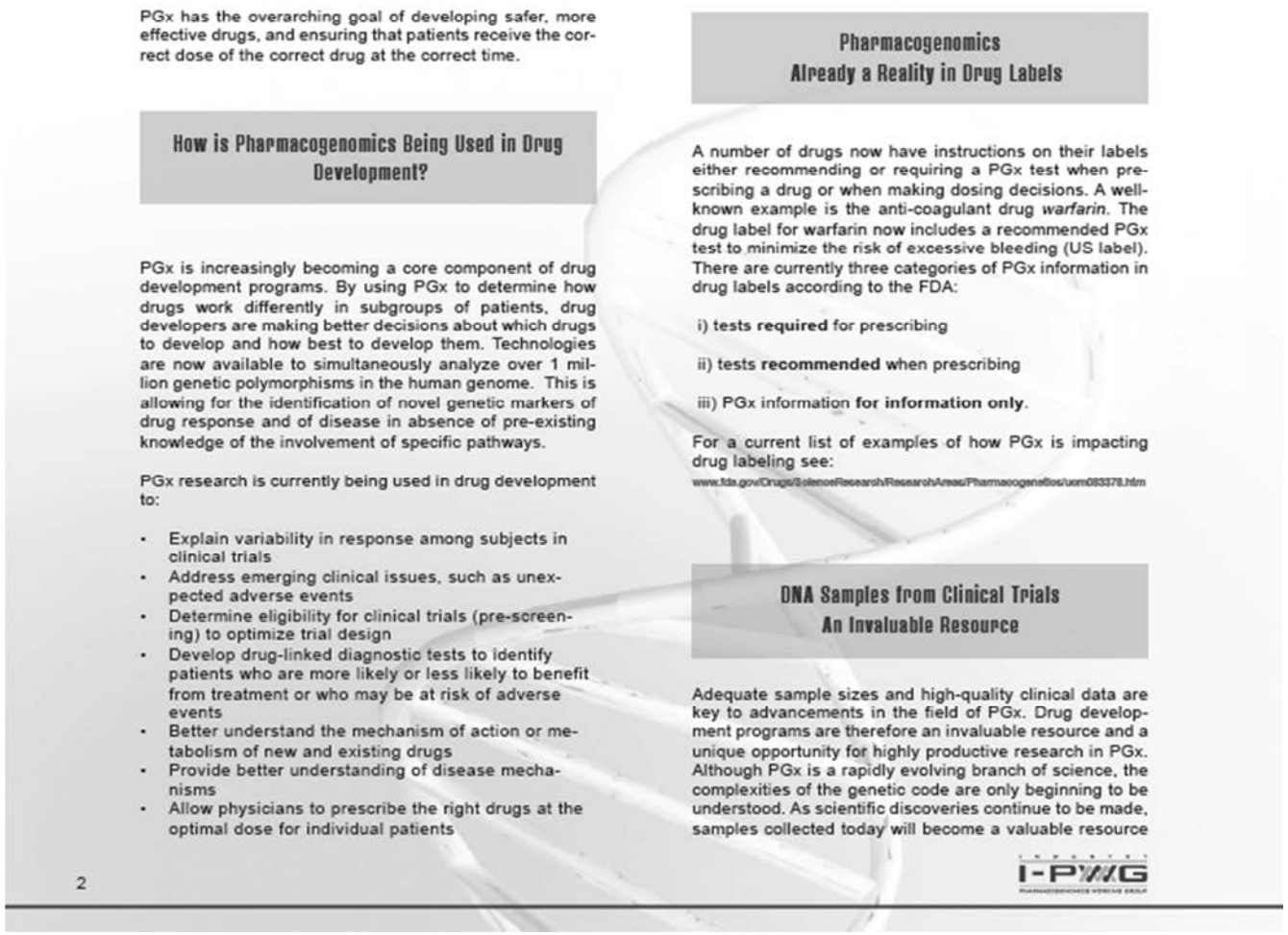

PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2008[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

3

Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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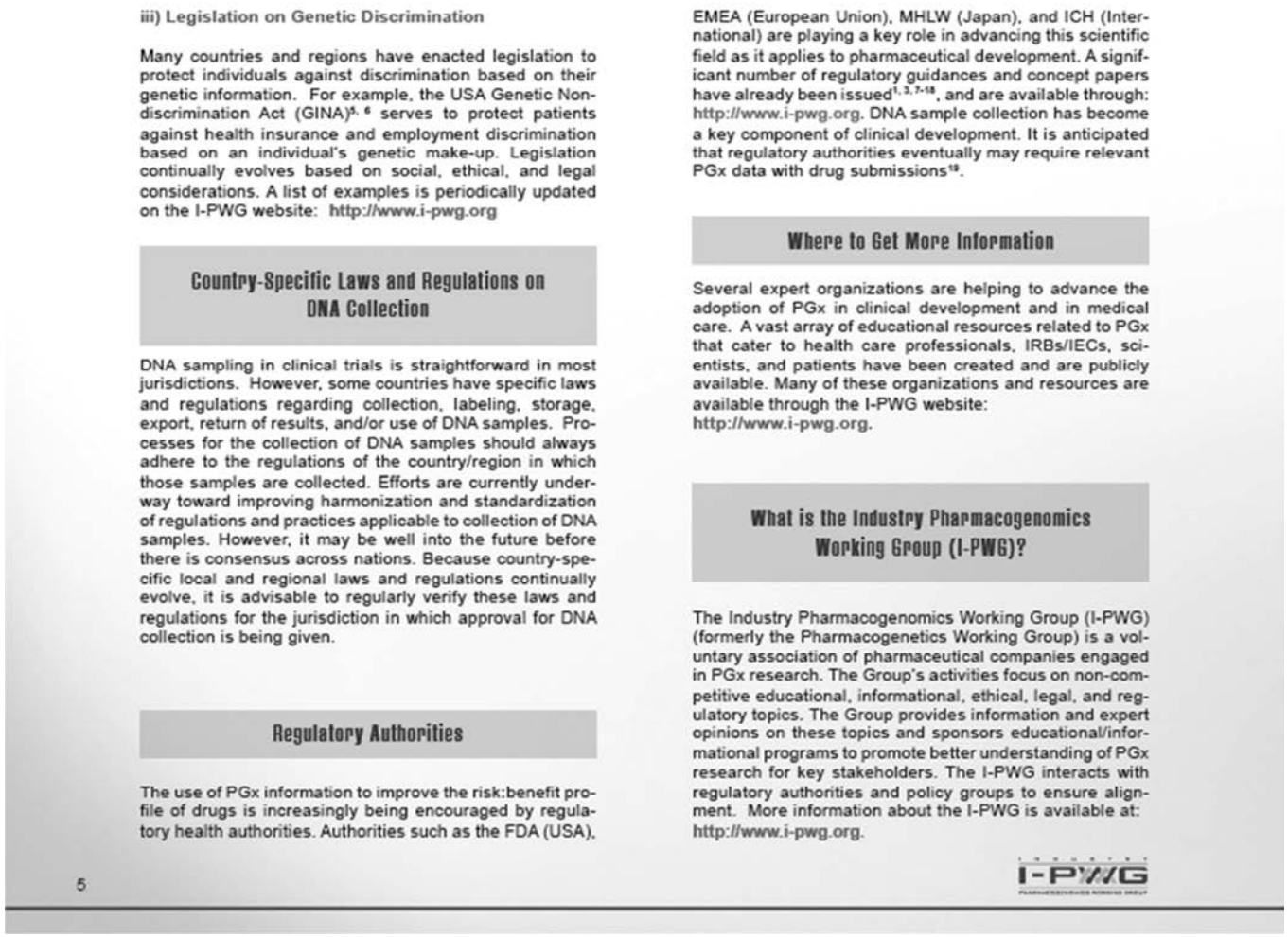

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[18].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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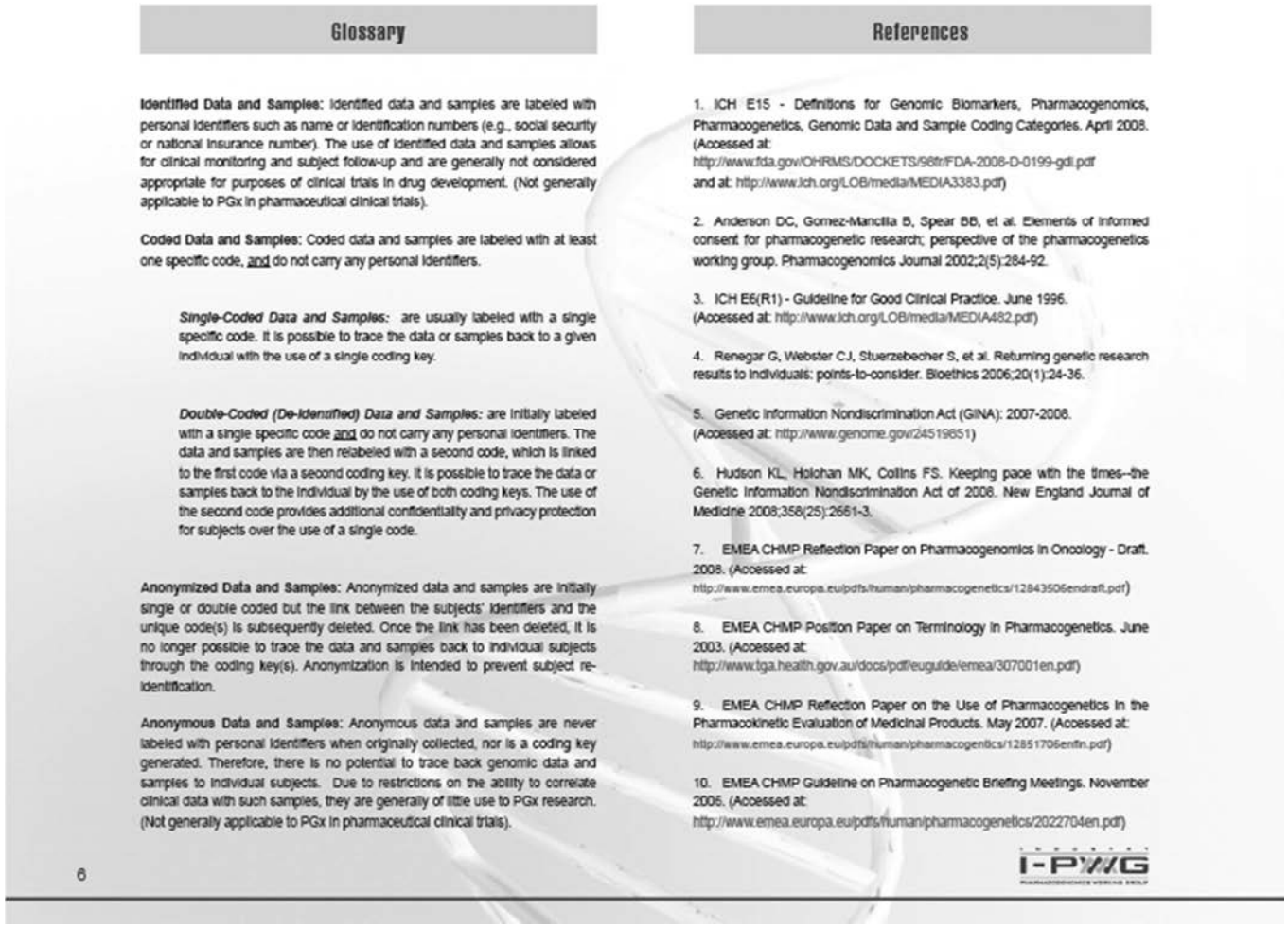

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

6

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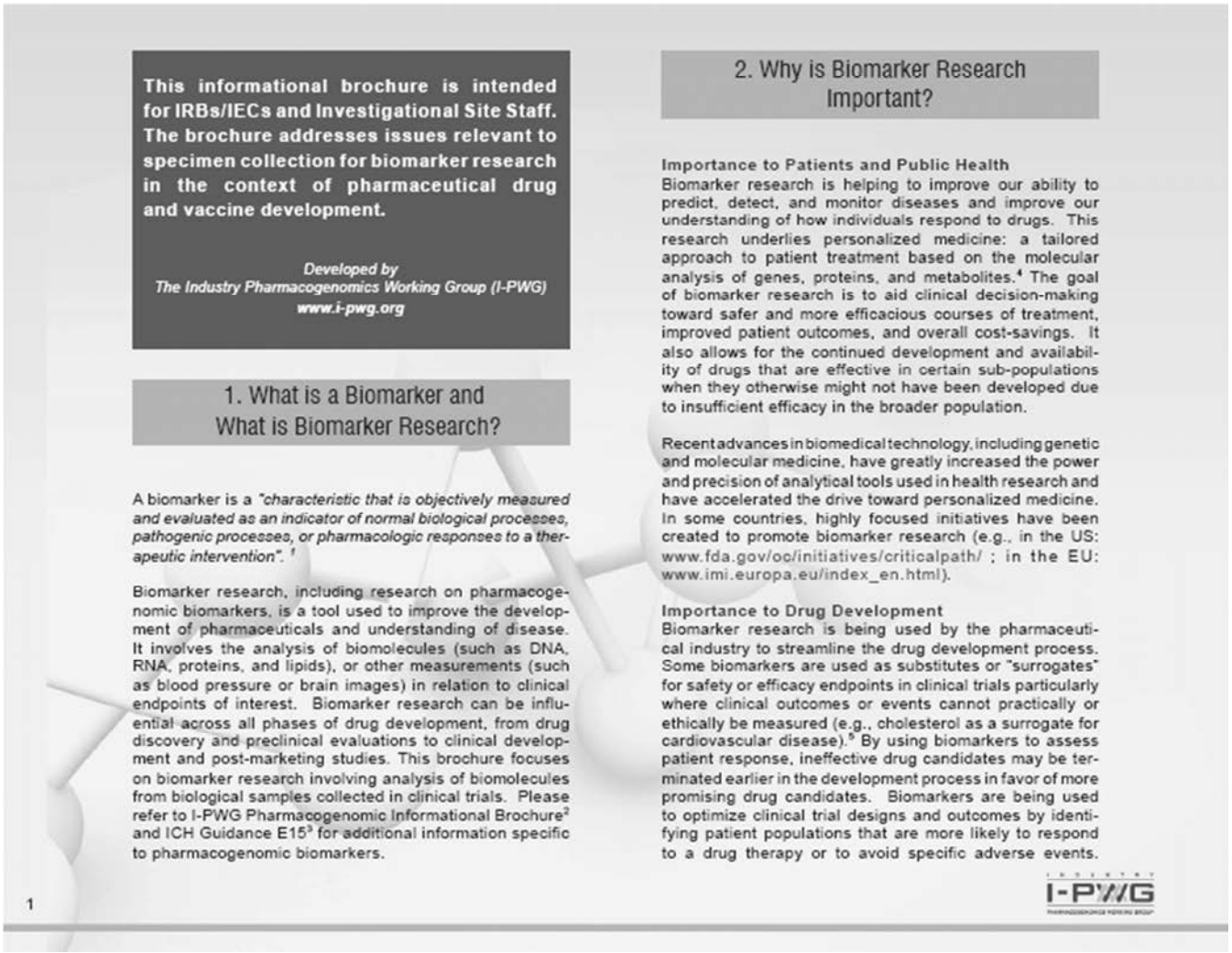

This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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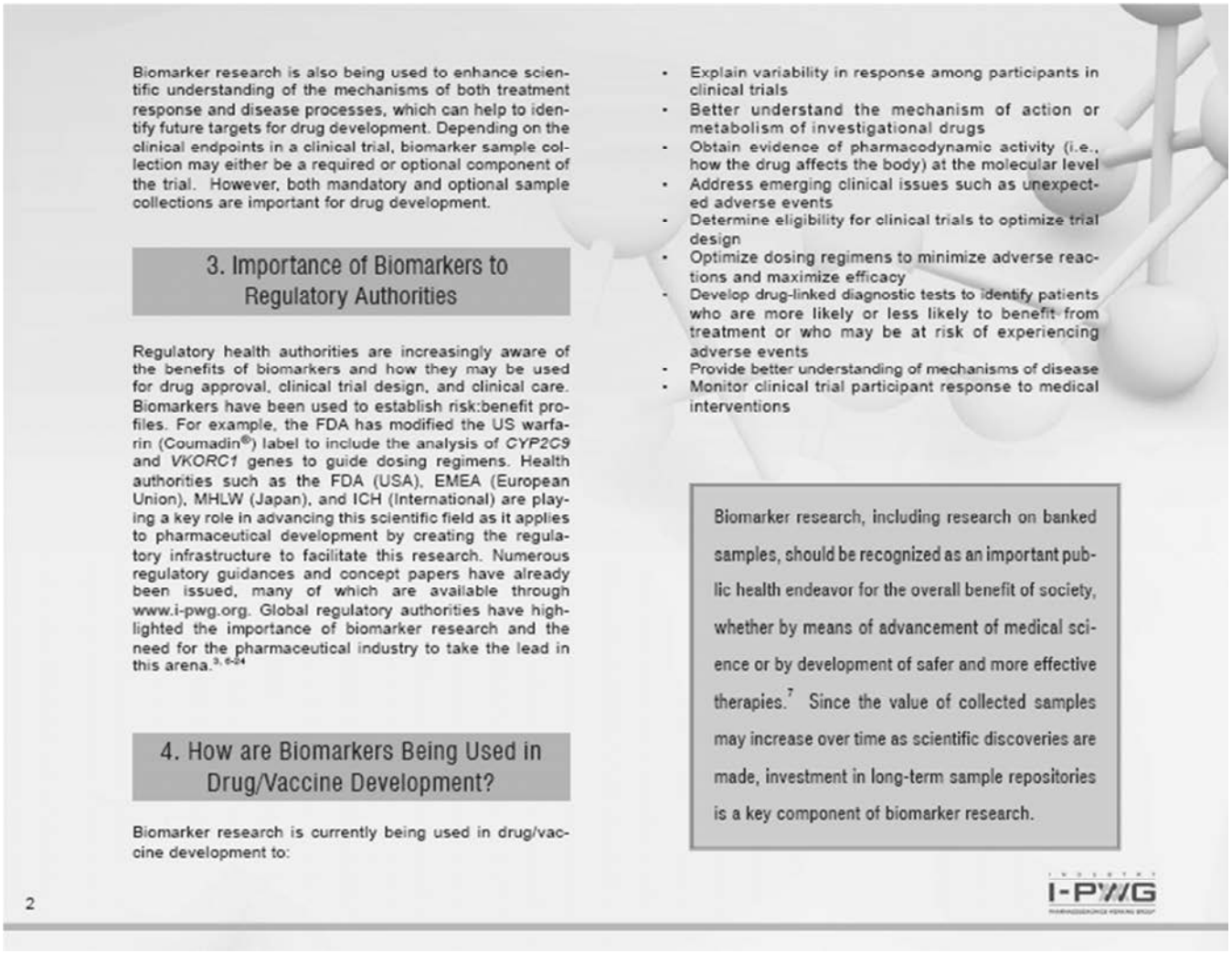
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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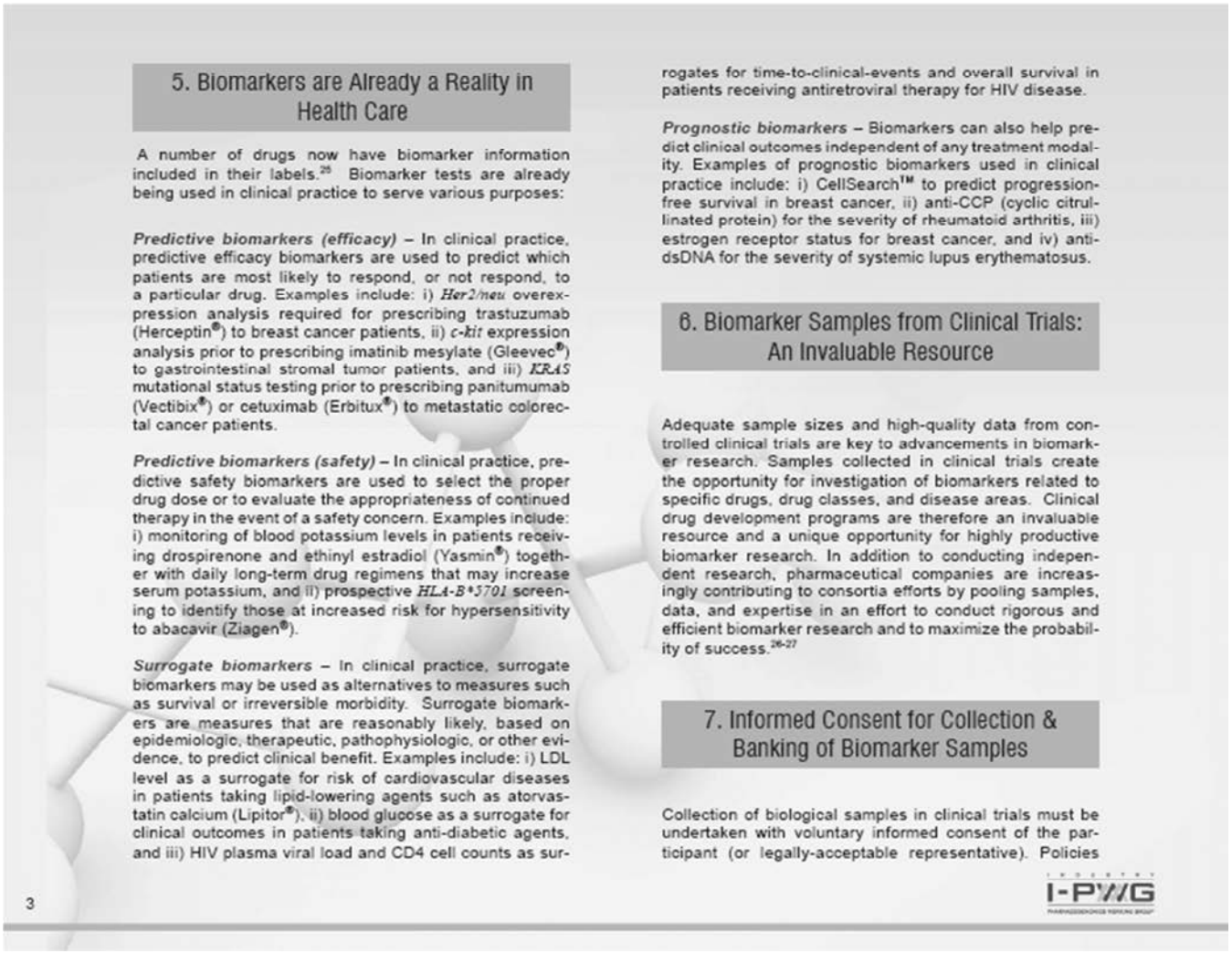

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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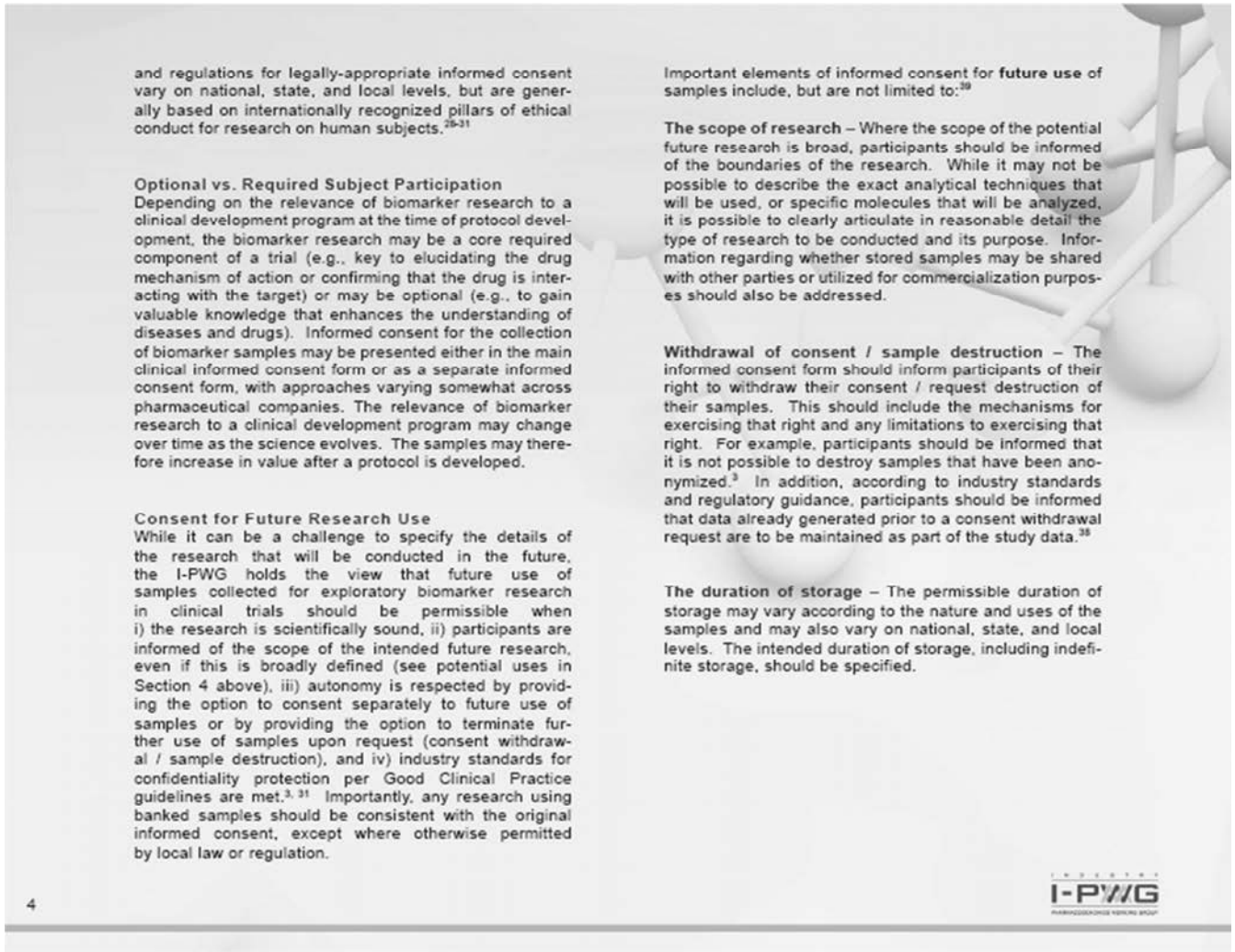

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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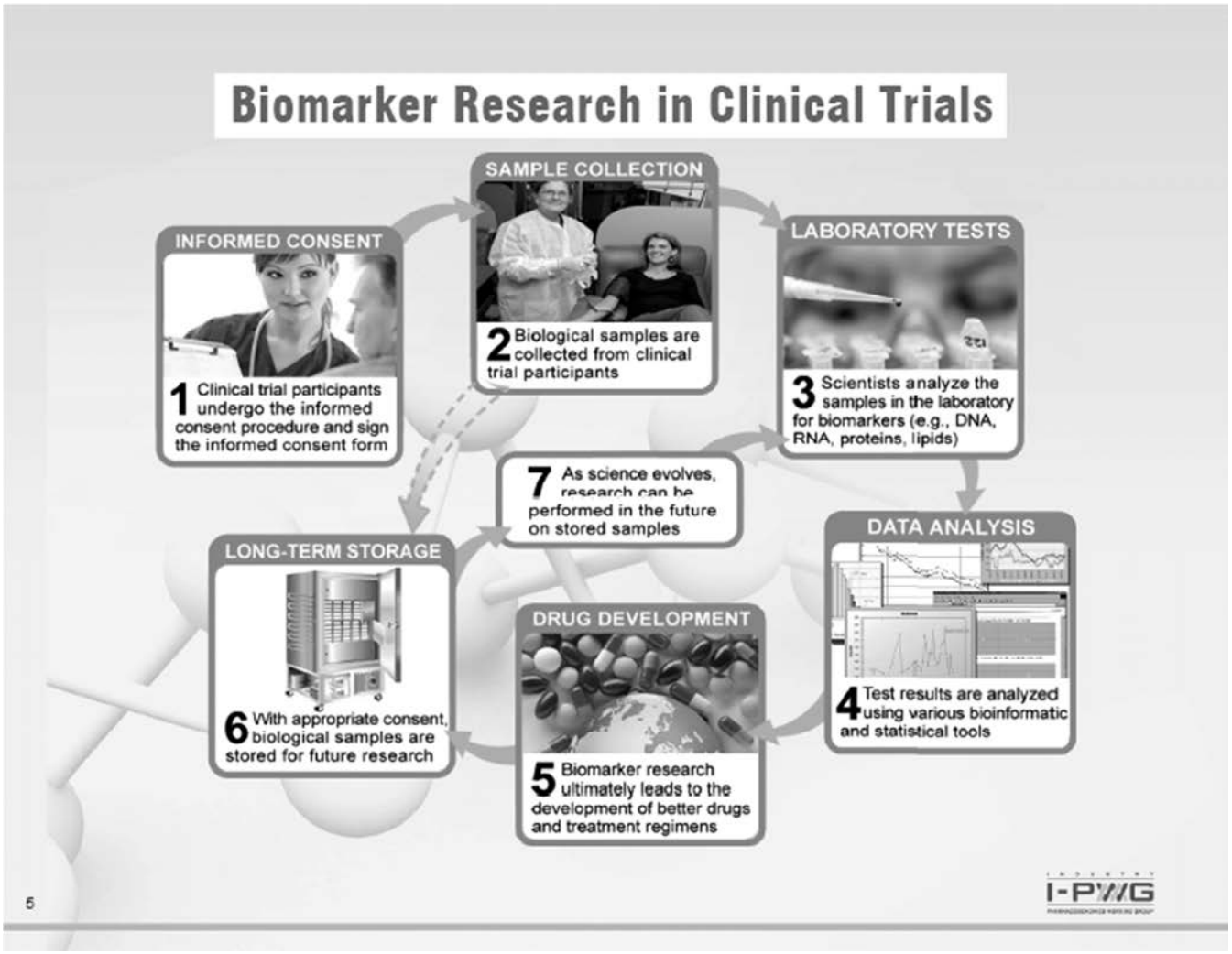
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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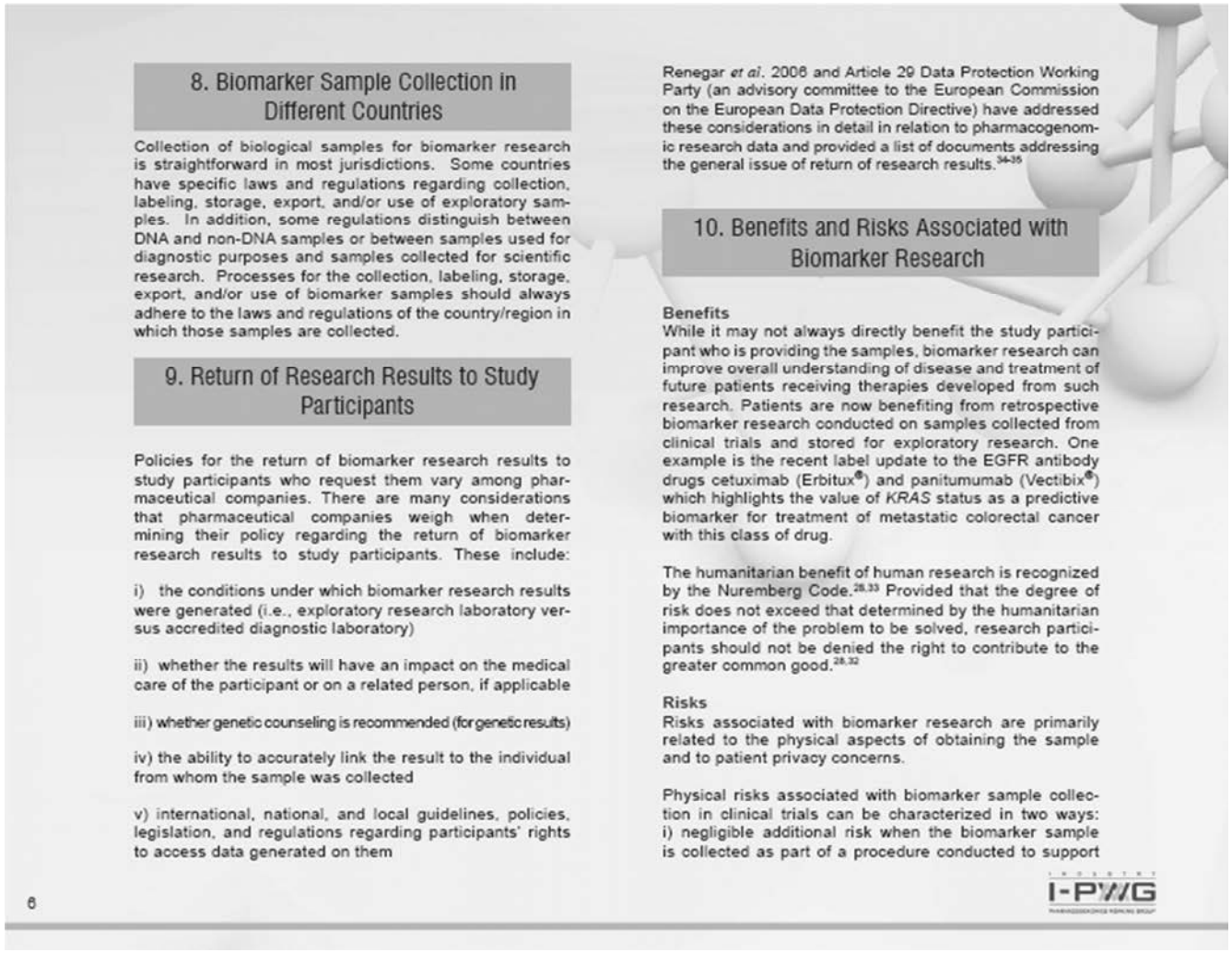

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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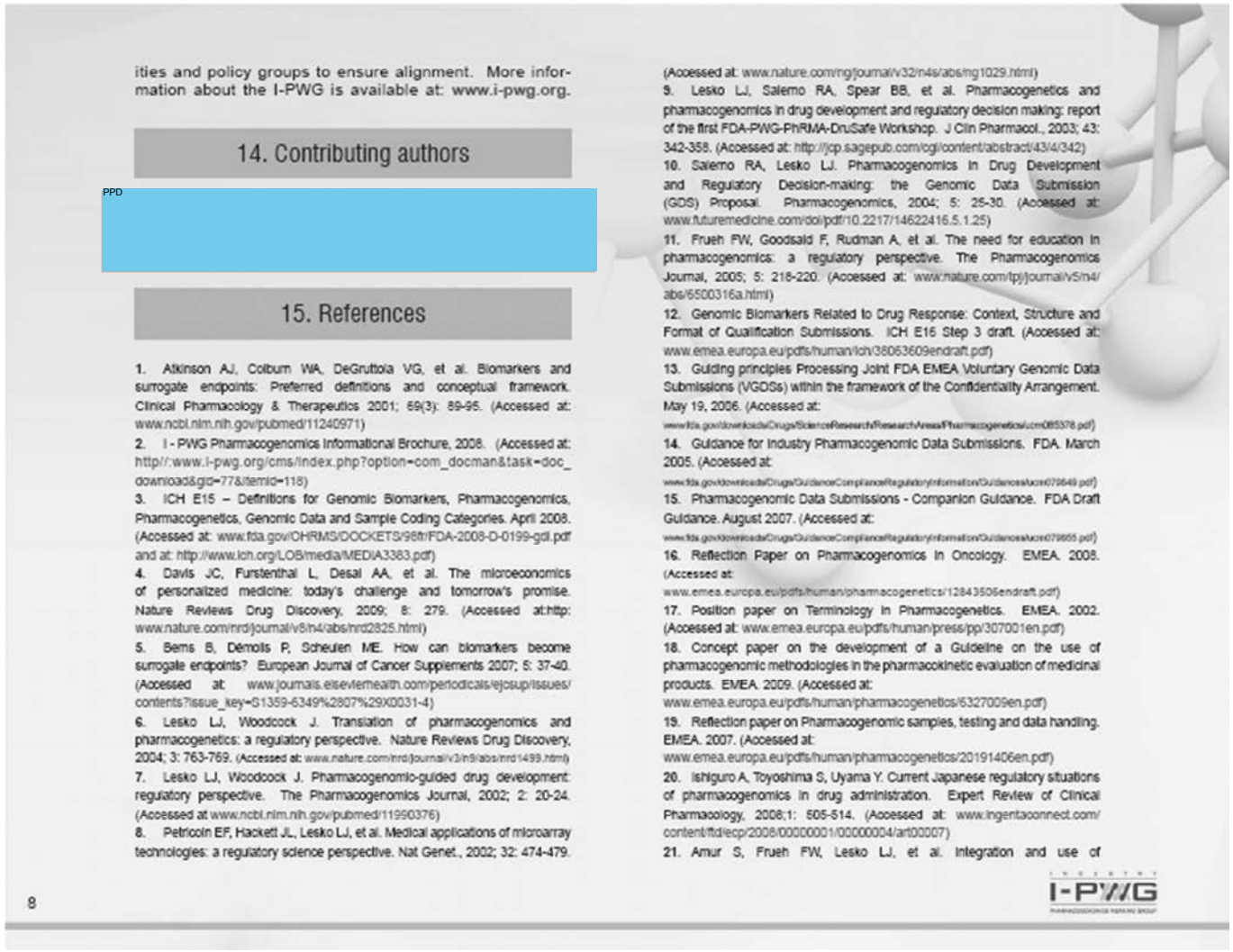
I-PWG



ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit/Cycle/etc:	Screening Visits 1-	Treatment Visit 2	Treatment Visit 4	Treatment Visit 6	Post-Treatment
Blood Parameter	**Approximate Blood Volume (mL)**				
Hematology	2	2	2	2	
Serum/Plasma Chemistry	8.5	8.5	8.5	8.5	
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	3.5				
Serum Follicle Stimulating Hormone (FSH)[b]	3.5				
HIV/Hepatitis Screen (at the discretion of the investigator and/or per site SOPs)[b]	3.5				
Blood for Genetic Analysis (DNA)		8.5			
Prolactin	3.5	3.5		3.5	
PK		6	18	6	
Lipids	3.5	3.5		3.5	
Fasting glucose	2	2	2	2	
Insulin	2	2		2	
Expected Total (mL)	32.0	36.0	30.5	27.5	

a. For female subjects of child bearing potential only
b. if applicable and dependent upon site SOP

12.5 Abbreviations

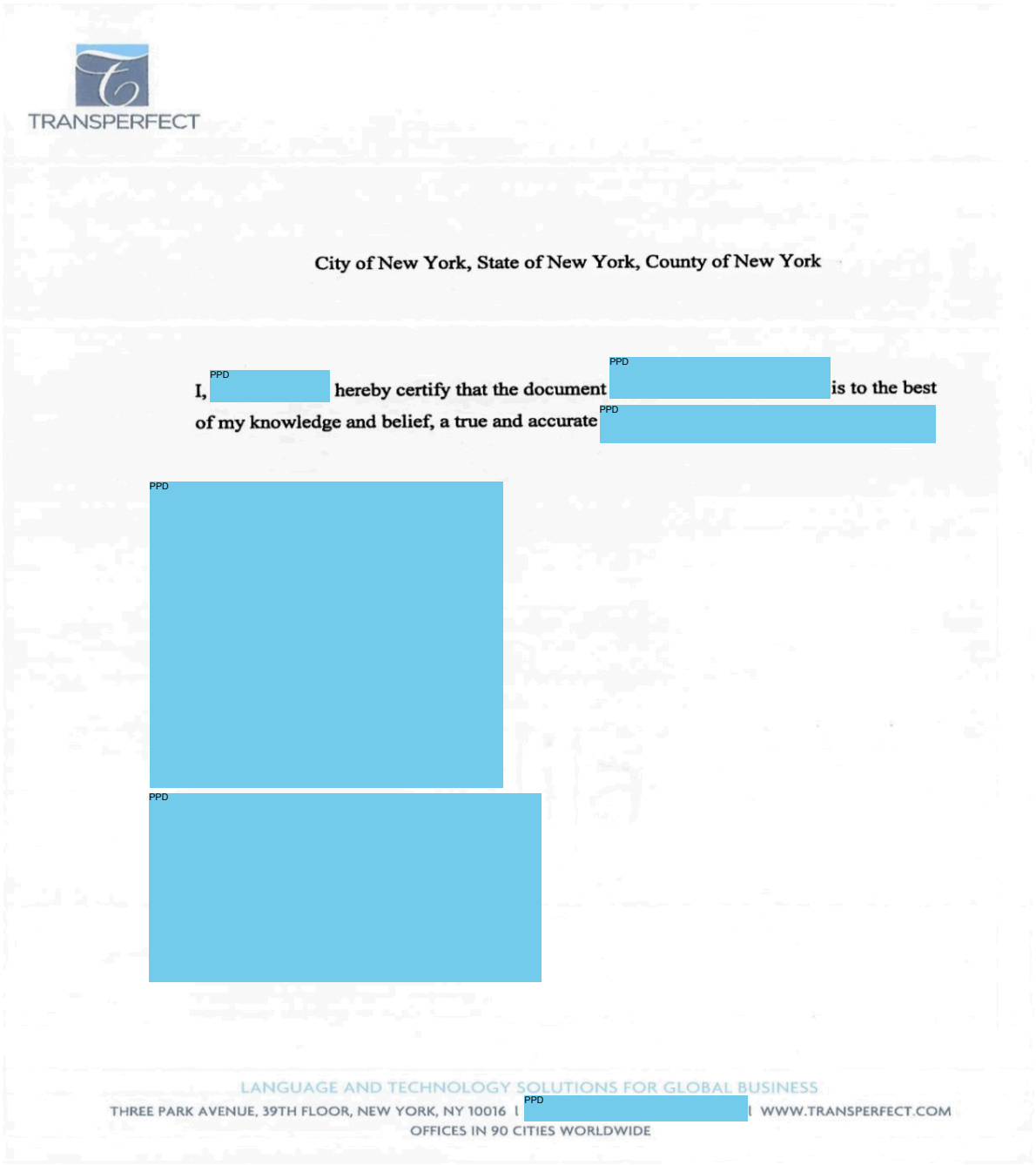
Abbreviation	Definition
AAP	Atypical Antipsychotic
AE	Adverse event/experience
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASaT	All subjects as treated
AST	Aspartate aminotransferase
βhGC	Beta human Chorionic Gonadotropin
BL	Baseline
BMI	Body mass index
BUN Blood urea nitrogen	Blood urea nitrogen
[redacted]	[redacted]
CGI-S	Clinical Global Impression Scale-Severity
[redacted]	[redacted]
CHMP	Committee for Medicinal Products for Human Use
cm	Centimeter
CNS	Central Nervous System
CR	Controlled release
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450 enzyme
DC	Discontinuation
DNA	Deoxyribonucleic Acid
DO	Doctor of Osteopathic Medicine
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
ECI	Event of Clinical Interest
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
eGFR	Estimated Glomerular Filtration Rate

Abbreviation	Definition
EO	Enzyme Occupancy
EPS	Extrapyramidal Symptoms
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
FAS	Full Set Analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration, USA
FDAMA	Food and Drug Administration Modernization Act
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
in	Inches
IND	Investigational New Drug
IP	Investigational Product. This term is interchangeable with the terms "study drug" and "study medication" as used in this protocol. IP refers to MK-8189 tablets , risperidone capsules and their respective placebos in the dosage form and strengths specified in the protocol
IP Dose	The quantity of investigational product taken at one dose For this protocol, subjects will take a specified equal number of IP tablets and capsules.
IRB	Institutional Review Board
ITT	Intent to Treat
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
kg	Kilograms

Abbreviation	Definition
lb	Pounds
LDL	Low density lipoprotein
MAO	Monoamine oxidase
MAR	Missing at Random
MD	Doctor of Medicine
MDRD	Modification of Diet in Renal Disease (calculation)
MINI	Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders
MIST	Metabolites in Safety Testing
NDA	New Drug Application
NP	Nurse Practitioner
NSAID	Nonsteroidal anti-inflammatory drug
PA	Physician's Assistant
PANSS	Positive and Negative Syndrome Scale
PC	Phone Call
PD	Pharmacodynamics
[redacted]	[redacted]
PE	Physical Exam
PhD	Doctor of Philosophy
pH	Numeric scale to measure acidity or basicity
PGt	Pharmacogenetic
PK	Pharmacokinetic(s)
PPDM	Department of Pharmacokinetics Pharmacodynamics and Drug Metabolism
QD	Once daily
QTcF	QT (waves) corrected-Fridericia
Rand	Randomization
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
(S)AE	All Adverse Events, including Serious Adverse Events

Abbreviation	Definition
SDME	Sponsor designated medical expert: a medically qualified sponsor representative who consults with sites on protocol-specific activities, such as the review of the Screening psychiatric evaluation intake forms to verify subject eligibility. An "external" SDME refers to a vendor SDME.
siDMC	Standard Internal Data Monitoring Committee
SME	Subject Matter Expert
SOC	System Organ Class
SOP	Standard Operating Procedure
T4	Thyroxine
TEAE	Treatment Emergent Adverse Events
TC	Telephone Contact
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
US, USA	United States of America
WBC	White Blood Cell

12.6 Risperidone Label



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[logo:] actavis

Package information leaflet: information for user

Risperidone-Actavis 2 mg
Coated tablets
Risperidone

Read the entire package information leaflet carefully before you start using this medicinal product because it contains important information.
- Keep the package information leaflet. You may want to read it again later.
- Please ask your physician or pharmacist if you have any further questions.
- This medicinal product was prescribed to your personally. Do not give it to third parties. It can harm other people even though they may have the same complaints as you.
- Contact your physician or pharmacist if you notice any side effects. This is also the case for side effects that are not described in this package insert.

What this package insert contains

1. What is Risperidone-Actavis and what is it used for?

Risperidone-Actavis is in a category of medicinal products called "antipsychotics"
Risperidone-Actavis is applied for treatment of the following clinical pictures:
- Schizophrenia, during which you see, hear or feel things that aren't there, can believe things that aren't true or feel unusually suspicious or confused.
- Mania during which you can feel very excited, euphoric, agitated, enthusiastic or hyperactive. Mania develops during an illness called "manic-depressive disease."
- Short-term treatment (up to 6 weeks) of long-lasting aggression in persons with Alzheimer's disease that harm themselves or others. Alternative (non-medicinal) treatments should have been applied before.
- Short-term treatment (up to 6 weeks) of long-lasting aggression in mentally handicapped children (from at least 5 years of age) and adolescents with behavioral problems.

2. What should you observe before application of Risperidone-Actavis?

Risperidone-Actavis may not be taken
- if you are allergic to Risperidone or one of the excipients of this medicinal product named in section 6.

If you aren't sure whether one of the above conditions applies to you ask your physician or pharmacist before taking Risperidone-Actavis.

Warnings and precautionary measures
Ask your physician or pharmacist before taking Risperidone-Actavis if:
- You have problems with your heart. Examples are an irregular heartbeat or if you tend to have low blood pressure or if you take a medicinal product for your blood pressure. Risperidone-Actavis can [text cut off]
- You have had involuntary movements of the tongue, the mouth or in the face.
- You ever had a condition the symptoms of which include fever, stiff muscles, bouts of sweating or impaired consciousness (also known as [text cut off]
- Medicinal products that lower your heart rate
- Medicinal products that cause a low potassium level in the blood (for example, certain diuretics)
- Medicinal products for treatment of hypertension. Risperidone-Actavis can cause low blood pressure
- Medicinal products for treatment of Parkinson's disease (for example Levodopa)
- Water pills (diuretics) that are applied in case of heart problems or swelling of body parts due to the collection of too much fluid (for example Furosemide or Hydrochlorothiazide). Risperidone-Actavis alone or applied with Furosemide can increase the risk of a stroke or death in older patients with dementia.

The following medicinal products can lower the effect of Risperidone:
- Rifampicin (a medicinal product for treatment of certain infections)
- Carbamazepine, Phenytoin (medicinal product against epilepsy)
- Phenobarbital

You may need a different dose of Risperidone if you start or stop taking these types of drugs.

The following medicinal products can increase the effect of Risperidone:
- Chinidine (used in certain types of heart disease)
- Antidepressants, such as for example Paroxetine, Fluoxetine, tricyclic antidepressants
- Medicinal products known as beta blockers (used for treatment of hypertension)
- Phenothiazines (for example used as a medicinal product to treat psychoses or for sedation)
- Cimetidine, Ranitidine (acid blockers for the stomach)

You may need a different dose of Risperidone if you start or stop taking these types of drugs.

[barcode]

If you are not sure if one of the above conditions applies to you ask your physician or pharmacist before you take Risperidone-Actavis.

Taking of Risperidone-Actavis together with foods, beverages and alcohol
You can take this medicinal product with meals or independent of them.
Avoid drinking alcohol while taking Risperidone-Actavis.

Pregnancy and nursing
- If you are pregnant or nursing or if you suspect being pregnant or intend to become pregnant ask your physician or pharmacist for advice before taking this medicinal product. Your physician will decide whether or not you can take it.
- The following symptoms can develop in newborn babies of mothers who took Risperidone-Actavis in the last trimester (last three months of pregnancy): trembling, muscle stiffness and/or weakness, somnolence, restlessness, respiratory complaints and difficulties nursing. You should contact your physician if your baby develops one of these symptoms.

Ability to drive and operate machines
Dizziness, fatigue and vision problems can develop during treatment with Risperidone-Actavis. You may not sit behind the wheel of a vehicle and you may not [text cut off]
[text cut off] sugars.

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on 31/JUL/ 2015 by PPD
Version 1.0

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3. How should Risperidone-Actavis be taken?
[text cut off] an irregular heartbeat or if you tend to have low blood pressure or if you take a medicinal product for your blood pressure. Risperidone-Actavis can cause low blood pressure. Your dose may have to be adjusted.
- You have known factors that facilitate a stroke, such as hypertension, cardiovascular diseases or problems with the blood vessels in your brain
- You have had involuntary movements of the tongue, the mouth or in the face.
- You ever had a condition the symptoms of which include fever, stiff muscles, bouts of sweating or impaired consciousness (also known as "malignant neuroleptic syndrome")
- You suffer from Parkinson's disease or dementia
- You are diabetic
- You suffer from epilepsy
- You are male and have already had a long-lasting or painful erection.
- You have problems controlling your body temperature or overheating
- You have kidney problems
- You have liver problems
- You have anomalously high values of the hormone prolactin in your blood or if you suffer from a tumor that may be dependent on prolactin
- You or a relative have had **venous thromboses** (blood clots) in the past, since these types of medicinal products are associated with the development of blood clots.

If you are not sure if one of the aforementioned conditions applies to you ask your physician or pharmacist before taking Risperidone-Actavis.

Risperidone-Actavis can cause weight gain. Significant weight gain can affect your health. Your physician should regularly check your weight.

Your physician should monitor you for signs of an elevated blood sugar level because diabetes mellitus or worsening of existing diabetes mellitus has been observed in patients taking Risperidone-Actavis.

[barcode]

Older patients with dementia
There is an increased risk of stroke in older patients with dementia. You should not take Risperidone if you suffer from dementia that was caused by a stroke. You should visit your physician regularly during treatment with Risperidone.
Medical treatment is immediately necessary if you or your caretaker notice a sudden change in your mental condition or sudden weakness or lack of feeling in the face, arms or legs, particularly on one side, or slurred speech, even for a short amount of time. These could be signs of a stroke.

Risperidone alone or applied with Furosemide can increase the risk of a stroke or death in older persons with dementia.

Children and adolescents
Before treatment of the behavioral disorder other reasons for aggressive behavior should have been ruled out.

Your weight or your child's weight should be determined before the treatment and regularly checked during the treatment.

If fatigue occurs during the treatment with Risperidone, a switch in the administration time can improve the attentiveness problems.

Taking of Risperidone-Actavis together with other medicinal products
Inform your physician or pharmacist if you are taking/applying other medicinal products, recently took/applied other medicinal products or intend to take/apply other medicinal products even if these are over-the-counter medicinal products and herbal medicinal products.

It is particularly important to speak to your physician or pharmacist if you are taking or applying one of the following medicinal products:
- Medicinal products that affect your brain in order to sedate you (benzodiazepines) or some painkillers (opiates), allergy drugs text cut off]

Dizziness, fatigue and vision problems can develop during treatment with Risperidone-Actavis. You may not sit behind the wheel of a vehicle and you may not operate tools or machines without consulting your physician first.

Risperidone-Actavis contains lactose
For this reason, please only take Risperidone-Actavis after consulting your physician if you know that you suffer from an intolerance to certain sugars.

3. How should Risperidone-Actavis be taken?

Always take Risperidone-Actavis exactly as instructed by your physician. Ask your physician or pharmacist if you are unsure.

How much should you take

In treatment of schizophrenia
Adults
- The conventional initial dose is 2 mg per day and may be increased to 4 mg per day on the second day.
- Afterwards the dose can be adjusted by your physician depending on how you respond to the treatment.
- Most people feel better when taking a daily dose of 4 to 6 mg.
- This total daily dose can be divided into one dose or two doses daily. Your physician will inform you what is best for you.

Older patients
- Your initial dose is generally 0.5 mg twice daily.
- Your dose can then be gradually increased by your physician to 1 to 2 mg twice daily.
- Your physician will inform you what is best for you.

Children and adolescents
- Children and adolescents under 18 years of age should not receive schizophrenia treatment with Risperidone-Actavis.

In treatment of mania
Adults
- Your initial dose is generally 2 mg once daily.
- Afterwards your physician may gradually adjust the dose depending on how you respond to the treatment.
- Most people feel better when taking a once daily dose of 1 to 6 mg.

Older patients
- Your initial dose is generally 0.5 mg twice daily.
- Afterwards your physician may gradually adjust the dose to 1 to 2 mg twice daily depending on how you respond to the treatment.

Children and adolescents
- Children and adolescents under 18 years of age should not receive Risperidone-Actavis treatment for mania within the scope of a manic-depressive disorder.

In treatment of persistent aggression in people with Alzheimer's disease
Adults (including older persons)
- Your initial dose is generally 0.25 mg twice daily.
- Afterwards your physician may gradually adjust the dose depending on how you respond to the treatment.
- Most people feel better when taking a twice daily dose of 0.5 mg. Some patients may require 1 mg twice daily.
- The duration of treatment in patients with Alzheimer's disease should not exceed 6 weeks.

In treatment of behavioral disorders in children and adolescents

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The dose depends on your child's weight:

In children who weigh less than 50 kg
- The initial dose is generally 0.25 mg once daily.
- The dose can be increased every other day in increments of 0.25 mg
  [text cut off]

[repeat text]

It is particularly important to speak to your physician or pharmacist if you are taking or applying one of the following medicinal products:
- Medicinal products that affect your brain in order to sedate you (benzodiazepines) or some painkillers (opiates), allergy drugs (some antihistamines). Risperidone can increase the sedative (calming and drowsy) effect of this medicinal product.
- Medicinal products that can change the electrical activity of your heart, for example, medicinal products for the treatment of malaria, dysrhythmia, allergies (antihistamines), some antidepressants or other medicinal products for the treatment of mental problems

[repeat text]

In treatment of behavioral disorders in children and adolescents
The dose depends on your child's weight:

In children who weigh less than 50 kg
- The initial dose is generally 0.25 mg once daily.
- The dose can be increased every other day at increments of 0.25 mg per day
- The conventional maintenance dose is 0.25 mg to 0.75 mg once daily.

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In children who weigh 50 kg or more
- The initial dose is generally 0.5 mg once daily.
- This dose can be increased every other day at increments of 0.5 mg per day
- The conventional maintenance dose is 0.5 mg to 1.5 mg once daily.

The therapeutic duration in patients with behavioral disorders should not exceed 6 weeks.

Children under the age of 5 with behavioral disorders should not be treated with Risperidone-Actavis.

Persons with kidney or liver problems
The initial doses and the following doses should be cut in half regardless of which disorder is being treated. The dose should be increased more slowly in these patients.
Risperidone should be used with caution on this patient group.

Your physician will inform you of how much of the medicinal product you should take over what time period. This depends on your respective condition and is different from person to person. The amount of the medicinal product to be taken is described in the section "How much should you take."

You should take your tablet with water.

If you have taken a larger amount of Risperidone-Actavis than you should have
- Immediately seek medical attention. Take the package of the medicinal product with you.
- In case of an overdose you might feel sleepy or tired or have anomalous body movements, problems standing or walking, feel dizzy due to low blood pressure or have an anomalous heartbeat or seizures.

If you forgot to take Risperidone-Actavis
- If you forgot to take a dose then take it as soon as you remember this. However, if it is almost time for your next dose skip the dose you missed and continue as usual. If you miss two or more doses consult your physician.
- **Do not take the double dose (two doses at the same time) to make up for the dose you missed.**

If you stop taking Risperidone-Actavis
You should not stop taking this medicinal product unless your physician has instructed you to do so. Otherwise your symptoms can recur. If your physician decides to discontinue the medicinal product your dose is gradually lowered over the course of a few days.

If you have any further questions on the administration of this medicinal product ask your physician or pharmacist.

4. What side effects are possible?

Like all medicinal products this medical product can also have side effects, but they may not occur in everyone.

Immediately inform your physician if you:
- develop blood clots in your veins, particularly in the legs (with swelling, pain and redness of the legs) that may reach your lung via the bloodstream, where they may cause thoracic pain as well as difficulties breathing. Immediately seek medical attention if you notice one of these symptoms in you.
- have dementia and you develop a sudden change in your mental condition or sudden weakness or numbness in the face, arms or legs, particularly on one side, or unclear speech, even for a short amount of time. These could be signs of a stroke.
- notice fever, muscle stiffness, bouts of sweating or impaired consciousness (a disorder called "malignant neuroleptic syndrome"). Immediate medical treatment may be necessary.
- are male and you develop a long-lasting or painful erection. This is called priapism. [text cut off]
- fainting, walking problems, sluggishness, decreased appetite resulting in malnutrition and low body weight. Feeling of "not being at one's best," balance problems, allergy, fluid retention, speech disorder, chills, anomalous coordination, anomalous taste sensation
- painful hypersensitivity to light, elevated blood flow to the eye, swollen eyes, dry eyes, increase in lachrymation
- complaints in the airways, congested lung, rales, congestion of the airways, problems speaking, difficulties swallowing, cough with expectoration, hoarseness/sibilant rales while breathing, flu-like disorder, congestion of the paranasal sinuses
- lack of reaction to stimuli, loss of consciousness, sudden swelling of the lips and eyes in connection with difficult breathing, sudden weakness or numbness of face, arms or legs, particularly on one side, or cases of slurred speech that last less than 24 hours (these are so-called minor strokes or strokes), involuntary movements of the face, the arms or legs, ringing in the ears, fluid retention in the face

Rare (1 to 10 of 10,000 treated persons):
- Inability to have an orgasm, menstruation problems
- Dandruff
- Drug allergy, feeling of coldness in arms and legs, swelling of the lips, inflammation of the lips
- Glaucoma, decreased visual acuity, crust formation on the edges of the eyelids, eye-rolling
- Lack of emotion
- Change in consciousness with elevated body temperature and muscle twitching, fluid retention in the entire body, drug withdrawal syndrome, decreased body temperature
- fast, flat breathing, difficulties breathing while sleeping, chronic middle ear inflammation
- Ileus
- Decreased blood flow to the brain
- Decrease in white blood cells, inadequate secretion of a hormone that controls the amount of urine
- Degeneration of muscle fiber and pain in muscles (rhabdomyolysis), movement problems
- Trembling of head
- Coma due to uncontrolled diabetes
- Yellow discoloration of the skin and eyes (jaundice)
- Inflammation of the pancreas
- Low blood sugar

Very rare (fewer than 1 of 10,000 treated persons):
- life-threatening complications of uncontrolled diabetes

[barcode]

Incidence not known (incidence cannot be estimated on the basis of the available data):
- severe allergic reaction that leads to breathing difficulties and shock
- lack of granulocytes (a type of white blood cell that helps fight infections)
- extended and painful erection
- dangerous excessive retention of water

Long-term effective injectable Risperidone
The following side effects were observed during the application of long-term effective injectable Risperidone.
You should visit your physician in case you develop one of the following even if you were not treated with injections with long-term Risperidone effect.

- Intestinal infection
- Abscess under the skin, tingling, stabbing or numbness of skin, eczema
- Depression
- Seizures

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- Twitching of the eyes
- Rotating or staggering feeling
- Slow heartbeat, hypertension
- Tooth pain, cramps in the tongue
- Pain in buttocks
- Weight loss

Contact your physician or pharmacist if you notice side effects. This is also the case for side effects that are not listed in this package insert.[repeat text]
- are male and you develop a long-lasting or painful erection. This is called priapism. Immediate medical treatment may become necessary.
- notice involuntary, rhythmic movements of the tongue, the mouth or in the face. Discontinuation of Risperidone may be necessary.

Please immediately consult a physician if you notice any of the aforementioned side effects.

The following side effects can occur:
Very common side effects (more than 1 of 10 treated persons):
- Parkinsonism. This is a medical description that includes many symptoms. Each individual symptom can occur in fewer than 1 of 10 persons.
  Parkinsonism includes: increase in salivary secretion or watery mouth, stiffness of skeletal musculature, increased flow of saliva from the mouth, reflexes during flexion of extremities, slow, reduced or impaired movements, inexpressiveness of the face, muscle tightness, stiff neck, muscle stiffness, small, scuffling, fast steps and absence of normal arm movements while walking, persistent blinking as a reaction to tapping on the forehead (an anomalous reflex)
- Headache, problems falling asleep or sleeping through the night

Common (1 to 10 of 100 treated persons):
- Drowsiness, exhaustion, restlessness, inability to sit still, irritability, state of anxiety, somnolence, dizziness, lack of attentiveness, being exhausted, sleeping problems, tremor
- Vomiting, diarrhea, constipation, nausea, increased appetite, abdominal pain or complaints, sore throat, dry mouth
- Weight gain, increase in body temperature, decreased appetite
- Problems breathing, lung infection (pneumonia), flu, infection of the airways, blurry vision, plugged nose, nosebleed, cough
- Urinary tract infection, bedwetting
- Muscle cramps, involuntary movements of muscles in the face or arms and legs, joint pain, back pain, swelling of the arms and legs, pain in arms and legs
- Skin rash, redness of skin
- Fast heartbeat, thoracic pain
- Elevated prolactin hormone level in blood

[barcode]

Occasional (1 to 10 of 1,000 treated persons):
- Excessive drinking of water, stool incontinence, thirst, very hard stool, hoarseness or voice problems
- Diabetes mellitus, high blood sugar
- Lung inflammation caused by the inhalation of food into the airways, infection of the bladder, conjunctivitis, infection of the paranasal sinuses, viral infection, ear infection, tonsillitis, infections under the skin, eye infections, stomach infection, discharge from the eye, fungal infection of the nails
- Anomalous electric stimulus conduction of the heart, drop in blood pressure after standing up, low blood pressure, dizziness after changing position of the body, anomalous electrocardiograms (ECG), anomalous heart rate, perception of heartbeat, accelerated or decelerated heartbeat
- Inability to urinate or incomplete emptying of the bladder, urinary incontinence, pain during urination, frequent urination
- Being confused, attentiveness disorder, low attentiveness, excessive sleeping, nervousness, elated mood (mania), lack of energy and interest
- Elevated liver enzymes, decreased number of white blood cells (including those that protect you from bacterial infections), low hemoglobin or low number of red blood cells (anemia), elevated number of eosinophils (special white blood cells), elevated blood-creatinine phosphokinase, decrease in number of platelets (blood cells that help to stop bleeding), elevated cholesterol and elevated triglycerides (blood fats)
- Muscle weakness, muscle pain, ear pain, neck pain, swollen joints, anomalous posture, stiff joints, muscle pain in ribcage, pain in chest
- Damage to the skin, skin diseases, dry skin, strong itching of the skin, acne, hair loss, skin inflammation caused by mites, discoloration of the skin, thickening of the skin, redness, [text cut off]

[repeat text]

5. How should Risperidone-Actavis be stored?

Store the medicinal product inaccessible to children.

You may no longer use this medicinal product after the expiration date on the container and the outer package indicated after "usable until." The expiration date refers to the last day of the indicated month.

Do not dispose of the medicinal product in wastewater or household trash. Ask your pharmacist how the medicinal product is to be disposed of if you no longer use it. You contribute to protecting the environment this way.

6. Content of package and further information

What Risperidone-Actavis contains
The active ingredient is Risperidone.
Each 2 mg Risperidone-Actavis coated tablet contains 2 mg Risperidone.

The excipients are:
Lactose, anhydrous, microcrystalline cellulose, corn starch, magnesium stearate (Ph.Eur.), Hypromellose, Macrogol 6000, titanium dioxide (E171).

What Risperidone-Actavis looks like and contents of package
Risperidone-Actavis 2 mg are oval, biconvex, white coated tablets with a snap tab and the imprint "T2" on one side.

The coated tablets can be divided into equal halves. Risperidone-Actavis is available in packages with 20 (N1) and 50 (N2) coated tablets.

Pharmaceutical company
Actavis Group hf.
Reykjavikurvegur 76-78
220 Hafnarfjördur
Iceland

Joint distribution
Actavis Deutschland GmbH & Co. KG
Willy-Brandt-Allee 2
81829 Munich
Telephone: 089/558909 – 0
Fax 089/558909 – 240

Manufacturer
Actavis hf.
Reykjavikurvegur 78
220 Hafnarfjördur
Iceland

or

Actavis Ltd.
BT 16 Bulebel Industrial Estate
Zejtun ZTN 08
Malta

or

Balkanpharma – Dupnitsa AD
3 Samokovsko Schosse Str.

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Dupnitsa 2600
Bulgaria

[repeat text]

This package information leaflet was most recently revised in April 2013.
[repeat text]

- Damage to the skin, skin diseases, dry skin, strong itching of the skin, acne, hair loss, skin inflammation caused by mites, discoloration of the skin, thickening of the skin, redness, decreased sensitivity to pain and touch, inflammation of the oily skin
- Lack of menstruation, sexual dysfunction, erectile dysfunction, ejaculation disorders, discharge from breasts, development of breasts in men, decreased sexual drive, irregular menstruation, vaginal discharge

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12.7 Mapping Between the 11 Categories of Suicidal Ideation and Behavior and the C-SSRS and CDR for Programming Standard Tables

Mapping Between the 11 Categories of Suicidal Ideation and Behavior and the C-SSRS	
Category	C-SSRS Questions (from eCRF)*
Suicidal ideation	
Passive	1. Wish to be dead
Active – nonspecific (no method, intent or plan)	2. Non-specific active suicidal thoughts
Active – method, but no intent or plan,	3. Active suicidal ideation with any methods (not plan) without intent to act
Active – intent, with or without a method, but no plan	4. Active suicidal ideation with some intent to act, without a plan
Active – method, intent and plan	5. Active suicidal ideation with specific plan and intent
Suicidal behavior	
Preparatory actions toward imminent suicidal behaviors	Preparatory acts or behavior
Aborted attempt	Aborted attempt
Interrupted attempt	Interrupted attempt
Suicide attempt	Actual attempt
Completed suicide	Completed suicide
Self-injurious behavior, no suicidal attempt	Has subject engaged in non-suicidal self-injurious behavior?
*Data are "Yes" of "No"	

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	