Official Protocol Title:	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin During Metformin Up-titration Compared with Metformin Up-titration Alone in Subjects with Type 2 Diabetes Mellitus
NCT number:	NCT02791490
Document Date:	08-Mar-2016

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin During Metformin Up-titration Compared with Metformin Up-titration Alone in Subjects with Type 2 Diabetes Mellitus

IND NUMBER: 65,495
EudraCT NUMBER: 2015-004224-59

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 TRIAL SUMMARY

Abbreviated Title	Sitagliptin Addition during Metformin Up-titration
Sponsor Product Identifiers	Sitagliptin
Trial Phase	III
Clinical Indication	Treatment of Type 2 Diabetes Mellitus (T2DM)
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
(Select Groups)	Metformin 1000 mg/b.i.d + Sitagliptin 100 mg Metformin 1000 mg/b.i.d + Sitagliptin-matching Placebo
Number of trial subjects	Approximately 380 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 17 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 up to approximately 35 weeks, from the time the subject signs the Informed Consent Form (ICF) through the final contact. This will include an approximately 1-week screening period (not to exceed an approximately 2 weeks) (Visit 1 to Visit 2); a metformin initiation/dose stabilization period of up to 10 weeks (Visit 2 to Visit 3); a 2-week single-blind placebo run-in period (Visit 3 to Visit 4); a 20-week double-blind, placebo-controlled treatment period (Visit 4 to Visit 7); and a post-treatment telephone contact 14 days after the last dose of blinded study drug.
Randomization Ratio	1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This trial is designed to evaluate, in adult subjects with T2DM and inadequate glycemic control on sub-maximal metformin mono-therapy (1000 mg/day), the effect of up-titration of metformin plus the addition of sitagliptin compared to up-titration of metformin alone on glycemic control.

This is a multicenter, randomized, double-blind, placebo-controlled, 2-parallel-arm clinical trial. In one arm, subjects will be randomized to receive 100mg/day of sitagliptin while in the other, subjects will receive placebo to sitagliptin. All subjects will receive metformin as background therapy. At randomization, all subjects will undergo up-titration of immediate-release metformin (Met-IR) from 1000 mg/day (500 mg b.i.d.) to 2000 mg/day (1000 mg b.i.d.). Approximately 380 subjects ≥18 years of age with T2DM diagnosed in accordance with American Diabetes Association (ADA) guidelines [1] who have inadequate glycemic control on monotherapy with metformin 1000 mg per day, as defined below, and who otherwise meet study enrollment criteria, will be randomized. This trial will be conducted in conformance with Good Clinical Practices.

The duration of the trial will be up to approximately 35 weeks (with 7 scheduled clinic visits) for each subject. This will include a 1 to 2 week screening period (Visit 1 to Visit 2); a period of up to 10 weeks for metformin dose stabilization (Visit 2 to Visit 3); a 2-week placebo run-in period (Visit 3 to Visit 4); a 20-week double-blind, placebo-controlled treatment period (Visit 4 to Visit 7 [with telephone contact at Day 9]); and a post-treatment telephone contact 14 days after the last dose of blinded study drug.

Management of Subjects Prior to Randomization

Pre-randomization management of subjects is summarized in Table 1 below. At Visit 1/Screening, subjects who meet criteria for one of the four groups presented in Table 1, based on their anti-hyperglycemic agent (AHA) status and A1C, and also meet other study eligibility criteria detailed in Section 5.0, will be eligible for enrollment. At Visit 2, all subjects will receive diet and exercise counseling and initiate/transition to AHA mono-therapy of Met-IR 1000mg/day (500mg b.i.d), if necessary. After lifestyle +/- AHA modification, subjects will enter a stabilization period of approximately 6-10 weeks prior to initiation of the placebo run-in. At Visit 3/Week-2, subjects will enter a two week placebo run-in period and randomization will occur at Visit 4/Day 1.

Eligibility for continued study participation will be assessed at Visits 1, 3, and 4 based on the criteria detailed in Section 5.1. This includes the requirement at Visit 3/Week -2 that A1C be ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol). The placebo run-in may be initiated at Visit 3/Week -2 while laboratory data, including A1C, are pending, but randomization may not occur until all eligibility criteria are confirmed. If a subject has initiated the placebo run-in but screen fails due to A1C or other laboratory data collected at Visit 3, they should be contacted and told to discontinue the placebo run-in.

Table 1 Pre-Randomization Management

AHA Regimen at Screening		Eligible A1C at Screening (Visit 1)	Subject Management Between Visit 2 and Visit 4
Metformin Dose and Duration at Screening	**Other AHA**		
Met-IR 1000 mg/day at stable dose for ≥ 8 weeks	none	≥7.5 and ≤11.0%	Start stabilization period at Visit 2. After a minimum 6 week period between Visit 2 and Visit 3 (while continuing Met-IR 1000 mg/day), proceed to Visit 3 and initiate placebo run-in as appropriate. Randomize at Visit 4 if subject continues to be eligible.
Met-XR 1000 mg/day at stable dose for ≥ 8 weeks	none	≥7.5 and ≤11.0%	Switch to Met-IR 1000 mg/day (500 mg b.i.d.) at Visit 2. After a minimum 6 week period on Met-IR 1000 mg/day, proceed to Visit 3 and initiate placebo run-in as appropriate. Randomize at Visit 4 if subject continues to be eligible.
None	On monotherapy with the following AHAs at a stable dose for ≥ 8 weeks •Sulfonylurea •Glinides •α-glucosidase inhibitors	≥7.5 and ≤11.0%	Discontinue AHA at Visit 2 and initiate Met-IR 1000 mg/day (500 mg b.i.d.). After a minimum 8 week stabilization period, proceed to Visit 3 and initiate placebo run-in as appropriate. Randomize at Visit 4 if subject continues to be eligible. **NOTE**: At the discretion of the study investigator, Met-IR may be initiated at 500 mg/day and then increased to 1000 mg/day (500 mg b.i.d.) after up to 4 weeks. The subject must be on Met-IR at 500 mg b.i.d. for at least 8 weeks prior to Visit 3.
None for ≥8 weeks	None for ≥8 weeks (≥12 weeks for thiazolidinediones)	≥8.5 and ≤12.0%	Initiate Met-IR 1000 mg/day (500 mg b.i.d.) at Visit 2. After 10 week period on Met-IR 1000 mg/day, proceed to Visit 3 and initiate placebo run-in as appropriate. Randomize at Visit 4 if subject continues to be eligible. NOTE: At the discretion of the study investigator, Met-IR may be initiated at 500 mg/day and then increased to 1000 mg/day (500 mg b.i.d.) after up to 4 weeks. The subject must be on Met-IR at 500 mg b.i.d. for at least 10 weeks prior to Visit 3.

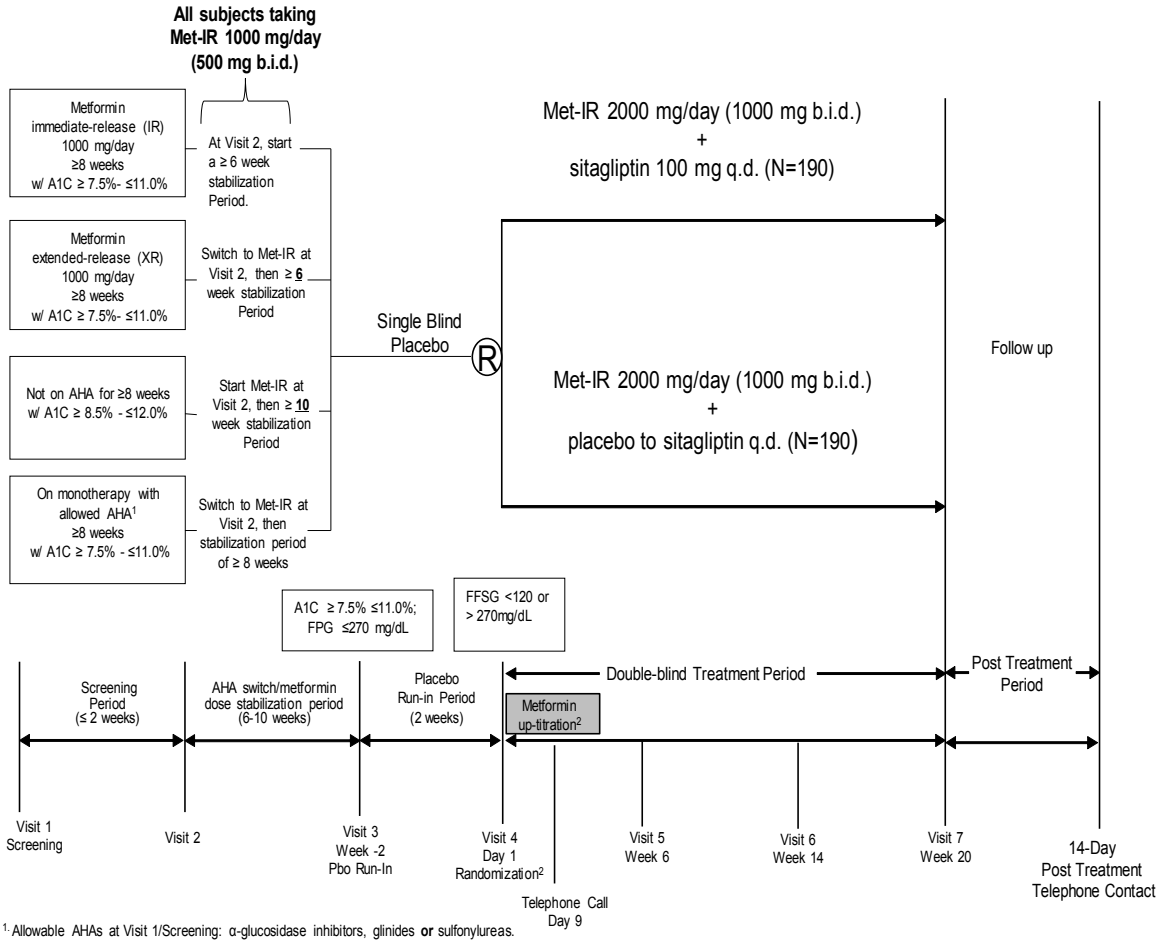
Management of Randomized Subjects

At Visit 4/Randomization (Day 1), subjects will enter the 20-week, double-blind, placebo-controlled treatment period. They will be randomized in a 1:1 ratio to once-daily sitagliptin 100 mg or matching sitagliptin placebo, administered on a background of open-label Met-IR 1000 mg twice daily (b.i.d.). At Visit 4/Day 1, all subjects will be up-titrated to Met-IR 1500 mg (1000 mg daily in AM and 500 mg daily in PM) from the 1000 mg/day (500 mg b.i.d.) dose taken prior to randomization. Subjects will again be up-titrated approximately 7 days (Day 8) post-randomization to Met-IR 2000 mg/day (1000 mg b.i.d.) and continue on this dose of Met-IR for the duration of study participation. Dose escalation of Met-IR to 1000 mg b.i.d. may occur more gradually at the discretion of the investigator. Every effort should be made to have subjects taking Met-IR 1000 mg b.i.d. by approximately 2 weeks after Visit 4/Day 1. If a subject is unable to tolerate 1000 mg b.i.d. Met-IR by Visit 5/Week 6, they should continue on the highest dose of Met-IR they have previously tolerated for the remainder of the study.

Every appropriate effort should be made to support subject study completion on the AHA regimen to which they are randomized. If a subject meets criteria for glycemic rescue therapy (see Section 5.6), rescue therapy will be initiated and taken **in addition to** blinded sitagliptin/placebo to sitagliptin and metformin. Subjects discontinued from blinded study therapy for personal or other reasons (see Section 5.8), should continue to return to the study site for all study visits, and undergo all scheduled safety and efficacy evaluations. If they are unwilling to do so, alternative efforts should be made to collect safety and efficacy information as summarized in Sections 5.8.1 and 7.1.4. Withdrawal of consent will result in discontinuation of all study procedures. Subjects withdrawing consent should be encouraged to complete procedures for the Discontinuation Visit.

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.

2.2 Trial Diagram



1. Allowable AHAs at Visit 1/Screening: α-glucosidase inhibitors, glinides **or** sulfonylureas.

2. Begin Metformin-IR 1000 mg qAM and 500 mg qPM at Visit 4/Randomization. Metformin-IR up-titration to 1000 mg b.i.d. to occur at approximately 7days (Day 8) after randomization

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with T2DM and inadequate glycemic control on treatment with metformin 1000 mg/day, after 20 weeks:

(1) **Objective:** To assess the effect of up-titration of metformin plus the addition of sitagliptin compared with the up-titration of metformin alone on reduction from baseline in A1C.

Hypothesis: Up-titration of metformin to 2000 mg/day (1000 mg b.i.d.) plus the addition of sitagliptin 100mg/day provides greater reduction in A1C compared to metformin up-titration alone.

(2) **Objective:** To assess the overall safety and tolerability of up-titration of metformin plus the addition of sitagliptin compared to up-titration of metformin alone.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with T2DM and inadequate glycemic control on treatment with metformin 1000 mg/day, after 20 weeks:

(1) **Objective:** To assess the proportion of subjects at the A1C goal of <7% (<53 mmol/mol) with up-titration of metformin plus the addition of sitagliptin compared with the up-titration of metformin alone.

Hypothesis: Up-titration of metformin plus the addition of sitagliptin results in a greater proportion of subjects at the A1C goal of <7.0% (<53 mmol/mol) relative to up-titration of metformin alone.

(2) **Objective:** To assess the effect of up-titration of metformin plus the addition of sitagliptin compared to up-titration of metformin alone on reduction from baseline in fasting plasma glucose.

Hypothesis: Up-titration of metformin plus the addition of sitagliptin provides greater reduction in fasting plasma glucose compared to metformin up-titration alone.

(3) **Objective:** To assess the proportion of subjects with baseline A1C ≥ 8.5% that are at the A1C goal of <7% (<53 mmol/mol) with up-titration of metformin plus the addition of sitagliptin compared with the up-titration of metformin alone.

(4) **Objective:** To assess the proportion of subjects receiving glycemic rescue therapy with up-titration of metformin plus the addition of sitagliptin compared with the up-titration of metformin alone.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to approved labeling for detailed background information on sitagliptin and metformin

4.1.1 Pharmaceutical and Therapeutic Background

There has been a steady increase in the global prevalence of T2DM, largely attributed to rising rates of excess body weight and obesity. In 2011, diabetes was estimated to affect more than 365 million people worldwide between the ages of 20-79 years, and the prevalence of diabetes is projected to reach more than 550 million by the year 2030 [2]. T2DM also represents one of the largest medical burdens in the United States, resulting in direct medical costs of $176 billion and $69 billion in loss of productivity in 2012 [3]. At present, it is estimated that 25.8 million people in the US have diabetes (8.3% of the population), of which 7 million remain undiagnosed [4]. T2DM accounts for approximately 90-95% of all cases of diabetes. Individuals with T2DM have an increased risk of developing both microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, and cardiovascular disease, and are 2 to 4 times more likely to die from cardiovascular disease than adults who do not have diabetes [5].

In recent years, diabetes experts have reached a consensus that glycemic targets and glucose-lowering therapies should be individualized [6]. Important comorbidities and adverse effects of anti-hyperglycemic agents (AHAs) are among the subject factors that should be considered. Diet, exercise, and education remain the foundation of treatment for T2DM, but most patients will eventually require AHA therapy. Hence, it is essential to understand the relative efficacy and safety/tolerability of available AHA therapies and treatment paradigms.

Metformin: Metformin is a well-established treatment for patients with T2DM which has been used in Europe for ~40 years and in the U.S. since 1995. Its antihyperglycemic effects are mediated via decreased hepatic glucose output, decreased peripheral insulin resistance, and delay in gastrointestinal absorption of glucose. It tends not to cause weight gain, may be associated with modest weight loss, and can be safely combined with other agents including dipeptidyl peptidase IV (DPP-4) inhibitors, sulfonylureas, sodium glucose co-transporter 2 (SGLT2) inhibitors, and TZDs. Its use has been associated with long-term benefit including decreased mortality. Metformin is contraindicated in patients with advanced renal dysfunction, hypersensitivity to metformin, and acute or chronic metabolic acidosis.

Sitagliptin: Sitagliptin is an orally active and highly-selective dipeptidyl peptidase IV (DPP-4) inhibitor indicated for the treatment of patients with T2DM. The therapeutic improvements in glycemic control associated with sitagliptin are mediated by increases in the active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which result from inhibition (by sitagliptin) of DPP-4, the enzyme responsible for inactivation of these peptide hormones. GLP-1 and GIP are released by enteroendocrine L- and K-cells respectively in response to a meal, and result in enhanced glucose-dependent insulin secretion from pancreatic β-cells. In addition, GLP-1 suppresses glucagon release from pancreatic α-cells and slows gastric emptying. These effects work in concert to lower both fasting and post-prandial glucose concentrations. Clinical studies have shown that sitagliptin (as monotherapy and in combination with other AHAs) is generally well-tolerated, effectively reducing blood glucose concentrations in patients with T2DM.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

In light of its long-established favorable safety and glycemic efficacy profiles, potential cardiovascular benefits, and low cost, metformin is widely used as the first-line pharmacologic anti-hyperglycemic agent (AHA) for patients with T2DM. Maximum approved doses of metformin for adults with T2DM are 2550mg (US) and 3000mg (EU). To mitigate gastrointestinal tolerance and permit use of the lowest effective dose, metformin treatment is typically initiated at a lower dose and increased periodically, guided by tolerability and glycemic response.

Unless contraindicated, metformin is typically initiated at or soon after diagnosis of T2DM, especially in individuals who have not or are unlikely to achieve glycemic targets with lifestyle intervention alone [6]. Metformin is commonly initiated at a dose 500-850 mg once daily, followed by up-titration to a sub-maximal dose (i.e., 1000 mg/day) and A1C re-assessment after a period (≥ 3 months) of stable dosing. For patients who are tolerating metformin well but have not achieved their glycemic target (typically A1c ≤ 7.0%), the metformin dose is increased in increments up to a final dose of ~ 2000 mg/day. If glycemic targets are still not achieved, a second AHA is then added.

Mean A1C decreases of -0.37 to 0.71% have been reported with a dose increase from 1000 mg/day metformin to 2000 mg/day metformin, with higher baseline A1C associated with greater response [7-9]. In patients with relatively high A1Cs already on sub-maximal metformin, the incremental glycemic benefit of maximizing the dose of metformin is unlikely to result in A1C goal achievement in more than a modest proportion of patients. Consistent with this, in T2DM subjects not at A1C goal with diet and exercise, treatment with 2000 mg/day metformin was only marginally more successful than 1000 mg/day metformin in achieving an A1C < 7.0% after 24 Weeks of treatment (38% vs. 23%) [10]. Therefore, for many T2DM patients not at A1C goal on a sub-maximal dose of metformin, up-titration of metformin alone does not result in successful A1C goal attainment. For these individuals, successful A1C goal attainment is substantially delayed by a treatment paradigm in which a second-line AHA is added only after metformin maximization is confirmed to be unsuccessful.

The goal of this study is to assess A1C response with a treatment paradigm in which patients who are not at A1C goal on a sub-maximal dose of metformin receive simultaneous metformin maximization plus initiation of sitagliptin in comparison to the more traditional paradigm of metformin maximization only. When used in combination with metformin, sitagliptin lowers A1C ~0.6-0.8% and is well tolerated [11]. Therefore, initiating sitagliptin in parallel with metformin maximization is anticipated to provide a greater reduction in A1C and thus substantially increase the proportion of individuals achieving an A1C ≤ 7.0% compared to metformin maximization alone. A population of male and female T2DM subjects with A1C ≥7.5 % and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol) while on a stable sub-maximal dose of metformin, will be randomized to make this comparison.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Metformin Dose

As summarized above, the population of interest for this study is individuals with T2DM not at glycemic target on sub-maximal metformin monotherapy. The required pre-randomization Met-IR dose of 1000 mg/day (500 mg b.i.d.) was selected as it reflects the clinical scenario of interest in which many clinicians would routinely complete up-titration of metformin before initiating a second AHA. After randomization, Met-IR will be up-titrated in all subjects from 1000 mg to a top dose of 2000 mg/day in 500 mg increments, an approach that is routinely used and well tolerated in clinical practice. If a subject is unable to tolerate 1000 mg b.i.d. Met-IR by Visit 5/Week 6, they will be continued on the highest dose of Met-IR they have previously tolerated well for the remainder of the study as this would be the clinically appropriate approach.

Met-IR will be administered to both treatment arms in a manner consistent with routine clinical practice. Therefore, it is considered background medication for this study (12).

4.2.2.2 Rationale for Sitagliptin Dose

Sitagliptin 100 mg q.d. has been shown to provide effective improvements across glycemic endpoints and to be well tolerated. Sitagliptin 100 mg q.d. is the approved treatment dose. Though patients with moderate or severe renal insufficiency require a dose reduction, they will be excluded from this study. Therefore, 100mg sitagliptin will be appropriate for all enrolled subjects.

4.2.2.3 Glycemic Rescue

During the double-blind treatment period, subjects who meet progressively more stringent glycemic rescue criteria (see Table 4) will receive glycemic rescue therapy at the discretion of the study investigator. These glycemic rescue thresholds are above standard treatment targets. However, the degree of hyperglycemia permitted over the relatively short study timeframe is not expected to have any long-term health consequence as complications related to chronic hyperglycemia (i.e. retinopathy, nephropathy, neuropathy, macrovascular disease) develop over much longer timeframes [13]. Permitting some degree of hyperglycemia without rescue is necessary to meet the scientific goals of this study with regard to comparing the glycemic efficacy of the two treatment paradigms being evaluated. This is consistent with recent National Research Council guidance emphasizing the importance of study designs that maximize the number of participants who are maintained on the protocol-specified intervention until the outcome data are collected to best address the scientific goals of a clinical trial [14].

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Glycemic efficacy endpoints will be A1C and FPG. A1C reflects average glucose concentrations in the past 3-4 months and, therefore, will provide a useful index of glycemic control at the end of the 20 week treatment period. It is a standard efficacy endpoint used to assess the glycemic efficacy of AHAs, and improvement in A1C correlates with reduction of risk of diabetic complications [6]. Assessment of FPG will provide useful insight into the time course of glucose control in this trial.

4.2.3.2 Safety Endpoints

Safety assessment will include collection of adverse events (AEs), a hypoglycemia assessment log (HAL) to collect information on each potential hypoglycemia episode (including concurrent fingerstick glucose value) and physical examination including vital signs. Laboratory safety studies will include blood chemistry, lipid panel, hematology, and urine pregnancy testing (performed in women of childbearing potential). Refer to Section 8.0 for further details.

4.2.3.3 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. 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

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects with T2DM at least 18 years of age 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:

At Visit 1/Screening

1. Have T2DM in accordance with ADA guidelines [1] and be ≥18 years of age on the day of signing the ICF.
2. Understand and be willing to comply with the study procedures, scheduled visits, treatment plan, alternative treatments available, laboratory tests, risks involved with the study, and other study procedures and have personally signed and dated the ICF indicating that he/she has been informed of all pertinent aspects of the trial and voluntarily agrees to participate.

   NOTE: 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.
3. Meet one of the following criteria:
   a. Be on stable Met-IR monotherapy 1000 mg/day for ≥8 weeks with a Visit 1/Screening A1C ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol).

      OR

   b. Be on stable Met-XR monotherapy 1000 mg/day for ≥8 weeks with a Visit 1/Screening A1C ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol).

      OR

   c. Not on any AHA for ≥8 weeks (≥12 weeks if previously taking thiazolidinediones) with a Visit 1/Screening A1C ≥8.5% and ≤12.0% (≥69 mmol/mol and ≤108 mmol/mol).

      OR

   d. Be on stable monotherapy with a sulfonylurea, a glinide, or an α-glucosidase inhibitor for ≥8 weeks with a Visit 1/Screening A1C ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol).
4. Have a body mass index (BMI) ≥18.0 kg/m^2.

5. Meet one of the following criteria:

    a. Subject is a male.

    b. Subject is a female not of reproductive potential defined as one who:

        1) Is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age), or

        2) Has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or had bilateral tubal ligation/occlusion at least 6 weeks prior to Visit 1/Screening.

        3) Has a congenital or acquired condition that prevents childbearing.

    c. Subject is a female of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 14 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. Use of <u>one</u> of the following methods is acceptable‡:

            - intrauterine device (IUD)
            - vasectomy of a female subject's male partner
            - contraceptive rod implanted into the skin
            - hormonal contraception including vaginal rings
            - condoms
            - diaphragm with spermicide
            - contraceptive sponge

        † 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.

At Visit 3/Week -2

6. Be on stable Met-IR monotherapy 1000 mg/day as described in Section 2.1, Table 1 with a Visit 3/Week -2 A1C of ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol)

   Note: For subjects requiring confirmation of A1C as well as other laboratory testing at Visit 3, placebo run-in may initiate while these data are pending, but randomization will not occur until the results are confirmed to be appropriate for study inclusion including an A1C of ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol).

At Visit 4/Day 1

7. Be ≥80% compliant with the placebo run-in medication (as determined by site performed pill count)

5.1.3 Subject Exclusion Criteria

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

At Visit 1/Screening

Diabetes Diagnosis and Prior Therapy Criteria

1. Has a history of type 1 diabetes mellitus or a history of ketoacidosis or subject is assessed by the investigator as possibly having type 1 diabetes mellitus confirmed with a C-peptide <0.7 ng/mL (0.23 nmol/L) or has a history of secondary causes of diabetes of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).

   Note: Only subjects assessed by the investigator as possibly having type 1 diabetes should have C-peptide measured at Visit 1/Screening.
2. Has a known hypersensitivity or intolerance to any DPP-4 inhibitor.
3. Has a known hypersensitivity or intolerance to metformin, including subjects who were previously unable to tolerate metformin at a dose >1000 mg/day or who have evidence of intolerance to the dose of metformin they are currently taking (for subjects who are taking metformin)
4. Has been treated with any of the following agents within 8 weeks (12 weeks for thiazolidinediones) of **Visit 1/Screening**:
   a. Insulin of any type (except for short-term use [i.e., ≤7 days] during concomitant illness or other stress)
   b. Dipeptidyl-peptidase 4 inhibitors (DPP-4 inhibitor)
   c. Pioglitazone or rosiglitazone (thiazolidinediones)
   d. GLP-1R agonists
   e. SGLT2 inhibitors
   f. Bromocriptine (Cycloset™)

g. Colesevelam (Welchol™)

h. Any other AHA with the exception of protocol-approved agents

5. Subject is on a weight loss program and not in the maintenance phase, or has started a weight loss medication or has undergone bariatric surgery within 12 months prior to signing the informed consent.

   Note: Saxenda™ (liraglutide 3.0mg/day) is approved as a weight loss medication. However, it contains the same active ingredient as the AHA Victoza™ (liraglutide 1.2 and 1.8mg/day) at a higher dose. Therefore, subjects taking Saxenda™ are not eligible for this study even if it was initiated >12 months prior to signing informed consent.

Concomitant Disease of Organs and Systems

6. Has a history of myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischemic attack, NYHA functional class III-IV heart failure, or severe peripheral vascular disease (e.g., claudication with minimal activity, a non-healing ischemic ulcer, or disease which is likely to require surgery or angioplasty) within 3 months of Visit 1/Screening.

7. Has a history of malignancy ≤5 years prior to signing the ICF (i.e., the diagnosis occurred, or any evidence of residual or recurrent disease occurred, within the past 5 years), except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

   Note: A patient with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded.

8. Has human immunodeficiency virus (HIV)

   a. with AIDS related complications, or

   b. has not been on a stable anti-retroviral regimen for >6 months, or

   c. has progressive disease, or

   d. using agents associated with glucose intolerance such as nucleoside reverse transcriptase inhibitors (NRTIs) such as azidothymidine (AZT), didanosine (ddI) and stavudine (d4T).

9. Is on or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

   Note: Inhaled, nasal, ophthalmic, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

10. Has undergone a major surgical procedure within 12 weeks prior to signing the ICF or has major surgery planned during the trial.

    Note: A subject who has undergone minor surgery within the 4 weeks prior to Visit 1/Screening and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

11. Has other medical, psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

Exclusion Criteria Based on Laboratory Abnormalities

12. Has an exclusionary laboratory value as listed in Table 2 below:

Table 2 Laboratory Exclusion Criteria

Parameter[1]	Population (if applicable)	Trial Limit for Exclusion
eGFR[2]		<60 mL/min/1.73 m^2
Alanine aminotransferase (ALT)		>2 times Upper Limit of Normal (ULN)
Aspartate aminotransferase (AST)		>2 times ULN
Thyroid-stimulating hormone (TSH)[3]		Outside central laboratory normal range
Hemoglobin	Male Female	<11 g/dL (110 g/L) <10 g/dL (100 g/L)
Triglycerides (TG)[4]		>600 mg/dL (6.78 mmol/L)

[1] Subjects with an exclusionary laboratory value may have one repeat determination performed if the investigator considers the Visit 1/Screening result to be inconsistent with prior determinations. Only the laboratory test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used for inclusion.

[2] Calculated by central laboratory using the 4- variable MDRD equation.

[3] Subjects excluded due to the TSH criterion may be re-screened after being on a stable thyroid replacement therapy for at least 6 weeks.

[4] Subjects with elevated TG levels may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 3/Week -2) no longer meets the exclusion criterion. Subjects on lipid-lowering medication must be on a stable regimen for at least 4 weeks prior to Visit 4/Randomization (Day 1).

Other Criteria

13. Subject is currently participating, or has participated, in a study in which the subject received an investigational compound or used an investigational device within the prior 12 weeks of signing informed consent or is not willing to refrain from participating in another study.

    Note: A subject who has participated in a non-interventional study may be enrolled.

14. Is pregnant or breast-feeding, has a positive urine pregnancy test, or is planning to conceive or donate eggs during the study, including 14 days following the last dose of blinded investigational product.

15. Subject has a recent history of alcohol or drug abuse (within 3 years) or is a user of recreational or illicit drugs at the time of screening.

16. 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.

At Visit 3/Week -2

17. Has a clinically significant ECG finding that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance) which exposes the subject to risk by enrolling in the study.

18. Has an FPG consistently (i.e., measurement repeated and confirmed within 7 days) >270 mg/dL (15.0 mmol/L).

19. Has a fasting TG level >600 mg/dL (6.8 mmol/L).

    Note: This criterion applies to subjects who met the exclusion criterion for TG levels at Visit 1/Screening and who require evaluation of TG levels at Visit 3/Week -2 to assess eligibility following initiation or adjustment of lipid-lowering medication.

At Visit 4/Randomization/Day 1

20. Has a site fasting fingerstick glucose (FFSG) of <120 mg/dL (6.7 mmol/L) or >270 mg/dL (15.0 mmol/ L).

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value is not consistent with the subject's current SMBG values and Visit 3/Week -2 FPG value, the subject should not be excluded at this time. This value can be repeated and the subject should be rescheduled for Visit 4/Day 1 within 7 days. Additional single-blind placebo run-in medication should be dispensed if needed.

    If the subject meets this FFSG exclusion criterion at the rescheduled **Visit 4/Day 1**, the subject MUST be excluded.

21. Has a positive urine pregnancy test.

22. Blood pressure, lipid, hormone replacement and/or birth control medications are not at a stable dose or regimen as specified in Section 5.5 (at least four weeks for blood pressure, lipid, and hormone replacement medications and at least one cycle for birth control medications).

23. Has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described trial exclusion criteria or which, in the opinion of the investigator, exposes the subject to risk by enrolling in the study.

Note: If at Visit 4/Day 1, a subject requires medication adjustment or initiation of a new medication to meet enrollment criteria, the subject should be rescheduled for a Visit 4/Day 1 to occur ≤ 2 weeks later. If needed, additional single-blind placebo run-in medication should be dispensed.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 3.

During the placebo run-in and double-blind treatment periods, each subject will take 1 oral tablet of blinded study drug each day (sitagliptin or matching placebo tablet).

All subjects will take Met-IR as background medication. During the placebo run-in, they will take 1 x 500 mg tablet Met-IR twice daily (1000 mg/day). After randomization, all subjects will be titrated to 2 x 500 mg tablets of Met-IR twice daily (2000 mg/day).

Table 3 Trial Treatment

Treatment Group	Drug/Dose	Use	Dose Frequency/ Treatment Period	Route of Administration
placebo run-in	matching placebo for sitagliptin 100 mg tablet	Placebo (trial drug)	Once daily (q.d.) for 2 weeks	oral
sitagliptin 100 mg	sitagliptin 100 mg tablet	experimental (trial drug)	Once daily (q.d.) for 20 weeks	oral
Placebo	Matching placebo to sitagliptin 100 mg tablet	experimental (trial drug)	Once daily (q.d.) for 20 weeks	oral

The first dose of single-blind matching placebo for sitagliptin will be administered at the trial site as a witnessed dose at Visit 3/Week -2. The first dose of double-blind sitagliptin/matching placebo will be administered at the trial site as a witnessed dose at Visit 4/Day 1. Subsequent dosing will be performed once-daily by the subject at approximately the same time each day.

Background therapy with Met-IR will be up-titrated at Visit 4/Day 1 to 1500 mg and will be up-titrated again (at Day 8) to the target dose of 2000 mg/day (1000 mg b.i.d.). A telephone contact will be made on Day 9 to assess the up-titration of Met-IR.

Sitagliptin and matching placebo will be supplied by the Sponsor. Met-IR will be sourced by the Sponsor's (or designee's) local subsidiary, the investigational site, or will be prescribed by the investigator, with the latter two options receiving reimbursement from the Sponsor.

Glycemic rescue medication will be sourced by the investigational site or will be prescribed by the investigator receiving reimbursement from the sponsor. The trial investigator will be responsible for managing the initiation and maintenance of rescue medication in accordance to the local country label.

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)

5.2.1.2.1 Dose Modification of Sitagliptin/Matching Placebo for Sitagliptin

The dose of sitagliptin or matching placebo cannot be modified throughout the 20-week double-blind treatment period.

5.2.1.2.2 Dose Modification/Titration of Metformin

All subjects will undergo a period of stabilization, between Visits 2 and 3, prior to the initiation of single-blind placebo run-in at Visit 3. During this time, all subjects will be taking Met-IR at a dose of 1000 mg/day (500 mg b.i.d.). As discussed in section 2.1, the duration of this stabilization period will be between ≥6 and ≥10 weeks depending on the AHA status at the time of screening. If an eligible subject is taking a stable dose of a permissible AHA (sulfonylurea, glinide, or α-glucosidase inhibitor) at screening, they will discontinue the AHA at Visit 2 and initiate Met-IR 1000 mg/day (500 mg b.i.d.).

Met-IR will be up-titrated to 2000 mg/day (1000 mg b.i.d.) in all study subjects. Dose escalation of Met-IR to 1000 mg b.i.d. may occur more gradually at the discretion of the investigator. Every effort should be made to have subjects taking Met-IR 1000 mg b.i.d. by approximately 2 weeks after Visit 4/Day 1. If a subject is unable to tolerate 1000 mg b.i.d. Met-IR by Visit 5/Week 6, they should continue on the highest dose of Met-IR they have previously tolerated well for the remainder of the study.

5.2.1.2.3 Glycemic Rescue Therapy

If the criteria for glycemic rescue (see Section 5.6) are met, the investigator should initiate what she/he considers to be appropriate glycemic rescue AHA therapy. **Note:** Rescue therapy is to be added to ongoing double-blind study drug and Met-IR 1000 mg b.i.d.

Since double-blind study drug may be sitagliptin, rescue therapy must not be a DPP-4 inhibitor. Additionally, background Met-IR should not be used as a glycemic rescue medication. Therefore, the dose of Met-IR should not be increased above the specified target dose of 2000 mg/day. Otherwise, the choice of the AHA agent, dose, regimen, and subsequent titration will be as directed by the investigator, as considered to be clinically appropriate.

After initiation of rescue therapy, subjects will continue with all protocol-specified activities including all safety and efficacy evaluations.

5.2.2 Timing of Dose Administration

At Visit 4/Randomization (Day 1), subjects will enter the 20-week, double-blind, placebo-controlled treatment period and be randomized in a 1:1 ratio to sitagliptin 100 mg q.d. or matching sitagliptin placebo with all subjects on Met-IR 2000 mg/day (1000 mg b.i.d.).

Subjects will take sitagliptin or matching placebo once-daily, at approximately the same time every day.

Subjects will take Met-IR b.i.d. with meals.

On days without clinic visits, subjects should take Met-IR twice daily and blinded study medication (sitagliptin or matching placebo) once daily at approximately the same times each day.

Subjects will be instructed not to take Met-IR and blinded study medication (sitagliptin or matching placebo) the morning of clinic visits. On clinic visit days, subjects will take Met-IR and blinded study medication (sitagliptin or matching placebo) after all study procedures are completed.

If a subject misses a dose of Met-IR or blinded study medication (sitagliptin or matching placebo) during the trial, he/she should be instructed to take it as soon as they remember, unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. Sitagliptin and matching placebo will be packaged identically so that blind/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 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to either sitagliptin 100 mg q.d. or sitagliptin 100 mg matching placebo, co-administered for all subjects with Met-IR 2000 mg/d (1000 mg b.i.d.).

5.4 Stratification

Treatment allocation/randomization will be stratified according to AHA status at screening based on the following levels:

1. Not on AHA at Visit 1/Screening
2. On Non-Metformin AHA at Visit 1/Screening
3. On Met-IR or Met-XR 1000 mg/day at Visit 1/Screening

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.

AHAs taken by the subject at any time prior to Visit 1/Screening, and any other medications taken within 8 weeks of Visit 1/Screening, should be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. Concomitant medications taken during the trial must also be recorded.

Subjects should be questioned about their use of concomitant medications at the time points indicated in the Trial Flow Chart (Section 6.0). Subjects should be instructed to contact the study investigator before initiating any prescription or non-prescription medications during study participation. If medical necessity requires initiation of a medication prior to discussion with the study investigator, the subject should communicate with the study investigator as soon as possible.

Prohibited Medications

Medications listed below are prohibited while subjects are receiving study medication during the double-blind treatment period:

NOTE: At the time points indicated in the Trial Flow Chart (Section 6.0), investigational sites should review the use of any prohibited medications, including AHAs with subjects. At these time points, subjects should be instructed regarding the importance of not taking AHAs other than metformin and blinded study medication (sitagliptin/placebo to sitagliptin) during study participation unless initiated by the study investigator as glycemic rescue.

1. DPP-4 inhibitors (except blinded sitagliptin)
2. Any other AHA with exception of metformin and rescue therapy

   Note: at Randomization/Day 1 subjects should be reminded to **not to take any other AHA medications other than the trial treatments** during their participation in the study unless the AHA is initiated as glycemic rescue therapy by the study investigator.

   Subjects should be counseled that if another physician prescribes such a treatment (i.e., any AHA), the subject and/or the prescribing physician should immediately contact the investigational site prior to initiation of such therapy (unless alternative AHA therapy is considered clinically to be immediately required).

   Subjects who were switched from another AHA to Met-IR after screening and prior to randomization should be reminded to remain off this agent while participating in the current trial, and to not re-start this agent post-study unless advised by their diabetes care-giver (whether the investigator or another physician).

If a subject initiates another AHA (other than Met-IR and rescue therapy initiated per protocol specifications [see Section 5.6]) and is unwilling to discontinue this other AHA, they may continue to take Met-IR and double blind study medication if the other AHA is **not** a DPP-4 inhibitor and the study investigator considers continued administration of Met-IR and blinded study medication to be medically appropriate. **If the other AHA is a DPP-4 inhibitor, blinded study medication must be discontinued.**

3. Corticosteroids: Treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of systemic corticosteroids are prohibited.

   Note: Inhaled, nasal, ophthalmic, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

4. Weight loss medications: Initiation of weight loss medications after screening is prohibited. If a subject is taking a weight loss medication which was initiated >12 months prior to screening, this is not an exclusion (see Section 5.1.3). However, it is preferable that the dose of weight loss medication remain stable during the double-blind treatment period.

Guidance for Other Medications

The investigator or subject's physician/health care provider is permitted to make adjustments in the subject's non-AHA therapies throughout the trial if clinically warranted. Guidance for specific medications which are permitted during the study is provided below.

1. Blood Pressure and Lipid Medications: Concurrent lipid lowering and antihypertensive medications are permitted. Subjects must be on a stable lipid and/or antihypertensive medication regimen for the 4 weeks prior to Visit 4/Day 1 (refer to Section 5.1.3, Table 2). It is preferable that doses of these medications remain stable during the double-blind treatment period.

2. Hormonal Replacement Therapy and Birth Control Medications: Hormone replacement therapy (HRT) and birth control medications are permitted. Subjects on HRT must be on a stable dose for at least 4 weeks prior to Visit 4/Day 1. Subjects on birth control medications must be using a single regimen for at least 1 cycle prior to Visit 4/Day 1. It is preferable that HRT dose and birth control medication regimens remain stable during the double-blind treatment period and 14 days after the last dose of study medication.

3. Thyroid Hormone Replacement Therapy: Thyroid hormone replacement medication (e.g., thyroxine) is permitted. Subjects who meet the TSH exclusion criterion specified in Table 2 may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.

4. Supplements and/or Traditional Medicines: The use of herbal supplements and other natural products should be discouraged. Subjects who do not discontinue the use of such supplements prior to Visit 3/Week -2 should be instructed not to change the use or dose of the supplement during the trial. Subjects should be instructed not to initiate new supplements during the trial.

5.6 Rescue Medications & Supportive Care

During the double-blind treatment period, subjects who meet progressively more stringent glycemic rescue criteria (see Table 4) will receive glycemic rescue therapy determined by the study investigator as summarized in Section 5.2.1.2.3. Glycemic rescue medication will be initiated at either a scheduled visit or at the investigational site, and not by a telephone contact.

Immediately prior to initiation of glycemic rescue therapy (at a scheduled visit), subjects must undergo the Rescue Visit procedures listed in the Trial Flow Chart –Section 6.0.

Subjects requiring rescue medication are to continue to receive Met-IR plus double-blind sitagliptin/placebo to sitagliptin unless they meet any of the discontinuation criteria listed in Section 5.8.

Table 4 Glycemic Thresholds for Rescue

Visit Intervals	Glycemic Thresholds
After Visit 4/Day 1 through Visit 5/Week 6:	FPG consistently >270 mg/dL (15.0 mmol/L)
After Visit 5/Week 6 through Visit 7/Week 20:	FPG consistently >240 mg/dL (13.3 mmol/L)
Note: A consistent value for FPG is defined as a repeat measurement performed within 7 days of notification from the central laboratory. Site should reinforce diet/exercise counseling prior to repeat measurement.	

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visit 2; follow-up at other visits may be done by other appropriate site personnel evaluating the subject.

The subject will receive counseling on diet consistent with the local guidelines of the country of the investigational site. At each subsequent visit, the subject will be asked about their diet and exercise, and counseling should be provided, as appropriate. Detailed dietary information will not be captured.

5.7.2 Alcohol, Caffeine and Tobacco

- Subjects will be counseled to limit alcohol use to moderate amounts (i.e., ≤2 drinks per day and no more than 14 drinks per week).
- Ingestion of caffeine will be prohibited for at least 30 minutes prior to scheduled ECGs and blood pressure determinations.
- Ingestion of nicotine-containing products will be prohibited for at least 30 minutes prior to the scheduled ECGs and blood pressure determinations.

5.7.3 Activity

Subjects will be counseled to maintain a medically appropriate, routine exercise program and a consistent physical activity level during the trial. Subjects should not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests for the duration of participation in the trial.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

Note: Withdrawal of consent should occur only in subjects who refuse to engage in **any** trial-related activity including telephone contact. Subjects unwilling to fully participate in the study should be discontinued from double-blind study therapy (sitagliptin/placebo to sitagliptin). Appropriate management of their diabetes should be instituted by their personal physician or the study investigator. Subjects should be encouraged to continue study participation on a more limited level to support the fullest evaluation of the treatment strategy being assessed. See section 5.8.1 for discussion of the approach to subjects who are unwilling to fully participate in this study but agree to continue with more limited participation.

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

1. Subject develops a contraindication to either metformin or sitagliptin.
2. Elevation in ALT and/or AST ≥3-times the upper limit of normal will require further evaluation in all cases. Depending on results of this evaluation, interruption or discontinuation of randomized therapy may be required. Refer to Appendix 12.4 for additional details on management and discontinuation of randomized therapy for subjects with elevated liver enzymes.

3. Reduction of renal function:
    - eGFR persistently <50 mL/min/1.73m^2 (MDRD formula)

      Note: A persistent eGFR value is defined as a repeat measurement, performed within 2 weeks after notification from the central laboratory, that remains <50 mL/min/1.73m^2, despite correction of potential causative factors (e.g., correction of volume depletion, discontinuation of nonsteroidal anti-inflammatory drugs [NSAIDs]). If the eGFR value continues to meet the discontinuation criterion but demonstrates stability or improvement relative to the prior result, an additional repeat may be performed within 7 days.
4. Ongoing use of a DPP-4 inhibitor other than blinded study medication (see Section 5.5).
5. Pregnancy.

   Note: A positive urine pregnancy test requires immediate interruption of double-blind study therapy (sitagliptin/placebo to sitagliptin) and metformin until serum β-hCG can be performed and found to be negative. Subject must be permanently discontinued from blinded study drug, and pregnancy should be reported and followed per Section 7.2.2 if pregnancy is confirmed by a positive serum pregnancy test.
6. Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the subject to risk by continuing in the trial or does not allow the subject to adhere to the requirements of the protocol.
7. Subject undergoes bariatric surgery.
8. The investigator or subject becomes unblinded to the subject's treatment assignment.

The Sponsor should be notified as soon as possible when a subject is discontinued from blinded study drug or blinded study drug is interrupted because of an AE or a laboratory safety test abnormality.

5.8.1 Follow-up for Subjects Who Discontinue Blinded Study Drug

5.8.1.1 Withdrawal of Consent

If a subject indicates his or her intention to stop active participation in the trial (i.e., chooses to no longer attend visits at the investigational site, take blinded study drug, and have other study-related procedures conducted at the investigational site) or if the investigator has recommended withdrawal of the subject from active participation in the trial, the subject should be encouraged to complete procedures for the Discontinuation Visit. Additionally, the investigator must clarify with the subject if he/she is willing to continue in the study with contact at intervals to provide a brief and focused update on health status (e.g., evaluate if the subject experienced any SAEs). It will be important for the subject to understand the importance of complete collection of information, and also the limited requirements for continuing to provide this information (i.e., a brief telephone contact, occurring at the time of the originally planned study visits).

The sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

5.8.1.2 Discontinuation from Blinded Study Therapy

If a subject discontinues randomized therapy for reasons other than withdrawn consent, the investigator should make every appropriate effort to maintain the subject in the ongoing study, implementing the study visit schedule (with efficacy and safety assessments) per study Trial Flow Chart, Section 6.0) It will be important for the subject to understand the importance of complete collection of information. Based upon this, subjects should be strongly encouraged to continue to participate in all scheduled clinic visits (which will continue as outlined in the Trial Flow Section 6.0, except those related to double-blind study drug).

All subjects discontinuing study medication (either early discontinuation of study medication or at completion of the 20-week double-blind treatment period) should complete procedures for the Discontinuation Visit and have a 14-day post-last study drug dose telephone contact (see Section 6.0 for details).

A subject who discontinues study medication prematurely but does not withdraw consent should continue to be followed by the investigational site, attending scheduled study visits and undergoing study procedures (other than those related to study medication). If subjects are not willing to return for on-site clinic visits, but agree to telephone contact follow-up, they should be followed by telephone contacts at the time of scheduled study visits until the end of the trial (Week 20). The purpose of these telephone contacts, as well as the 14-day post-treatment telephone call, is to collect information about subjects' health status.

Subjects who discontinue treatment with blinded study drug but who continue to participate in the trial by providing follow-up information should receive medical and diabetes management by their managing physician or investigator, as appropriate. These subjects may initiate any other therapy as needed (previously prohibited medications will not apply to them). After discontinuation of blinded study drug, the Sponsor will continue to reimburse rescue medication (for those rescued) until trial completion (Week 20).

If the trial site loses contact with the subject, the site should make at least three attempts for a telephone contact. If the three attempts of telephone contact are unsuccessful, the site should make at least one attempt to reach the subject via certified letter. All attempts to contact a subject and information received during contact attempts must be documented in the subject's medical record. If attempts to contact the subject via telephone contacts and certified letters are unsuccessful, alternative measures should be implemented, which may include contacting family members and health care providers and, when applicable, using subject location services. In any circumstance, every effort should be made to document subject outcome, if possible.

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

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Trial Period:	Screening and Run-in Period			Randomization	Double-Blind Treatment					Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**TC**	**Visit 5**	**Visit 6**	**Visit 7**	**Rescue**	**Discontinuation**	**Follow-up**
Scheduled Day, Week:			Week -2	Day 1	Day 9	Week 6	Week 14	Week 20	Rescue	At time of discontinuation[a]	14-Day Post Treatment Telephone Contact
Scheduling Window Days etc.:			± 5 days	± 5 days	± 1 day(s)	± 7 days	± 7 days	± 7 days			+3 days
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research[b]	X										
Assignment of Screening Number	X										
Contact IVRS	X		X	X		X	X	X		X	
Inclusion/Exclusion Criteria	X		X	X							
Review Prior/Concomitant Medication[c]	X	X	X	X	X	X	X	X	X	X	
Review use of any prohibited medications, including AHAs; counsel patients on importance of not taking other AHAs[c]	X	X	X	X	X	X	X	X	X	X	
Counsel subject to switch current AHA or adjust background metformin (if applicable)		X									
Dispense subject identification card		X									
Dispense Hypoglycemia Assessment Log (HAL) and instruct on Hypoglycemia Symptoms and Management		X									
Dispense blood Glucose Meter / provide Self-Monitoring Blood Glucose (SMBG) Instruction		X									

Trial Period:	Screening and Run-in Period			Randomization	Double-Blind Treatment					Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**TC**	**Visit 5**	**Visit 6**	**Visit 7**	**Rescue**	**Discontinuation**	**Follow-up**
Scheduled Day, Week:			Week -2	Day 1	Day 9	Week 6	Week 14	Week 20	Rescue	At time of discontinuation[a]	14-Day Post Treatment Telephone Contact
Scheduling Window Days etc.:			± 5 days	± 5 days	± 1 day(s)	± 7 days	± 7 days	± 7 days			+3 days
Diet and exercise counseling/monitoring[d]		X	X	X		X	X	X	X	X	
Assignment of Randomization Number				X							
Study and Rescue Medication											
Dispense single-blind run-in medication			X								
Witness dose of blinded study medication and Met-IR in clinic			X	X							
Dispense double-blind study medication				X		X	X				
Assess compliance with double-blind study medication and				X		X	X	X	X	X	
Clinical Procedures/Assessments											
Demographics and Medical History	X										
Vital Signs measured in duplicate (heart rate, blood pressure)	X		X	X		X	X	X	X	X	
Full Physical Examination			X								
Brief Physical Examination[e]								X	X	X	
Height (measured in duplicate)	X										
Weight (measured in duplicate)	X		X	X		X	X	X	X	X	
12-Lead Electrocardiogram (read locally)			X								

Trial Period:	Screening and Run-in Period			Randomization	Double-Blind Treatment					Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**TC**	**Visit 5**	**Visit 6**	**Visit 7**	**Rescue**	**Discontinuation**	**Follow-up**
Scheduled Day, Week:			Week -2	Day 1	Day 9	Week 6	Week 14	Week 20	Rescue	At time of discontinuation[a]	14-Day Post Treatment Telephone Contact
Scheduling Window Days etc.:			± 5 days	± 5 days	± 1 day(s)	± 7 days	± 7 days	± 7 days			+3 days
Site A1C fingerstick measurement[f]	X										
Fasting fingerstick glucose in clinic[g]				X							
Review of SMBG measurements and HAL			X	X	X	X	X	X	X	X	
Adverse events monitoring	X	X	X	X	X	X	X	X	X	X	X
Subject telephone contact (TC) to assess titration of metformin to 2,000mg					X						
Lab Procedures/Assessments											
Hematology	X										
Chemistry panel	X		X	X				X		X	
Fasting plasma glucose (FPG)	X		X	X		X	X	X	X[h]	X	
Hemoglobin A_{1C} (A1C)	X		X	X		X	X	X	X	X	
C-Peptide[i]	X										
Lipid panel				X				X		X	
Thyroid stimulating hormone (TSH)	X[j]										
Fasting Triglycerides	X		X[k]								
Urine Pregnancy Test (as applicable)[l]	X			X		X	X	X	X	X	
Dipstick urinalysis	X[m]										
Plasma and serum for Future Biomedical Research[b]				X				X		X	

Trial Period:	Screening and Run-in Period			Randomization	Double-Blind Treatment					Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**TC**	**Visit 5**	**Visit 6**	**Visit 7**	**Rescue**	**Discontinuation**	**Follow-up**
Scheduled Day, Week:			Week -2	Day 1	Day 9	Week 6	Week 14	Week 20	Rescue	At time of discontinuation[a]	14-Day Post Treatment Telephone Contact
Scheduling Window Days etc.:			± 5 days	± 5 days	± 1 day(s)	± 7 days	± 7 days	± 7 days			+3 days
Blood (DNA)for Future Biomedical Research [b]				X							

a. See section 5.8.1 for additional information regarding follow-up after premature discontinuation of study medication..
b. Informed consent for future biomedical research samples must be obtained to collect the DNA, plasma, and serum sample.
c. Subjects should be reminded to **not to take any other AHA medications other than the trial treatments** (background metformin and sitagliptin/placebo to sitagliptin) during their participation in the study. They should be counseled that if another physician prescribes such a treatment (i.e., any AHA), the subject and/or the prescribing physician should immediately contact the investigational site prior to initiation of such therapy (unless alternative AHA therapy is considered clinically to be immediately required). Subjects who were washed off of another AHA should be reminded to remain off this agent while participating in the current trial, and to not re-start this agent post-study unless advised by their diabetes care-giver (whether the investigator or another physician)
d. Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visit 2; follow-up at other visits may be done by other appropriate site personnel evaluating the subject.
e. Brief physical examination includes assessment of heart, lungs, abdomen, extremities and skin.
f. Site fingerstick A1C is not mandatory, but may be used, at the discretion of the investigator, for screening a subject. However, a fingerstick A1C cannot substitute for a central laboratory measured A1C to determine if a subject meets entry criteria
g. FFSG values performed in the clinic will be used to assess exclusion criteria prior to randomization at Visit 4/Day 1.
h. FPG values obtained at the central laboratory will be used to assess if the subject meets glycemic rescue criteria. Refer to Section 5.6 for further details.
i. C-peptide test at Visit 1/Screening is only for subjects assessed by the investigator as possibly having Type 1 diabetes.
j. A patient excluded due to TSH criterion may be re-screened after being on a stable, adjusted thyroid replacement regimen for at least 6 weeks.
k. Only subjects with TG meeting the exclusion criterion at Visit 1 should have a repeat test at Visit 3/Week-2, as described in exclusion criterion #12.
l. Women of childbearing potential will have a urine pregnancy test (and serum pregnancy test if required by site's Institutional Review Board [IRB]/Ethics Committee [EC]). Subjects with a positive urine pregnancy test during double-blind treatment period will interrupt blinded study drug and background therapy metformin, and undergo a serum pregnancy test.
m. If dipstick (midstream urine specimen) is positive for blood, WBC (e.g., leukocyte esterase, nitrates), or protein, then a urine sample for a complete urinalysis (dipstick and microscopy) should be sent to the central laboratory

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. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

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 by the investigator or qualified designee to ensure that the subject qualifies for the trial.

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 will be obtained by the investigator or qualified designee. The use of tobacco should be collected as part of the medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use. AHAs taken by the subject at any time prior to Visit 1/Screening and non-AHAs taken within 8 weeks prior to Visit 1/Screening should be recorded on the appropriate eCRF. The site may rely on subject report for this information.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record any medication taken by the subject during the trial on the appropriate eCRF.

7.1.1.6 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.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Please refer to the Trial Flow Chart (see Section 6.0) and the Trial File Binder for specific details on the screening/rescreening visit requirements

7.1.1.7 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.

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

Adherence to both randomized double-blind therapy (sitagliptin/placebo to sitagliptin) and background therapy (Met-IR) will be assessed by subject report during the double-blind treatment period. Every effort will be made to maintain adherence as close to 100% as possible. Compliance will be documented in the source documentation and in the study medication eCRF.

Interruptions from the protocol specified treatment plan for >7 days OR compliance <75% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.8.1 Diet and Exercise Counseling

Refer to Section 5.7 for further details.

7.1.1.8.2 Dispense Hypoglycemia Assessment Log and Instruct on Hypoglycemia Symptoms and Management

At Visit 2 the site will dispense the Hypoglycemia Assessment Log (HAL) and review the symptoms and management of hypoglycemia with the subject. The site will counsel the subject to immediately perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), but also to avoid delay in treating these symptoms.

The subject will be instructed to complete the HAL for any symptomatic episodes he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (i.e., within ≤5 minutes) after treating, the value should be recorded in the log. In addition, subjects will be instructed to record in the log any fingerstick glucose values ≤70 mg/dL (3.9 mmol/L) regardless of the presence of symptoms.

Subjects should be instructed to contact the investigational site to report:

- any episode of hypoglycemia for which assistance was required (i.e., severe hypoglycemia),
- any episode of fingerstick glucose ≤70mg/dL (≤3.9 mmol/L) with or without symptoms .

Note: As indicated, subjects will record symptoms and/or fingerstick glucose measurements that they believe are related to hypoglycemia on the HAL. Each episode should be evaluated by the investigator. For episodes of documented symptomatic hypoglycemia with a concurrent glucose measurement of ≤70 mg/dL (≤3.9 mmol/L), and for all episodes of severe hypoglycemia regardless of biochemical documentation, the Hypoglycemia Assessment (HA) eCRF must also be completed.

Investigators should report any event of hypoglycemia they consider to be an adverse event on the appropriate AE eCRF.

7.1.1.8.3 Dispense Glucose Meter and Self-Monitoring Blood Glucose (SMBG) Instructions

Glucose meters will be supplied to all subjects at Visit 2 in order to perform SMBG. Subjects will be instructed on the procedure to perform fingerstick glucose measurements. Subjects will monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator.

During the run-in period, subjects should be counseled to contact the trial site if fingerstick glucose levels are >270 mg/dL (15.0 mmol/L) ≥2 times per week. Furthermore, in order to assess the need for rescue and/or discontinuation from blinded study drug, subjects should be instructed to contact the site for fingerstick glucose values that are >270 mg/dL (15.0 mmol/L) after Visit 4/Day 1 through Visit 5/Week 6, or >240 mg/dL (13.3 mmol/L) after Visit 5/Week 6 through Visit 7/Week 20. Subjects will be instructed to contact the site at any time from initiation of the run-in period through Visit 7/Week 20 if any fingerstick glucose values are ≤70 mg/dL (≤3.9 mmol/L).

7.1.1.8.4 Witness Dosing

Administration of blinded study drug and Met-IR will be witnessed by the investigator and/or trial staff at Visit 3/Week -2 (start of the placebo run-in) and at Visit 4/Day 1 (the first visit of the double-blind treatment period) after completion of all trial procedures including the collection of all fasting blood samples.

7.1.1.8.5 Dispense Single-Blind Placebo Run-in

Subjects will be dispensed single-blind study drug (matching placebo for sitagliptin 100 mg) at Visit 3/Week -2 and instructed to take one tablet orally per day approximately the same time of day in the morning. The last dose of placebo run-in should be taken on the day prior to Visit 4/Day 1.

Refer to Section 5.2.2 for further details.

7.1.1.8.6 Dispense Double-Blind Study Drug

Subjects will be dispensed double-blind study drug (sitagliptin or sitagliptin-matching placebo) at all trial visits from Visit 4/Randomization (Day 1) through Visit 6/Week 14 and instructed to take the double-blind study drug once a day, orally at approximately the same time every day.

Refer to Section 5.2.2 for further detail.

7.1.1.8.7 Medication Compliance Monitoring

All subjects will be directed to bring any used and unused bottles of blinded study drug and Met-IR to each visit. The investigator must maintain a complete and current accountability record for the blinded study drug.

Compliance will be assessed by subject report (see Section 8.11). Every effort will be made to maintain compliance as close to 100% as possible.

Subjects who, based on self-report, are <80% compliant with single-blind placebo to sitagliptin and/or Met-IR during the 2-week, single-blind placebo run-in are ineligible for randomization.

The investigator or designee will counsel subjects who report taking <80% of the double-blind study drug and/or Met-IR following randomization. The investigator or designee will determine factors that resulted in <80% compliance and will take steps to improve compliance. Subjects will be counseled on the importance of taking their medication as prescribed. Subject counseling will be documented in source documents.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vital Signs (Sitting Blood Pressure and Pulse Rate)

Vital sign measurements include a duplicate measurement of sitting blood pressure and pulse rate. Blood pressure and pulse rate will be measured using an automated, oscillometric blood pressure measuring device at time points noted in the Trial Flow Chart – Section 6.0 Site personnel should use the same blood pressure measuring device throughout the study for each subject. Refer to the Trial File Binder for additional details.

7.1.2.2 Height and Weight

Height and weight will be measured at each of the pre-defined nominal time points outlined in the Trial Flow Chart – Section 6.0. Body weight will be measured using a standardized, digital scale (provided by the sponsor).

7.1.2.3 Physical Examination

Full and brief physical examinations will be performed as outlined in the Trial Flow Chart – Section 6.0. Unless the study investigator feels there is a specific need, genitourinary, rectal and breast examination should be omitted from the full physical examination. Brief physical examinations will include assessment of the heart, lungs, abdomen, and extremities. Other body systems may be evaluated as per the judgment of the investigator or as needed to evaluate adverse events. Abnormalities considered clinically significant should be reported as adverse events.

7.1.2.4 12-Lead Electrocardiogram

A supine 12-lead ECG will be obtained at time point noted in the Trial Flow Chart – Section 6.0.

- Subjects should avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes prior to the scheduled ECGs and blood pressure determinations.
- 12-lead ECGs should be performed after the subject has rested quietly **for at least 10 minutes** in a supine position.

12-lead ECGs should be obtained prior to the nominal time assessment of blood pressure, and pulse rate as well as prior to blood collection.

The investigator is responsible for retaining all copies of the ECG reports.

7.1.3 Laboratory Procedures/Assessments

All laboratory tests outlined in the Trial Flow Chart - Section 6.0 will be performed by the central laboratory. The optional site fingerstick A1C at Visit 1/Screening, the fasting fingerstick glucose measurement at Visit 4/Day 1, and all urine pregnancy tests will be performed at the investigational site.

Laboratory test results for chemistry, hematology, urinalysis, and lipids will not be masked. Glycemic measurements (e.g., glucose and A1C) will be masked from Visit 4/Day 1. However, in order for the investigator to perform an evaluation for possible rescue or discontinuation from the blinded study drug, the central laboratory will report to the investigator in an unmasked manner if an FPG value meets criteria for glycemic rescue (see Section 5.6).

In addition, the central laboratory will flag the following safety measurements meeting specific criteria for discontinuation from blinded study drug:

- eGFR <50 mL/min/1.73 m^2;
- elevations ≥3X the laboratory upper limit of normal (ULN) in liver transaminases (ALT and AST) (see Appendix 12.4 for guidance on retesting);
- elevations in ALT and/or AST ≥3X the ULN with concurrent total bilirubin ≥2X the ULN and alkaline phosphatase <2X the ULN;
- positive serum pregnancy test

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Refer to the Trial Flow Chart - Section 6.0 for specific laboratory tests performed at each trial visit.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Others	Urinalysis
• Hemoglobin • Hematocrit • RBC Count • Platelet Count • WBC Count • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes	• BUN • Serum Creatinine (eGFR calculated using the MDRD formula) • Glucose • Sodium • Potassium • Chloride • Total Carbon Dioxide (Bicarbonate) • AST (SGOT) • ALT (SGPT) • Alkaline Phosphatase • Total Bilirubin • Direct (conjugated) Bilirubin[a] • Indirect (unconjugated) Bilirubin[a] •	• TSH • Fasting C-peptide • A1C • FPG • Pregnancy Tests (where applicable) • Lipid Panel (i.e., Total Cholesterol, HDL-C, non-HDL-C, LDL-C, and Triglycerides)	• Blood • Glucose • Protein • Leukocyte esterase • Nitrates • Specific Gravity • Microscopic exam, if abnormal results are noted

[a] Both direct and indirect bilirubin measured only when total bilirubin is greater than ULN.

Laboratory tests will be performed after at least a 10-hour fast (i.e., no food, double-blind study drug, metformin, or drink except water and non-AHA non-study drug as prescribed).

Subjects who have not fasted prior to Visit 1/Screening should return to the clinic fasting prior to Visit 4/Randomization for fasting TG and FPG measurements. After randomization, subjects who do not fast before a scheduled visit will be required to return fasting for the study visit within three days.

7.1.3.2 Future Biomedical Research Sample Collection

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

- DNA for future research
- Plasma for future research
- Serum for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the discontinuation visit 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. All subjects discontinuing study medication should have a 14-day post-last study drug dose telephone contact (see Section 6.0 for details). .

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 PPD, 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 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:

Digital scale: The study site is responsible for conducting accuracy checks (approximately monthly) to ensure the Sponsor-supplied scale to measure body weight is working correctly. Additional details are provided in the Trial File Binder.

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.

Refer to the Trial File Binder for details regarding study visit requirements including subject telephone contacts.

7.2 Assessing and Recording Adverse EventsAdverse Events and Patient/Device 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 Electronic Data Capture (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

An overdose must be reported if any of the following occurs during the conduct of this trial: (1) Dosing of >400 mg/day of sitagliptin or matching placebo, (2) Dosing >200 mg/day of sitagliptin or matching placebo for more than 28 days.

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 serious adverse event, even if no other seriousness 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 Event of Clinical Interest (ECI), 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;
- 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. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

Refer to Table 6 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 overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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).

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 6. The investigator's assessment of causality is required for each adverse event. Refer to Table 6 for instructions in evaluating adverse events.

Table 6 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**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	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.

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 a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study.

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	Sitagliptin addition during metformin uptitration
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to metformin (1000 mg b.i.d.) + sitagliptin group or metformin (1000 mg b.i.d.) group. Stratification Factor: AHA status at screening (Not on AHA; On non-metformin AHA; On metformin)
Analysis Populations	Efficacy: modified Full Analysis Set (mFAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	A1C – change from baseline at Week 20
Key Secondary Endpoints	Proportion of subjects with A1C <7.0% at Week 20 Fasting Plasma Glucose (FPG) – change from baseline at Week 20
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary analysis will compare the efficacy of up-titration of metformin plus the addition of sitagliptin relative to up-titration of metformin alone in change from baseline in A1C at Week 20. The mean change from baseline in A1C at Week 20 with up-titration of metformin plus the addition sitagliptin will be compared to that of up-titration of metformin alone via a constrained longitudinal data analysis (cLDA) model. For the analysis of the proportion of subjects with A1C <7.0% at Week 20, the Miettinen and Nurminen method will be used. The cLDA model used for the analysis of A1C will be used to impute missing data. Change from baseline in FPG at Week 20 will be analyzed using a cLDA model.
Statistical Methods for Key Safety Analyses	The study has no tier 1 safety endpoints. For Tier 2 endpoints, 95% confidence intervals will be provided for between-group differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [15].

Interim Analyses	No interim analyses are planned for this study.
Multiplicity	The study-wise type I error rate will be controlled at $\alpha = 0.05$ (two-sided) using an ordered testing procedure, beginning with change from baseline in A1C, followed by A1C goal <7.0% and then change from baseline in FPG. All tests will be conducted at $\alpha = 0.05$ (two-sided).
Sample Size and Power	The planned sample size of 190 subjects per treatment arm will provide 93% power to detect a 0.4% between-group difference (metformin+sitagliptin vs. metformin) in change from baseline in A1C. For A1C goal <7.0%, the planned sample size will provide approximately 90% power to detect a between-group difference of 14 to 15 percentage points in the proportion of patients at goal, assuming that the proportion at goal is 14% to 18% in the metformin group. The planned sample size will provide approximately 90% power for change from baseline in FPG, if the underlying treatment difference is -16 mg/dL.

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, 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).

8.3 Hypotheses/Estimation

Objectives and hypotheses of this study are stated in Sections 3.1 and 3.2.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and between-treatment differences are listed below.

The baseline value will be defined as the Visit 4/Week 0/Day 1 (Randomization) measurement. If this measurement is not available, the Visit 3/Week -2 measurement will be used as the baseline value. If neither measurement is available, the baseline value will be treated as missing.

8.4.1 Efficacy Endpoints

The descriptions of the efficacy measurements and time points at which they are measured are described in Section 4.2.3.1 and Section 6.0 (Trial Flow Chart), respectively. The efficacy endpoints to be analyzed are listed in Table 7.

Table 7 Efficacy Endpoints

Primary Endpoint
Change from baseline in A1C at Week 20
Key Secondary Endpoints
Proportion of subjects with A1C < 7.0% at Week 20 Change from baseline in FPG at Week 20
Other Endpoints
Proportion of subjects with baseline A1C ≥ 8.5% with A1C <7.0% at Week 20 Proportion of subjects receiving glycemic rescue therapy

8.4.2 Safety Endpoints

The descriptions of the safety measurements and time points at which they are measured are described in Section 4.2.3.2 and Section 6.0 (Trial Flow Chart), respectively. The safety endpoints to be analyzed are listed in Table 9 in Section 8.6.2. These endpoints will be analyzed over 20 weeks.

8.5 Analysis Populations

Summaries of subject disposition will include all randomized subjects. Summaries of baseline characteristics will be performed in the All Subjects Treated (AST) population, consisting of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group to which they were randomized for both populations.

8.5.1 Efficacy Analysis Populations

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

- receive at least one dose of study treatment,
- have at least one observation for the analysis endpoint (baseline or post-baseline).

Analyses in the mFAS population will exclude data after the initiation of rescue therapy [Section 5.6] or sustained use of prohibited antihyperglycemic agents (AHAs) [Section 5.5] as well as data after the last dose of study medication plus an offset of 5 days. Sustained use of additional AHAs is defined as >7 days (not necessarily consecutive).

The intention-to-treat (ITT) population will be a secondary population for efficacy analyses. The ITT population will consist of the same subjects as mFAS. However, analyses in the ITT population will include all available data, including data obtained after the initiation of rescue or prohibited AHAs as well as after the last dose of study medication in subjects who remain in the study after discontinuing study medication.

A secondary population for the analysis of A1C Goal < 7.0% (for the Missing = Failure supportive analysis approach) will be the All Subjects Treated (AST) population, consisting of all randomized subjects who received at least one dose of study treatment. This analysis will exclude data after the last dose of study medication plus an offset of 5 days.

For all efficacy analyses, subjects will be included in the treatment group to which they are randomized, regardless of the treatment received during the course of the trial. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

Analyses of safety data will be performed in the All Subjects as Treated (ASaT) population consisting of all randomized subjects who received at least one 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. This will be the treatment group to which they are randomized except for any subjects who take incorrect study treatment for the entire treatment period. Such subjects will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one 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.

Safety analysis will be based on observed data only. No imputation will be performed for missing data.

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. All statistical tests will be conducted at 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 estimands for the study consist of the following elements:

- Target population: Patients with T2DM who have inadequate glycemic control on metformin
- Endpoint: Mean change from baseline (in A1C, in FPG) at Week 20, proportion of patients with A1C <7.0% at Week 20
- Measure of intervention effect: Difference in means or ratio of proportions (i.e., risk ratio) in the effect of randomized treatments on the endpoint if all subjects remained on treatment through Week 20

For the primary analysis of change from baseline in A1C, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [16] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for treatment, time, AHA status at screening, the interaction of time by AHA status at screening, and the interaction of time by treatment. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The treatment difference in terms of mean change from baseline at Week 20 will be estimated and tested from this model.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of subjects who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation code are given in the sSAP.

Analyses of the change from baseline in other continuous efficacy endpoints at Week 20 will be performed using the cLDA model as described above.

The present primary approach assumes data missing at random in compliance with the current ICH E9 guidance. In the event that the ICH E9 guidance on missing data is updated and no longer regards the MAR assumption as valid for missing data handling, then the Jump-to-Reference (J2R) pattern mixture model will be used as the primary approach and the cLDA analyses will become a supportive approach for all three endpoints in the hypotheses.

The cLDA method assumes that data are missing at random (MAR). In this study, it is expected that Missing at Random and Missing Completely at Random (MAR/MCAR) mechanisms will underlie most of the missingness, and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small. However, because the MNAR mechanism can never be ruled out, sensitivity analyses will be performed to assess the robustness of the conclusions from the cLDA analyses to departures from MAR. These analyses will be performed only if significance is achieved in the respective hypothesis test.

- Pattern mixture model in conjunction with the tipping point approach in Ratitch et al [17]. With this method, missing values will be imputed based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values obtained the cLDA assuming MAR. For each imputed value, a positive adjustment Δ_1 will be added to the metformin+sitagliptin group (to the detriment of metformin+sitagliptin). For each value of Δ_1, a negative adjustment Δ_2 will be added to the metformin group (to the improvement of metformin). The inference will be carried out for a range of values of Δ_1 and Δ_2, a two-dimensional adjustment. A contour plot will be constructed of values of Δ_1 and Δ_2 that render the significant result into non-significant, which provides a measure of robustness of the primary result.

- J2R imputation, which falls under the category of pattern mixture models known as reference-based imputation (RBI, Carpenter et al 2013) [18], and is described below.

  In J2R, missing data in the control group are imputed under the MAR assumption, while missing data in the treatment groups are imputed under a MNAR assumption using the control group profile for time points after withdrawal.

  Standard multiple imputation techniques are overly conservative as they tend to overestimate parameter variances. Therefore, a more appropriate variance for the J2R based on pattern mixture model approximation (Liu and Pang, 2015) [19] will be used for the J2R sensitivity analysis of change from baseline in A1C and change from baseline in FPG. Details describing this methodology with relevant equations, model specifications, assumptions, and the SAS implementation code will be provided in the sSAP.

A detailed accounting of missing data will be provided, including a tabulation of the reasons for missingness (where known), distribution of missing and non-missing data by visit, and plots of the profile of mean A1C responses among subjects with different missingness patterns.

For the analysis of percentages of individuals at the A1C goal of <7.0% (53 mmol/mol) at Week 20 or the analysis of percentages of individuals with baseline A1Cs ≥ 8.5% at the A1C goal of <7.0% (53 mmol/mol) at Week 20, the cLDA model that is used for the analysis of A1C assuming MAR will also be used to impute the missing data on A1C. Imputations of the missing data will be based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values from the cLDA model. Ten sets of imputations of each missing value will be constructed from the cLDA model. Observed data will not be imputed. Subjects will be categorized as 'at goal' or 'not at goal' based on Week 20 A1C value after imputations.

To estimate the between-group rate difference, each of the 10 imputed data sets will be summarized to obtain the proportion of subjects at the goals within each group. The estimated proportions of subjects at the goals from the 10 imputed data sets will be combined using standard multiple imputations (MI) techniques proposed by Rubin [20] to yield an overall estimate of the response rate and associated variance for each group. The estimated response rates and adjusted effective sample sizes will then be used to obtain the confidence interval for between-group difference in proportion and relative risk via M&N [15] method. The p-value will be provided for the relative risk based on the M&N method stratified by the AHA status at screening.

Sensitivity analyses will be performed to assess the robustness of the conclusions from the M&N A1C goal < 7.0% analyses to departures from MAR. One sensitivity analysis for the proportion of subjects at the A1C goal of <7.0% will also be performed, with imputation of "Missing=Not at Goal". The percentages of subjects at target A1C control at Week 20 will be analyzed assuming that all missing Week 20 A1C values were not at target. This analysis will be performed in the AST population.

A second sensitivity analysis for the proportion of subjects at the A1C goal of <7.0% will be performed in the mFAS population. In this approach, 1000 bootstrap samples (with replacement and stratified by treatment and AHA status at screening) of individual patients will be created. Within each bootstrap sample, 10 sets of complete data will be generated with missing A1C data imputed under the J2R assumption. The bootstrap distribution of the between-group difference in proportion of subjects at goal and risk ratio will be constructed based on the mean of the estimates across the 10 imputed data sets from each of the 1000 bootstrap samples. The 95% CI for the between-group difference in proportion at A1C goal and risk ratio will be computed using the estimated bootstrap mean and standard deviation. The p-value will be provided for the relative risk. Details describing this methodology will be provided in the sSAP.

The proportion of patients rescued in each treatment group will be summarized. A time-to-rescue analysis will be performed using the Kaplan-Meier estimator and the log-rank test. For this analysis, subjects will be censored at the time of discontinuation from the study medication, discontinuation/completion from the study, or initiation of a sustained use of AHAs other than study medication or rescue therapy, if one of these occurred prior to the initiation of rescue therapy.

Analyses of A1C and FPG will also be performed to address the intention-to-treat (ITT) estimand. The target population and endpoints for ITT will be the same as for the primary estimand. However, the measure of intervention effect for ITT will be the difference in means (or ratio of proportions) at Week 20 comparing randomized treatments plus other AHAs (as needed) regardless of whether treatment continued to Week 20. Statistical methods for ITT will be the same primary methods used for the primary estimand.

Table 8 summarizes the key efficacy analyses.

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint	Primary vs. Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint/Primary Hypothesis				
Change from baseline in A1C at Week 20	P	cLDA	mFAS	Model-based
	S	cLDA	mFAS	PMM (tipping point)
	S	cLDA	mFAS	PMM (J2R)
	S	cLDA	ITT	Model-based
Key Secondary Endpoints/Secondary Hypotheses				
Proportion of subjects with A1C < 7.0% at Week 20	P	M&N	mFAS	MI
	S	M&N	AST	Missing=Not at Goal
	S	Bootstrap	mFAS	PMM (J2R)
	S	M&N	ITT	MI
Change from baseline in FPG at Week 20	P	cLDA	mFAS	Model-based
	S	cLDA	mFAS	PMM (tipping point)
	S	cLDA	mFAS	PMM (J2R)
	S	cLDA	ITT	Model-based
Other Endpoints				
Proportion of subjects with baseline A1C ≥ 8.5% with A1C < 7.0% at Week 20	P	M&N	mFAS	MI
Proportion of subjects receiving glycemic rescue therapy	P	Kaplan-Meier	All randomized subjects	N/A

[†]P=Primary approach; S=Supportive approach.

A1C=Glycosylated hemoglobin; AST=All Subjects Treated; cLDA=Constrained longitudinal data analysis; mFAS=modified Full analysis set; FPG=Fasting Plasma Glucose; J2R = Jump to Reference; N/A=Not applicable; M&N= Miettinen and Nurminen; MI=Multiple Imputation; PMM = Pattern Mixture Model

The strategy to address multiplicity issues with regard to multiple hypotheses 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 adverse experiences (AEs), laboratory tests, and vital signs.

The following analysis approaches will be used:

- To avoid the confounding effect of rescue therapy, the primary approach for all safety analyses will exclude those safety-related data points that occurred following the sustained use of additional antihyperglycemic agents (AHAs). This analysis approach will consider all on-treatment data up to Week 20 and data up to and including the 14-day post-treatment follow-up.

- A secondary approach will include those safety-related data points that occurred following the sustained use of additional antihyperglycemic agents (AHAs). The analysis will include all on-treatment data up to Week 20 and data up to and including the 14-day post-treatment follow-up.

- A third approach to safety analyses that applies only to AE summary measures, specific AEs, and serious AEs will include data after the first dose of double-blind study medication regardless of whether the subject has discontinued from study medication and will consider all data up to Week 20 and data up to and including the 14-day post-treatment follow-up.

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. There are no "Tier 1" safety endpoints. Therefore all safety endpoints will be considered Tier 2 or Tier 3.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs parameters 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 and predefined limits of change 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 and predefined limits of change.

Continuous measures such as changes from baseline in laboratory and vital signs 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. Mean change from baseline over time will be plotted with the corresponding standard errors.

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, and who discontinued due to an AE, documented hypoglycemia episodes will also be considered Tier 2 endpoints. The 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [15], an unconditional, asymptotic method.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Not applicable		
Tier 2	Any AE†	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	Selected hypoglycemia endpoints (see below)	X	X
	Specific AEs†, SOCs, or PDLCs (incidence ≥4 subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 of subjects in all of the treatment groups)		X
	Change from Baseline Results (Laboratory measurements, Vital Signs)		X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not already pre-specified as Tier-2 endpoints.
SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

Analysis of Hypoglycemia

The Tier 2 analysis for hypoglycemia will include the numbers and percentages of subjects experiencing one or more of the following:

- Documented symptomatic hypoglycemia with a concurrent glucose measurement of ≤70 mg/dL (≤3.9 mmol/L).

A listing of all hypoglycemia episodes with a concurrent glucose measurement of ≤70 mg/dL (≤3.9 mmol/L) will be provided. For each event, the listing will include glucose level, symptoms, precipitating factors, and severity. Severe hypoglycemia will be defined as episodes of hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained. Severe episodes will be included regardless of biochemical documentation.

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 and/or graphs. 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, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The following demographic/anthropometric, diabetes-related, and baseline efficacy variables will be summarized by treatment either by descriptive statistics or categorical tables. Depending on the variable of interest, statistics such as sample size, mean, SD, median, range and proportion will be provided.

- Continuous baseline demographic variables: age (years), weight (kg), height (cm), and body mass index (BMI; kg/m^2).
- Categorical baseline demographic variables: age (< median, ≥ median), gender (male, female), and race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-Racial), ethnicity (Hispanic/Latino or not).
- Baseline A1C, and distribution of A1C at baseline (A1C levels <8%, ≥8% and <9%, ≥9% and <10%, ≥10%)
- Baseline FPG
- AHA Status at Screening (Not on AHA, On non-metformin AHA, On Metformin)
- Time since diagnosis of diabetes mellitus (years)
- Geographic region (Americas, Europe, Asia, Other)

The above summaries will be provided for all subjects who received at least one dose of study therapy.

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

The study-wise type I error rate will be controlled at $\alpha = 0.05$ (2-sided) using an ordered testing procedure.

The study will first test for change from baseline in A1C. If the success criterion for A1C is met, the secondary hypothesis for A1C goal of <7% at Week 20 will be tested. If the success criterion for A1C goal of <7% at Week 20 is met then the secondary hypothesis for FPG will be tested. All three tests will be conducted at $\alpha = 0.05$ (2-sided).

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

This study will randomize approximately 380 subjects (in a 1:1 ratio) into the metformin+sitagliptin group and metformin group.

The study will have 93% power to establish that up-titration of metformin plus the addition of sitagliptin is superior to up-titration of metformin alone in lowering A1C, at α=0.05 (2-sided), if the underlying treatment difference is -0.4 %.

The power and sample size are based on the following assumptions at Weeks 6, 14, and 20:

1) Cumulative attrition rate (due to dropout and/or censoring caused by initiation of a sustained use of additional antihyperglycemic agents (AHAs) at Week 6, Week 14, and Week 20 are 1%, 3% and 18% in the metformin+sitagliptin group and 2%, 5% and 27% in the metformin group. The attrition rates were estimated through simulation studies based on data from the sitagliptin+metformin factorial study (Study 036) and metformin add-on studies (Studies 053 and 403).

2) Conditional correlation matrix (correlation matrix of the post-randomization measurements conditional on the baseline value) is

1.00	0.85	0.77
0.85	1.00	0.92
0.77	0.92	1.00

3) Conditional standard deviation of 1.1%

4) An underlying true between-group difference in A1C change of -0.40% based on the expected effect of the combination therapy in the study population with an effective sample size of 174 within the metformin only group and 180 in the metformin+sitagliptin group.

A sample size of 190 patients per group will provide approximately 90% power for A1C goal <7.0% at Week 20 to detect a between-group difference of 14 to 15 percentage points in the proportion of patients at goal, assuming that the proportion at goal is 14% to 18% in the metformin group. The assumed proportions at goal with metformin and between-group difference in proportions were based on simulations assuming different baseline A1C distributions.

Table 10 shows the power for A1C goal <7.0% under various assumptions.

Table 10 Power (%) for the Analysis of A1C Goal < 7.0% at Week 20

A1C < 7.0% at Week 20 for Metformin (%)	True Difference (%) (Met+sita vs. Met)	Power (%)	95% CI Half Width (%)
14	14	89	8.7
15	14	88	8.8
15	15	92	8.9
17	15	90	9.1
18	15	89	9.2

The calculation for the A1C goal analysis using the M&N method is based on effective sample sizes of 170 and 163 in the metformin+sitagliptin group and metformin group, respectively. The effective sample sizes were estimated from simulation studies that took into account data attrition and missing data imputation.

Table 11 below shows the power for change from baseline in FPG based on the cLDA model at α=0.05 (2-sided). The study will provide ≥90% power if the true difference in FPG reduction is -16 mg/dL or greater, assuming a SD of 45 mg/dL, and an effective sample size of 164 in the metformin group and 173 in the metformin+sitagliptin group.

Table 11 Power (%) Under Various FPG Assumptions

Sample Size Per Arm Randomized	True Difference (mg/dL)	Conditional Standard Deviation (mg/dL)	Power (%)	95% CI Half-Width (mg/dL)
190	-18	40	99	8.6
	-18	45	96	9.6
	-16	40	96	8.6
	-16	45	90	9.6

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect at Week 20 is consistent across various subgroups listed below, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of each subgroup.

- Baseline A1C (A1C levels <8.5%, and ≥8.5%)
- Age categories: ≤ or > median age
- Gender (female, male)
- AHA Status at Screening (Not on AHA, On non-metformin AHA, On Metformin)

In addition, a forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

The consistency of the treatment effect will be assessed in the context of a repeated measures ANCOVA (RMANCOVA) method, which is a generalization of the standard ANCOVA to accommodate repeated measurements. Subgroup analyses will not use the cLDA method that is used for the primary analysis because the assumption of equal baseline means that is made by the cLDA method will not apply within subgroups. The RMANCOVA model will adjust for treatment, subgroup, and treatment-by-subgroup interaction. Time is treated as a categorical variable and time-specific versions of each term listed above at each week will be used to acknowledge the repeated nature of the measurements. An unstructured covariance matrix will be used to model the correlation among repeated measurements. Treatment effects and nominal 95% CIs by category for the classification variables listed above will be reported as well as presented graphically. Formal statistical testing of treatment-by-subgroup interactions will not be performed.

The treatment effect across study centers will be summarized for A1C at Week 20 with descriptive statistics.

Results from the subgroup analyses should be reviewed cautiously. Because sample sizes within subgroups will be smaller than the overall study sample size, estimation may not be precise and 95% CIs will usually be wide in the subgroup analyses.

8.11 Compliance (Medication Adherence)

The computation of compliance in the All Subjects Treated (AST) set will be based on the study medication case report form. Both the assigned treatment and any matching placebo pills will be included in the compliance calculation.

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

$$\text{Compliance} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Double-blind Treatment Period}} \times 100\%.$$

A day within the Double-blind Treatment Period will be considered a compliant day if the subject takes 1 tablet of sitagliptin 100 mg or matching placebo, as well as the appropriate dose of Met-IR background medication. The dose of Met-IR is intended to be 1500 mg (3 x 500 mg tablets) per day from Visit 4/Day1 to Day 7 and 2000 mg (4 x 500 mg tablets) per day after Day 7. If the subject is unable to tolerate the study-prescribed dose of Met-IR and, at the discretion of the study investigator, continues participation at a lower dose of Met-IR, they will be considered compliant if they take the dose of Met-IR prescribed by the study investigator.

If the study medication eCRF indicates general compliance problems with sitagliptin/matching placebo or Met-IR, the subject will be considered non-compliant for that day regardless of the number of tablets reported.

The "Number of Days in Double-blind Treatment Period" for the compliance calculation is defined for each subject as the total number of days from the first dose of double-blind study medication (sitagliptin/sitagliptin-matching placebo) to the last day of double-blind study medication.

Summary statistics will be provided on percent compliance by treatment group.

8.12 Extent of Exposure

The extent of exposure to double-blinded study treatment will be evaluated by summary statistics (N, mean, median, standard deviation and range) and frequencies for the "Number of Days on Therapy" by treatment group, based on daily dosing records on the study medication eCRF.

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 12.

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 12 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Sitagliptin Phosphate 100 mg	Tablet	Provided by the sponsor
Sitagliptin Phosphate 100 mg Placebo	Tablet	Provided by the sponsor

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.

Subjects will receive blinded Sitagliptin Phosphate 100 mg or Placebo Finished Good Bottles. Each bottle at Visit 3 will contain 21 tablets. Each bottle in the treatment phase from Visit 4 through Visit 6 will contain 63 tablets.

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 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. 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 Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. 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 FDAAA or the EMA clinical trials directive 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 FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

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. American Diabetes Association. Standards of medical care in diabetes–2014. Diabetes Care. 2014;37(Suppl 1):S14–80.
2. Danaei G, Finucane MM, Lu Y, et. al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011; 378(9785):31-40.
3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013: 1-14.
4. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
5. Cade, WT. Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Phys Ther. 2008 Nov; 88(11): 1322–1335.
6. American Diabetes Association. Standards of medical care in diabetes–2015. Diabetes Care. 2015;38 (Suppl 1): S33-40.
7. Folazof C, Schwartz S, Foley J. Effect of vildagliptin as add-on therapy to a low-dose metformin. World J Diabetes 2010; 1(1): 19-26.
8. Hermans M, Delibasi T, Farmer I et al. Effects of saxagliptin added to sub-maximal doses of metformin compared with uptitration of metformin in type 2 diabetes: the PROMPT study. Current Medical Research and Opinion 2012; 28(10): 1635-1645.
9. Effects of rosiglitazone added to sub-maximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Current Medical Research and Opinion 2005; 21(12): 2029-2035

10. Goldstein B, Feinglos M, Lunceford J et al. Effects of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007; 30 (8): 1979-1987.
11. Januvia US Product Circular. 2015.
12. The Rules for Governing Medicinal Products in the European Union Volume 10-Guidance Documents Applying to Clinical Trials Guidance on Investigational Medicinal Protducts (IMPS) and Non Investigational Medicinal Products (NIMPS)(Rev. 1, March 2011)
13. Nathan, David M., Long-Term Complications of Diabetes Mellitus. The New England Journal of Medicine. (June 10, 1993).
14. National Research Council. The prevention and treatment of missing data in clinical trials. Washington, DC: National Academies Press, 2010 (http://www.nap.edu/catalog.php?record_ id-12955).
15. Miettinen OS, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985;4:213-226
16. Liang, K. Y. and Zeger, S. (2000). Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankhyā: The Indian Journal of Statistics, Series B 62, 134–148.
17. Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics. 2013, 12:337 – 347.
18. Carpenter, James R., Roger, James H., and Kenward, Michael G (2013). Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation. Journal of Biopharmaceutical Statistics, 23: 1352 – 1371.
19. Liu, G. Frank and Pang, Lei (2015). On Analysis of Longitudinal Clinical Trials with Missing Data Using Reference-Based Imputation. Journal of Biopharmaceutical Statistics. 2015: DOI: 10.1080/10543406.2015.1094810.
20. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987; Wiley, New York.

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 7.1.3.2 – Future Biomedical Research Sample Collection 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 the Sponsor 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 the Sponsor or those working for or with the Sponsor.

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.

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.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

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, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines 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.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. 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 specific analysis is performed will be reported to the Sponsor.

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 the Sponsor using the designated mailbox PPD and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent 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 the end of the main study. 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 Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-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 Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives 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 on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

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. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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.

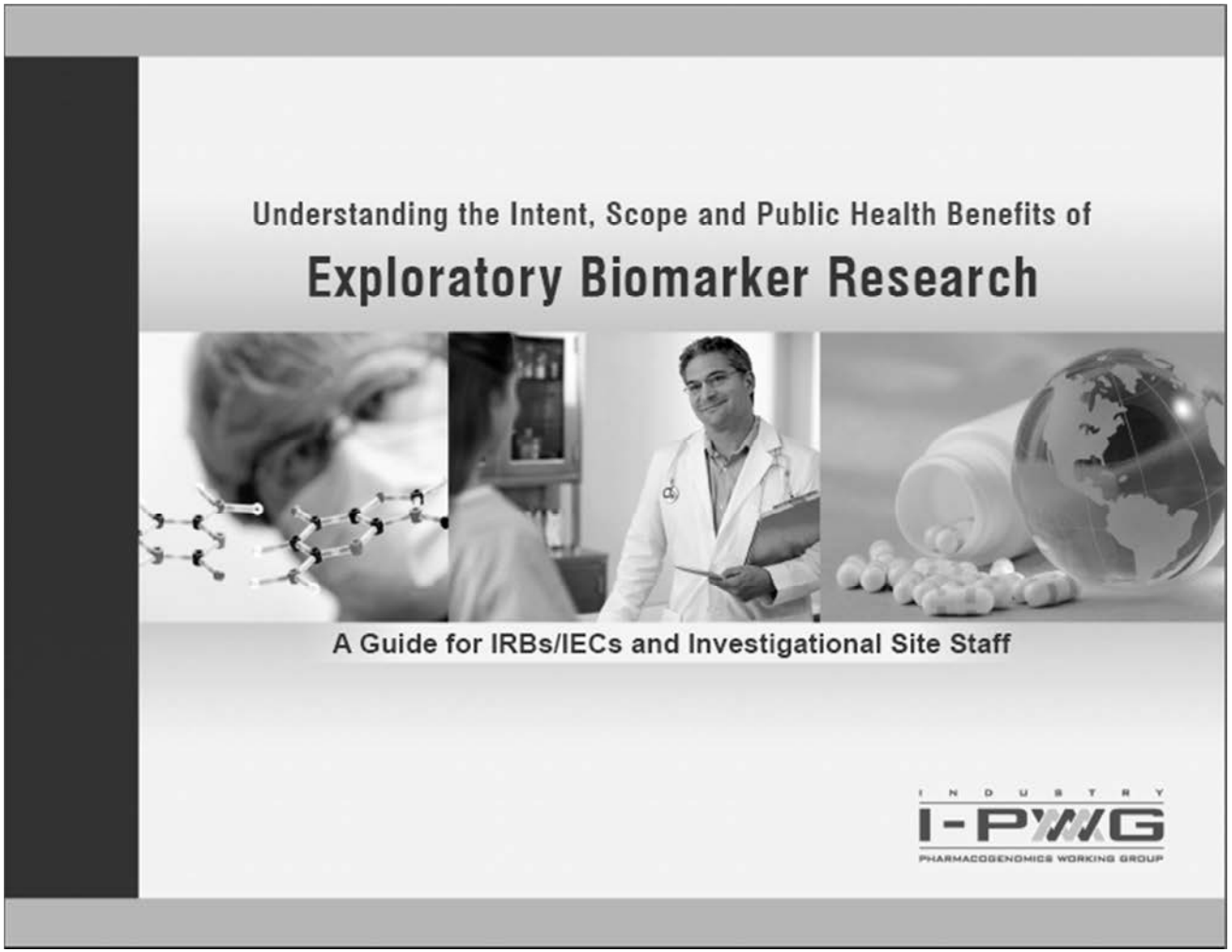
12. Questions

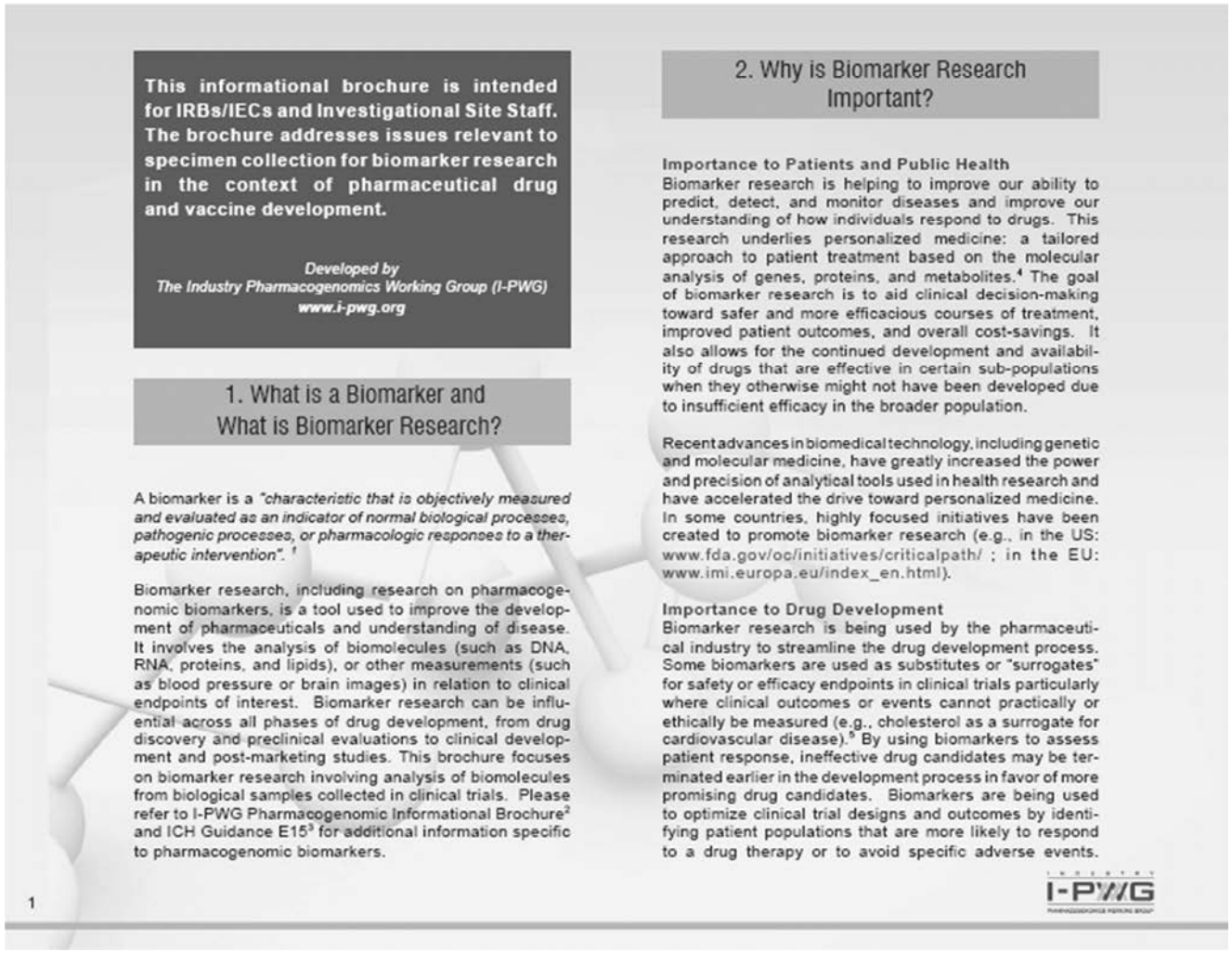
Any questions related to the future biomedical research should be e-mailed directly to PPD .

13. 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 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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.

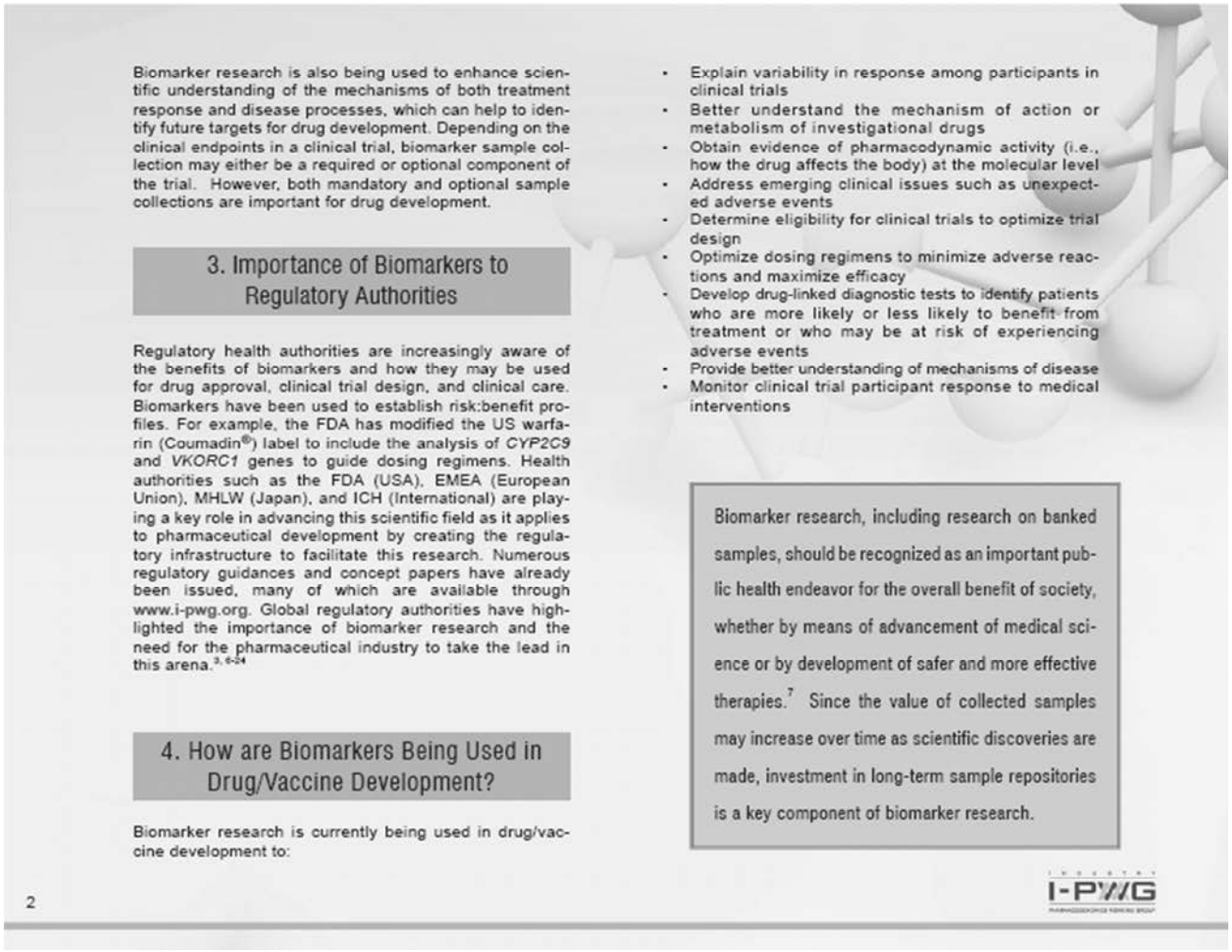
Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to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

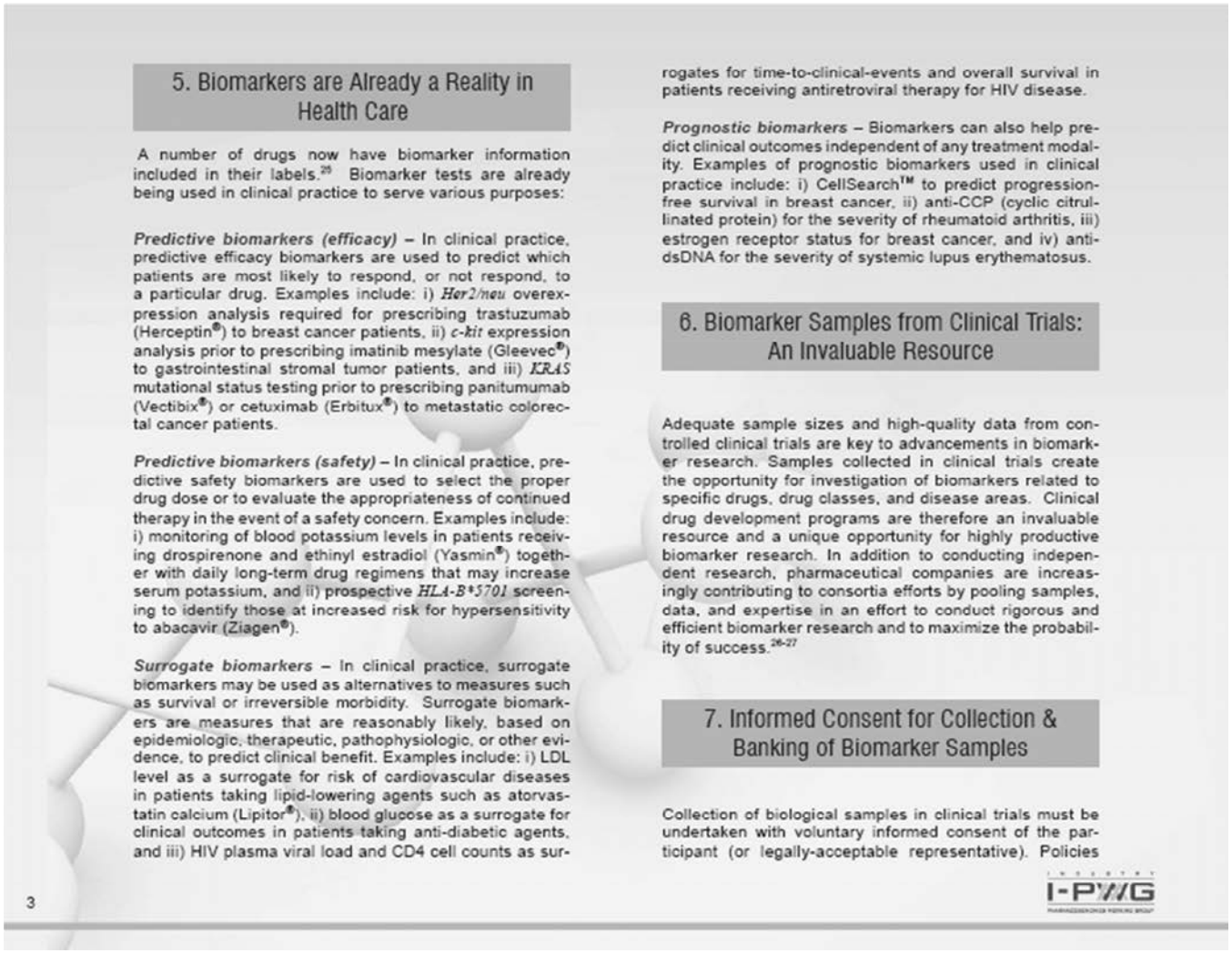
Importance to Drug Development

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.

I-PWG

1


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.
2
I-PWG



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

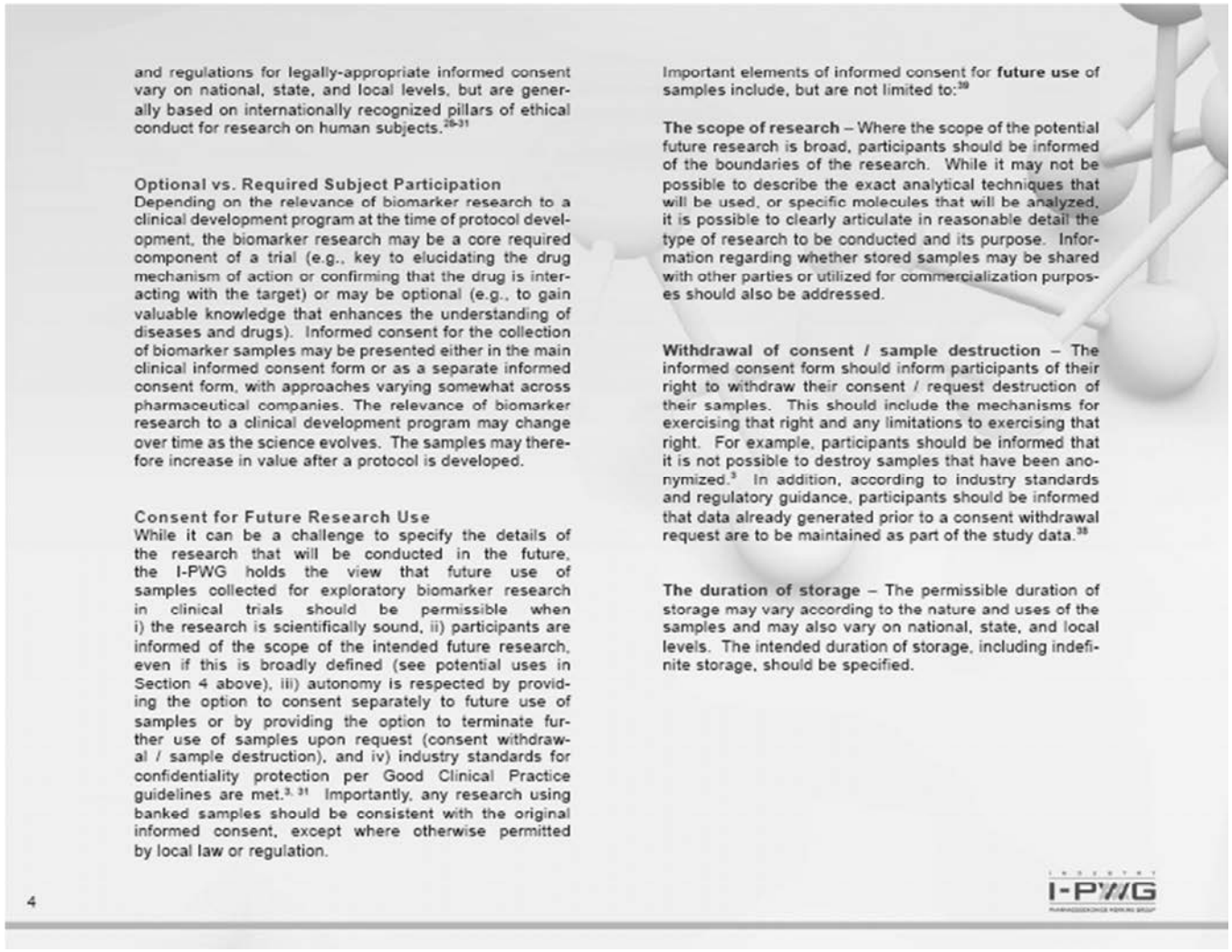
Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development 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

3

I-PWG



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]

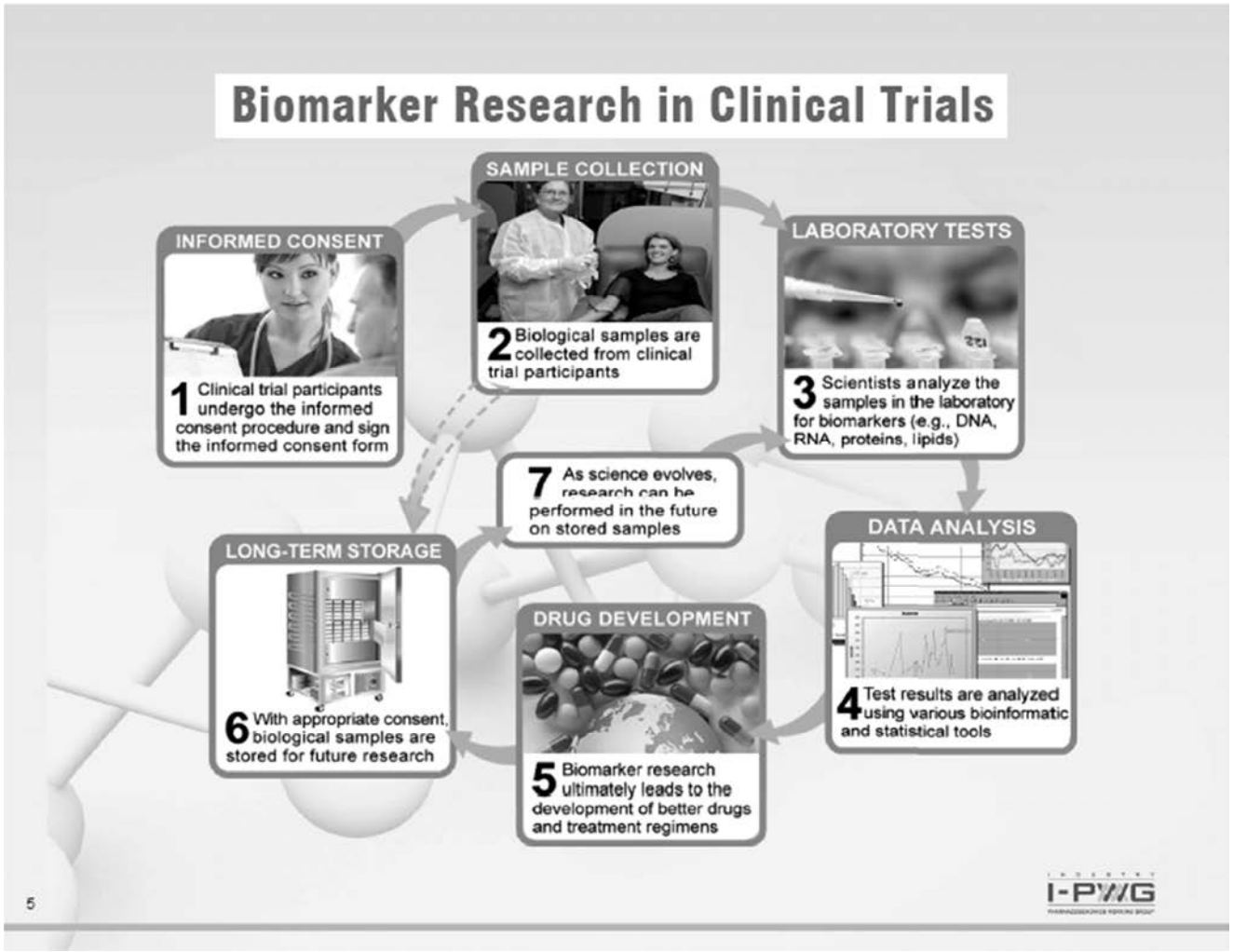
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible 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.

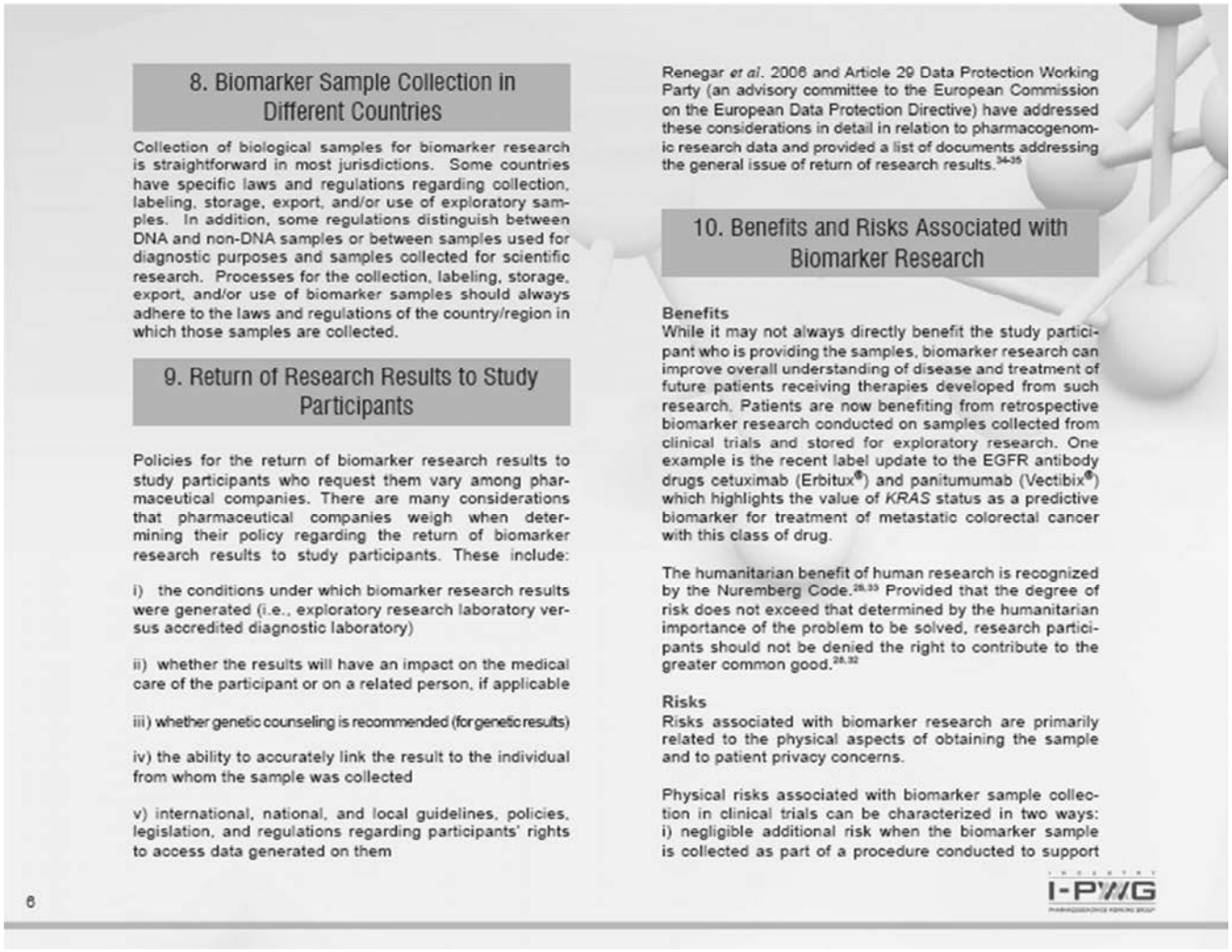
Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants 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.

4

I-PWG


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
5
I-PWG



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

6

I-PWG

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?

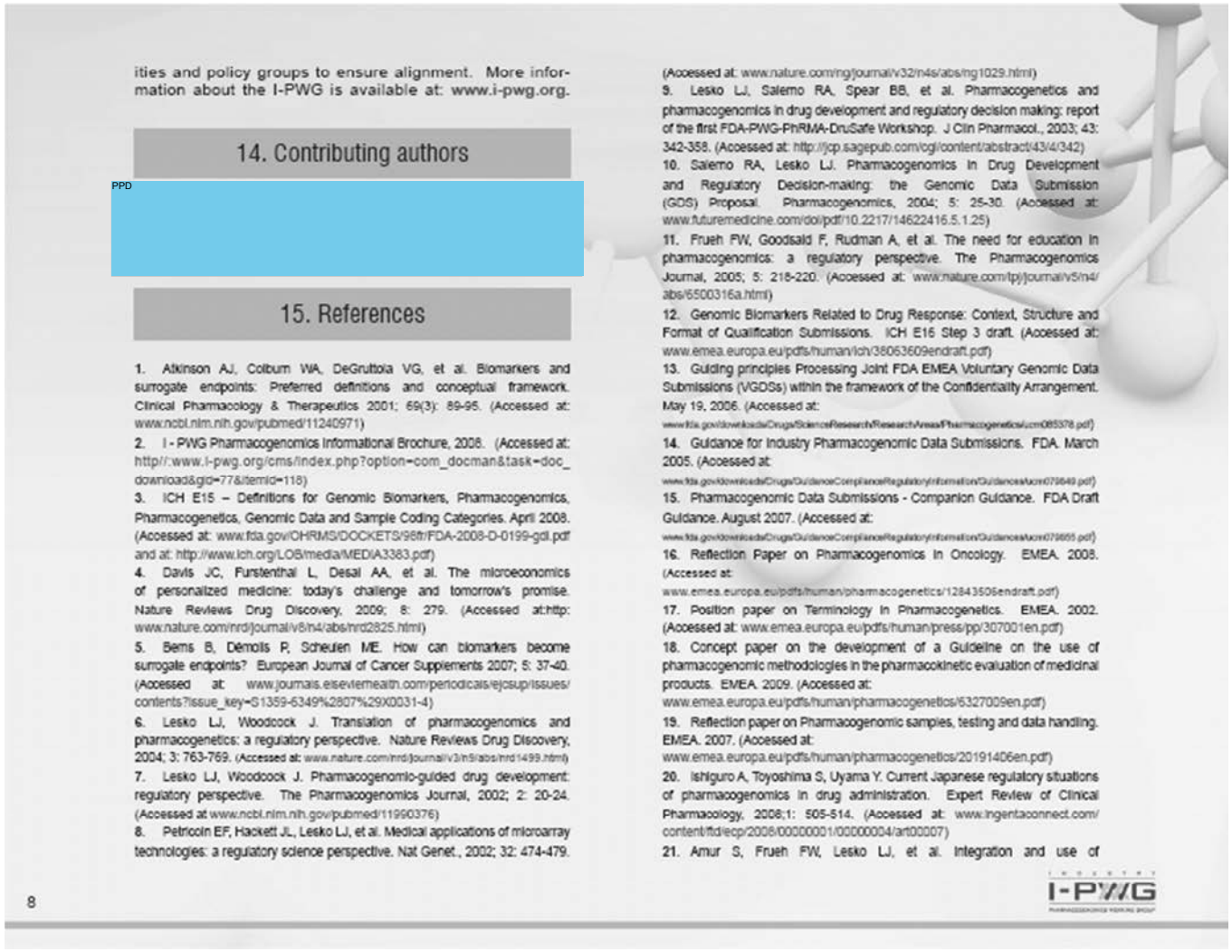
Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

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-

7

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

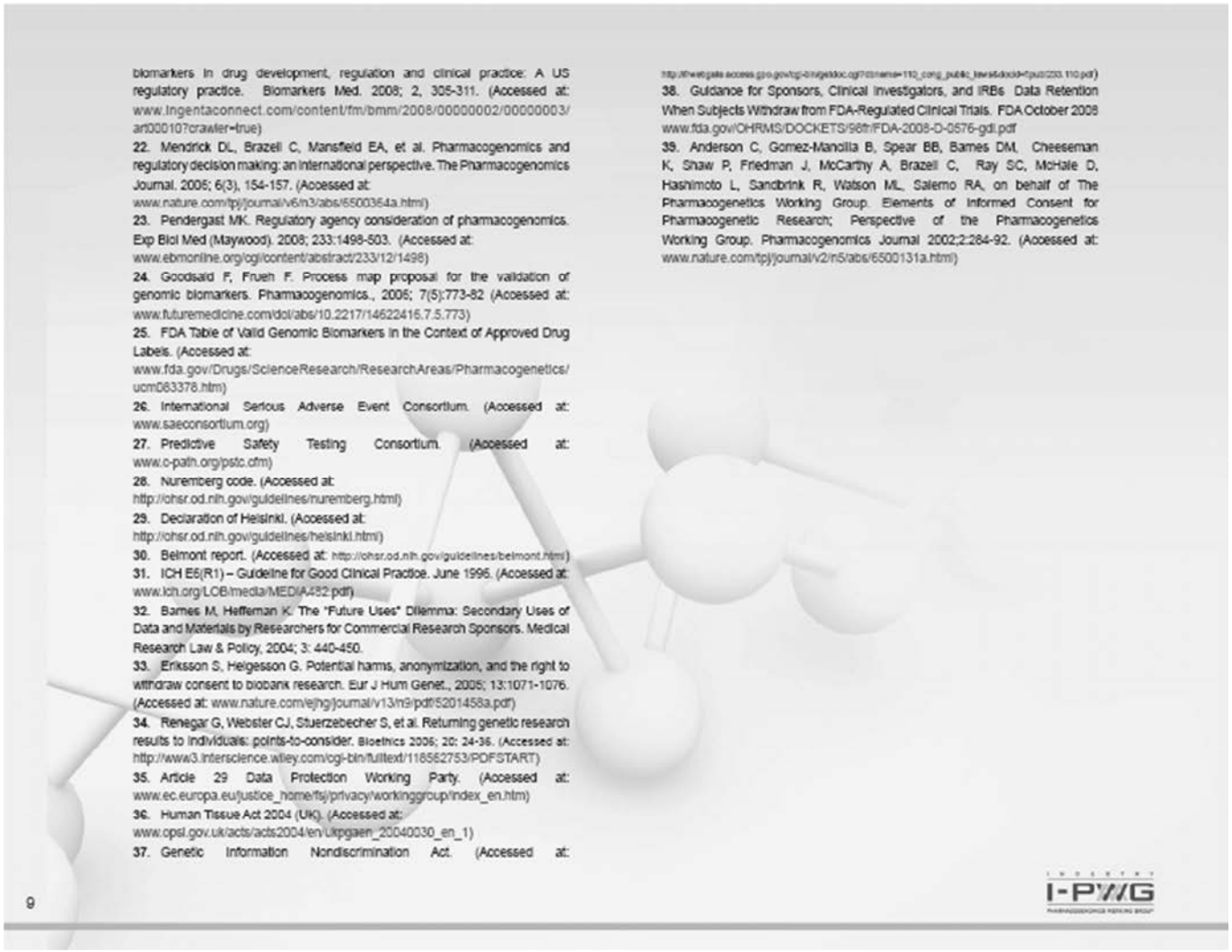
PPD

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheufen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/fid/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

I-PWG



biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2005; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy. 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://thomas.loc.gov/cgi-bin/query/z?c110:s.358.enr:)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Manolla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)

9

I-PWG


www.i-pwg.org

12.4 Management of Subjects with Elevated Liver Enzymes (ALT or AST ≥3X ULN)

Every increase in ALT, and/or AST, above the limits described in the protocol is defined as clinically significant (i.e., ALT or AST ≥3-times the upper limit of normal [ULN]). Under these circumstances, the Central Laboratories will alert the Investigators/ Coordinators.

In addition, when ALT and/or AST levels are elevated beyond the clinical significant margin above, the Investigators/Coordinators must recall the patient, attempt to identify the cause of the elevation, and repeat the blood test(s). Detailed instructions are provided below.

For patients who have ALT or AST increases (either ALT or AST ≥3-times the ULN) with a total bilirubin lab value ≥2-times ULN and, at the same time, the alkaline phosphatase lab value is <2-times ULN, please follow the guidance document entitled "Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials" located in the Investigator Trial File Binder and refer to the ECI guidance in the protocol (Section 7.2.3.2).

For patients with ALT or AST increases (either ALT or AST ≥3-times the ULN) but who *do not* also meet the above criteria for both total bilirubin and alkaline phosphatase, the process below should be followed. These events do not qualify as ECIs per protocol.

A. Patients should return to the center within 3 days for the following: (history can be obtained over the phone in the interim)

1. Obtain further information.

2. Careful questioning of recent alcohol consumption, including a recent change in pattern of alcohol use.

3. Search for drug-related causes of hepatitis and liver injuries (acetaminophen; amiodarone; aspirin; chlorpromazine; dantrolene; erythromycin; halothane; isoniazid; methyldopa; nitrofurantoin; oxyphenisatin; perhexiline maleate; phenytoin; propylthiouracil; rifampin; sulfonamides; tetracyclines) or other new medications.

4. Search for alternative medical causes such as cholelithiasis, recent alcohol consumption, history of intercurrent illness (e.g., viral syndrome), hepatitis, or potential exposure to viral hepatitis (transfusion).

5. Repeat determination of ALT, AST, total bilirubin, and alkaline phosphatase (within 3 days of initial report of abnormal level).

6. Perform serologic tests including: (a) Hepatitis A (IgM); (b) Hepatitis B (surface antigen and core IgM); (c) Hepatitis C (antibody).

B. Actions

ALT and/or AST elevations ≥3-times ULN at any visits will result in a mandatory re-test within 3 days of initial report. Based upon initial abnormal ALT/AST level:

1. If ALT or AST levels are ≥3-times ULN, but ≤5-times ULN, consideration can be given to keeping patient on randomized therapy until repeat determination (performed within 3 days of initial abnormal level).

2. If ALT or AST levels are >5-times ULN, patients should have their randomized therapy interrupted immediately.

Once interrupted, reinstatement of therapy must occur only after consultation with a Clinical Monitor (SPONSOR or its delegate).

Based upon repeat determination (performed within 3 days of initially reported abnormal ALT or AST level):

1. If ALT and/or AST levels are confirmed as being elevated but <3-times ULN**,** consultation with a Clinical Monitor (SPONSOR or its delegate) is required prior to continuing the patient in the study.

2. If ALT and/or AST levels are confirmed as being elevated ≥3-times ULN, patients will be discontinued from the study.

Note: If the repeat determination is still ≥3-times elevated, but has substantially decreased (>30% decline) from the initial abnormal value, a second repeat should be performed within 3 days of the initial repeat. If ALT and/or AST levels return below the 3-times margin consideration can be given to continue the patient in the study after a discussion with, and approval by, the Clinical Monitor (SPONSOR or its delegate).

All persistent elevations in ALT or AST ≥3-times ULN at the completion/ discontinuation of the study will warrant follow-up including a repeat blood test within 1 week and until complete resolution of the abnormality.

12.5 Predefined Limits of Change (PDLC)

Laboratory Test	Predefined Limits of Change† Criterion	Categories Assessed for Each Criterion	
		At Least One Value	Last On-Treatment Value
Laboratory – Chemistry			
Serum Creatinine (mg/dL)	1. Increase ≥0.3 mg/dL	N	Y
Total Bilirubin (mg/dL)	1. Value >2x ULN	Y	Y
AST (IU/L)	1. Value ≥3x ULN	Y	Y
ALT (IU/L)	1. Value ≥3x ULN	Y	Y
AST (IU/L) or ALT (IU/L)	1. Value ≥3x ULN	Y	Y
AST (IU/L) or ALT (IU/L)+ Total Bilirubin (mg/dL)	1. ALT ≥3× ULN or AST ≥3× ULN with concurrent Bilirubin >2× ULN	Y	Y
Alkaline Phosphatase (IU/L)	1. Value >1.5x ULN	Y	Y

† Increases and decreases are relative to baseline.
‡ LLN = Lower limit of normal.
§ ULN = Upper limit of normal.

"At Least One Value" will include results meeting the PDLC criterion at any time during the Treatment Period (defined as the period from randomization up to 2 days after the final dose of study medication). "Last On-treatment Value" will include only the last available result during the Treatment Period. A listing of all post Treatment Period values that meet PDLC criteria will also be provided.

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 – TRIAL PROCEDURES (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	