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| **Official Protocol Title:** | A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR (a Fixed-Dose Combination Tablet of Sitagliptin and Extended-Release Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin) |
| **NCT number:** | NCT01760447 |
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## SPONSOR:

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## TITLE:

A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR (a Fixed-Dose Combination Tablet of Sitagliptin and Extended-Release Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin)

## INVESTIGATOR:

**PRIMARY:**

**CLINICAL PHASE:** III

**US IND NUMBER:** 101,964

**EudraCT NUMBER:** 2012-004035-23

## SITE:

## INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

# Table of Contents

## SUMMARY OF CHANGES

**Primary Reasons for This Amendment**

| Section Number | Section Title | Description of Change | Rationale |
|---|---|---|---|
| 1.5 | Sample | The sample size was updated. | Sample size is being increased to allow an additional contribution of patients to support the safety and efficacy summary. |
| 2.4.3 | Beginning and End of Study Definition | Section was added. | To reflect protocol template updates and to indicate when the study will be completed and post study reporting activities initiated. |
| 3.5.5.1 | Statistical Methods for Efficacy Analyses | -Provided clarification on analysis using the treatment effect estimand.<br>-Added analyses using the treatment policy estimand, including the 'retrieved dropout' (RD) and 'return-to-baseline' approaches for handling missing data. | -To define estimands as recommended by ICH E9 (R1).<br>-To comply with regulatory request. |

**Additional Changes for This Amendment**

| Section Number | Section Title | Description of Change | Rationale |
|---|---|---|---|
| 1.5 | Sample | Clarified the definition for stable dose of background insulin. | To provide additional details for different types of insulin (basal and bolus) administration. |
| 1.6 | Dosage/Dosage Form, Route, and Dose Regimen | | |
| 2.2 | Patient Inclusion Criteria | - Clarified the definition for stable dose of background insulin.<br>- Clarified that the screening laboratory assessments must be repeated if the duration between the Screening Visit and Visit 3 is >28 days. | - To provide additional details for different types of insulin (basal and bolus) administration.<br>- To ensure patient laboratory results for eligibility assessment are recent. |
| 2.3 | Patient Exclusion Criteria | Clarified that the screening laboratory assessments must be repeated if the duration between the Screening Visit and Visit 3 is >28 days. | To ensure patient laboratory results for eligibility assessment are recent. |
| 2.4.1 | Summary of Study Design | The number of patients per group was removed from the Study Design figure. | The sample size was modified. |
| 2.4.2.1 | Study Visits General Information | -Clarified that patients should also fast ≥10 hours prior to Rescue and Discontinuation Visits.<br>-Window between Visit 2 and Visit 3 was added. | -To clarify instructions outlined in Section 1.7 Study Flow Chart.<br><br>-To clarify the duration of the placebo run-in period and to harmonize with the current guidance to investigators. |

| Section Number | Section Title | Description of Change | Rationale |
|---|---|---|---|
| 2.4.2.3 | Visit 2 Single-Blind Placebo Run-In | Emphasized completion of procedures before dosing. | To ensure that results from procedures are not affected by administration of study medication. This approach is also used at the placebo-run in Visit to maintain consistency with other visits. |
| 2.4.2.4 | Visit 3/Randomization Visit to Visit 6/Week 20 | | |
| 2.4.2.5 | Visit 6/Week 20 through Visit 9/Week 54 | | |
| 2.7.3 | Power and Sample Size | Power and sample size were updated. | To reflect revised sample size. |
| 3.1.4 | Rationale for Dose Regimen | Updated information on study P296. | Study P296 has completed. |
| 3.2.3.6 | Laboratory Monitoring | Clarified that patients should only be fasting for Visits 1, 3, 6, 9, Rescue, and Discontinuation, but not for other visits. | To limit patient burden of fasting for visits where fasting is not required. |
| 3.2.3.17 | Blinding/Unblinding | Text on unblinding of patients was updated. | To reflect protocol template updates. |
| 3.5.1 | Responsibility for Analyses/In-House Blinding | Added that 1 CSR will be written for this study, and pooled analyses with P170 (base and extension) will be included in a separate report. | To clarify the reporting plan. |
| 3.5.4.1 | Efficacy Analysis Populations | Completers population was removed. | The population not related to estimands. |
| 3.5.5.2 | Statistical Methods for Safety Analyses | Changed safety analyses approach – primary approach will include data after rescue except for hypoglycemia endpoints. | Simplification of analysis approach. |
| 3.5.7.1 | Sample Size and Power for Efficacy Analyses | Updated sample size and power information. | To reflect revised sample size. |

| Section Number | Section Title | Description of Change | Rationale |
|---|---|---|---|
| 3.5.7.2 | Sample Size and Power for Safety Analysis | Updated sample size. | To reflect revised sample size. |
| 3.5.8 | Subgroup Analyses | Subgroup analyses for P289 alone were removed. | Subgroup analyses will be based on pooled data instead of P289 alone. |
| 3.5.10 | Compliance (Medication Adherence) | Adherence definition was added. | To reflect compliance based on time in study. |
| 3.6.1 | Patients and Replacement Information | Updated sample size. | To reflect revised sample size. |
| 5 | List of References | List of references was updated. | Deleted references that are no longer applicable. |
| 6.8 | Mapping of Relative Day Ranges to Weeks | Information was updated. | To clarify how results will be mapped to individual time points during analysis. |
| 6.12 | List of Prior Amendments | List was updated. | Update. |
| Entire document | | -The word 'subject' was replaced with the word 'patient'.<br>-Editorial and formatting changes. | Consistency throughout the document. |

# 1. SUMMARY

## 1.1 TITLE

A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR (a Fixed-Dose Combination Tablet of Sitagliptin and Extended-Release Metformin) in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin)

## 1.2 INDICATION

For the treatment of pediatric patients (10-17 years of age, inclusive) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

## 1.3 SUMMARY OF RATIONALE

This study, MK-0431A P289, is designed to assess the safety and efficacy of the addition of sitagliptin (administered as MK-0431A extended-release [XR]) compared with the addition of placebo to therapy with extended-release metformin (metformin XR) for the treatment of T2DM in pediatric patients (10-17 years of age, inclusive) who have inadequate glycemic control on metformin therapy (alone or in combination with insulin).

Based on data from adult patients, the safety and efficacy of the addition of sitagliptin is not expected to differ based on the background metformin therapy; therefore, the safety and tolerability of the addition of sitagliptin to metformin XR are expected to be similar to that of adding sitagliptin to metformin. Hence, the data from the P170 base study and from the first 20 weeks of P289 will be combined for the primary analyses of each study.

A separate study, MK-0431A P170 base study, is a 20-week study to assess the safety and efficacy of sitagliptin added to ongoing metformin therapy compared with the addition of placebo to ongoing metformin therapy for the treatment of T2DM in pediatric patients (10-17 years of age, inclusive) with inadequate glycemic control on metformin (alone or in combination with insulin). MK-0431A P170 has an extension study to the original 20-week P170 base study and is designed to provide an assessment of safety for an additional 34 weeks in patients from the P170 base study who agree to participate in the extension study. Week 0 to Week 54 data from P289 will be combined with Week 0 to Week 54 data from P170 (base + extension) for this longer-term assessment. Refer to Sections 3.1 and 3.5 for additional details.

## 1.4 SUMMARY OF STUDY DESIGN

This is a multinational, randomized, double-blind, parallel-group study. The study will be approximately 56 weeks in duration, including a screening period of 1 week (**Visits 1 to 2**), a 1-week single-blind placebo run-in period (**Visits 2 to 3**), and a 54-week double-blind treatment period (**Visits 3 to 9**). The treatment periods will consist of Phase A (a 20-week placebo-controlled period [**Visits 3 to 6]**) and Phase B (a 34-week active-

controlled period [**Visits 6 to 9**]), as shown in Figure 2-1 (Section 2.4.1). A telephone contact will be performed 14 days after the last dose of study medication (whether due to study completion or premature discontinuation from the study medication) to assess for any serious adverse events (SAEs). Please refer to Section 3.2.3.16.2 for details.

At **Visit 1**, patients 10-17 years of age (inclusive) with T2DM on a stable dose of metformin (≥1500 mg/day, for ≥12 weeks) without insulin or those on stable doses of metformin (≥1500 mg/day, for ≥12 weeks) and insulin (of any type, variance in dose to be ≤15% of total daily dose, for ≥12 weeks) will be eligible to be screened.

At **Visit 2**, eligible patients with inadequate glycemic control (hemoglobin $A_{1c}$ [A1C] of ≥6.5% and ≤10.0% on metformin monotherapy and ≥7.0% or ≤10.0% for those on dual therapy with metformin and insulin at **Visit 1**) will undergo diet and exercise counseling. Based on their current dose of metformin (immediate-release [IR] or XR), patients will be switched to the appropriate corresponding dose of Sponsor-supplied metformin XR and initiate MK-0431A XR placebo. Those patients who enter the study on background insulin will continue their insulin throughout the study.

**At Visit 3/Day 1**, patients will be randomized in a 1:1 ratio to treatment with either MK-0431A XR and metformin XR placebo or with metformin XR and MK-0431A XR placebo. Randomization will be stratified by the following: 1) dose of metformin at **Visit 1** and 2) insulin use at **Visit 1**. The dose of double-blind study medication will remain stable for the duration of the study. At **Visit 6/Week 20** (end of Phase A treatment period, beginning of Phase B) and subsequent visits in Phase B, all patients will remain on their randomized double-blind study medication and if their glycemic values meet the protocol-specified thresholds (Section 2.4.2), patients on background insulin will uptitrate their background insulin and patients not on background insulin will initiate insulin glargine.

## 1.5 SAMPLE

At least 90 patients, but no more than 110 patients (10 to 17 years of age, inclusive) with T2DM who have inadequate glycemic control will be eligible to participate if they meet ONE of the following enrollment criteria:

- A1C of ≥6.5% and ≤10.0% at **Visit 1** on a stable dose of metformin (≥1500 mg/day, for ≥12 weeks) without insulin.

OR

- A1C ≥7.0% and ≤10.0% at **Visit 1** on stable doses of metformin (≥1500 mg/day, for ≥12 weeks) and insulin (of any type, variance in dose to be ≤15% of total daily dose, for ≥12 weeks). This stable regimen can include (1) a stable dose of basal insulin (±15%) AND/OR (2) stable prescribed doses of bolus insulin (±15%) (a) for each fingerstick glucose range for patients on sliding scale AND, if applicable, (b) for corrective doses and carbohydrate coverage.

**Note:** Patients on stable doses of metformin ≥1000 mg and <1500 mg/day (±insulin) for ≥12 weeks can participate if there is documentation in the patient's medical records that they cannot tolerate higher doses of metformin.

At least 30% of the randomized patients will be 10 to 14 years of age.

## 1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

MK-0431A XR (sitagliptin/metformin XR: 50/500 mg, 50/1000 mg tablets), metformin XR (500 and 1000 mg tablets), and their matching placebos, will be supplied by the Sponsor (see Table 2-2). All insulin will be sourced locally.

During the 1-week single-blind placebo run-in period, patients will receive the following treatments:

- two tablets of metformin XR (500 mg x 2; 500 mg and 1000 mg; or 1000 mg x 2) and two tablets of MK-0431A XR placebo (matching the metformin XR dose), administered once daily with a meal, preferably in the evening

During the 54-week double-blind treatment period, patients will receive one of the following treatments:

- two tablets of MK-0431A XR (50/500 mg x 2; 50/500 mg and 50/1000 mg; or 50/1000 mg x 2) and two tablets of metformin XR placebo (matching the metformin dose in MK-0431A XR), administered once daily with a meal, preferably in the evening

- two tablets of metformin XR (500 mg x 2; 500 mg and 1000 mg; or 1000 mg x 2) and two tablets of MK-0431A XR placebo (matching the metformin XR dose), administered once daily with a meal, preferably in the evening

Open-label insulin (for background) and open-label insulin glargine will be sourced locally and administered subcutaneously based on instructions provided by the Investigator (based on accepted local, national or international guidelines for use of insulin).

Doses of background insulin should remain stable (of any type, variance in dose to be ≤15% of total daily dose) for the duration of the trial (See Section 2.4.2.5 and 2.4.2.6 for uptitration, Section 3.2.3.1 for down-titration of insulin, and Section 1.5 for insulin stable regimen definition).

Note: Not all specific insulin types that are approved in adults are approved for use in pediatric patients with T2DM, although the use of insulin therapy in pediatric patients is supported by practice guidelines.

## 1.7 STUDY FLOW CHART

| | Screening | Run-In | Random-ization | Double-Blind Treatment Phase A | | | | | | Double-Blind Treatment Phase B | | | | | Post-Study Phone Contact |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V.1 | V.2 Wk -1 | V.3 Day 1 | TC Wk 2 | TC Wk 4 | V.4 Wk 6 | V.5 Wk 12 | TC Wk 16 | V.6 Wk 20 | TCs[1] | V.7 Wk 28 | V.8 Wk 40 | V.9 Wk 54 | Visit Rescue[2]/ D/C[3] | Wk 56 or 14 days post-discon. |
| **Study Procedures** | | | | | | | | | | | | | | | |
| Obtain informed consent and assent[4] | X | | | | | | | | | | | | | | |
| Obtain informed consent and assent for Future Biomedical Research (FBR) | X | | | | | | | | | | | | | | |
| Dispense patient identification card | | X | | | | | | | | | | | | | |
| Evaluate Inclusion/Exclusion criteria | X | X | X | | | | | | | | | | | | |
| Monitor for Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[5] |
| Collect medical history[6] | X | | | | | | | | | | | | | | |
| Review prior/concomitant medication | X | X | X | | | X | X | | X | | X | X | X | X | |
| Perform physical exam | | | X | | | | | | X | | | | X | X | |
| Perform Tanner Staging | | | X | | | | | | X | | | | X | X | |
| Measure vital signs (HR, BP measured twice) | X | | X | | | X | X | | X | | X | X | X | X | |
| Measure weight (measured twice) | X | | X | | | | | | X | | | | X | X | |
| Measure height (measured 3 times) | X | | | | | | | | X | | | | X | X | |
| Determine BMI Percentile | X | | | | | | | | | | | | | | |
| Measure waist circumference (measured twice) | | | X | | | | | | X | | | | X | X | |
| Perform 12-lead ECG (locally read) | | X[7] | | | | | | | X | | | | X | X | |
| Site Assessment of Swallowability | | X | X | | | | | | X | | | | | | |
| Swallowing Ability Questionnaire | | X | X | | | X | X | | X | | X | X | X | X | |
| Diet/exercise counseling[8] | | X | | | | | | | | | | | | | |
| Diet/exercise monitoring and re-inforcement | | | X | X | X | X | X | X | X | | X | X | | | |
| Dispense hypoglycemia assessment tool(s)[9] | | X | | | | X | X | | X | | X | X | | | |
| Instruct on hypoglycemia symptoms and management | | X | X | X | X | X | X | X | X | | X | X | | | |
| Review of hypoglycemia assessment tool(s) | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense 2 glucose meters and provide instructions for Self- Monitoring of Blood Glucose (SMBG) | | X | | | | | | | | | | | | | |
| Dispense ketone testing kit and provide instructions | | X | | | | | | | | | | | | | |
| Review thresholds for rescue (Phase A) and initiating insulin glargine (Phase B)[10] | | | X | X | X | X | X | X | X | | X | X | | | |
| Witness Dose | | X | X | | | | | | X | | | | | | |
| Dispense single-blind placebo medication | | X | | | | | | | | | | | | | |
| Assess for single-blind medication compliance | | | X | | | | | | | | | | | | |
| Dispense double-blind study medication | | | X | | | X | X | | X | | X | X | | | |
| Initiate insulin glargine[11] | | | | | | | | | (X) | | (X) | (X) | | | |

| | Screening | Run-In | Random-ization | Double-Blind Treatment Phase A | | | | | | Double-Blind Treatment Phase B | | | | | Post-Study Phone Contact |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V.1 | V.2 Wk -1 | V.3 Day 1 | TC Wk 2 | TC Wk 4 | V.4 Wk 6 | V.5 Wk 12 | TC Wk 16 | V.6 Wk 20 | TCs[1] | V.7 Wk 28 | V.8 Wk 40 | V.9 Wk 54 | Visit Rescue[2]/ D/C[3] | Wk 56 or 14 days post-discon. |
| **Study Procedures** | | | | | | | | | | | | | | | |
| Assess/Reinforce double-blind medication compliance | | | | X | X | X | X | X | X | X | X | X | X | X | |
| Review/Reinforce SMBG measurements | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Monitoring and Central Laboratory Procedures** | | | | | | | | | | | | | | | |
| Site fingerstick A1C[12] | X | | | | | | | | X | | (X) | (X) | | | |
| Fasting plasma glucose[13] | X | | X | | | | | | X | | | | X | X | |
| A1C | X | | X | | | X | X | | X[14] | | X | X | X[14] | X[15] | |
| Site fingerstick glucose | | | X | | | | | | X | | (X) | (X) | | | |
| Fasting C-peptide[13] | X | | | | | | | | | | | | | | |
| Complete Blood Count (CBC)/Differential | X | | X | | | | X | | X | | X | | X | X | |
| Chemistry panel | X | | X | | | | X | | X | | X | | X | X | |
| Fasting Insulin and Proinsulin[16] | | | X | | | | | | X | | | | | X[17] | |
| Lipid panel[13] | X | | X | | | | | | X | | | | X | X | |
| TSH | X | | | | | | | | | | | | | | |
| Dipstick Urinalysis[18] | X | | X | | | | | | X | | | | X | X | |
| Urine microalbumin/creatinine ratio[19] | | | X | | | | | | X | | | | X | X | |
| Urine Pregnancy test (for all females)[20] | X | | X | | | X | X | | X | | X | X | X | X | |
| Blood sample (serum and plasma) for FBR[21] | | | X | | | | | | X | | | | X | X | |
| Blood sample (for genetics) for FBR[22] | | | X | | | | | | | | | | | | |

NOTE: Clinic **Visit 4, Visit 5, Visit 7**, and **Visit 8** *may* be performed by a qualified health professional at the patient's home/location other than the site if approved by the country and local IRB/EC.

1. Perform telephone contacts to the patient weekly between the visit at which insulin/insulin glargine is uptitrated/initiated and the next clinic visit; additional phone contacts may be done at the discretion of the investigator.
2. All rescue procedures should be performed prior to the initiation of rescue therapy. If the **Rescue Visit** occurs on a scheduled study visit, all procedures for that visit should be performed. If the Discontinuation Visit occurs on a scheduled study visit, all **Visit 9** procedures should be performed. If the **Rescue or Discontinuation Visit** is performed at an unscheduled visit within 4 weeks of **Visit 3** or **Visit 6**, do not perform a physical examination, Tanner Staging, height and waist circumference measurements, ECG, hematology, chemistry, and lipid blood panel measurements, dipstick urinalysis, urine microalbumin/creatinine measurements, urine pregnancy test, and FBR sampling. Note: the Discontinuation Visit is conducted for all patients who stop or discontinue study medication, but is only a study discontinuation visit for patients who are stopping study medication due to withdrawal of consent. All patients who discontinue study medication will be counseled and encouraged to remain in the study and to return to the site for the Week 20 and Week 54 visits, as applicable (described in Section 3.2.3.16.2).
3. After the 14 day post-study medication discontinuation telephone contact is made, patients who do not withdraw consent (1) should return to the clinic for key visits (Week 20 and/or Week 54 as applicable) to have the following procedures performed: physical examination (including Tanner Staging), laboratory assessment of glycemic endpoints (A1C and FPG), and safety parameters (CBC, chemistry panel, urine microalbumin to creatinine ratio, and dipstick urinalysis), and collection of adverse events. Patients who are unable or unwilling to return to the clinic at key visits will be contacted by phone to obtain adverse events, concomitant medications and weight. For patients unable or unwilling to return to the clinic at key visits who receive their diabetes care from the study doctor, A1C and FPG values will be obtained from their records, if available; such patients who receive their diabetes care from someone other than the study doctor should have their diabetes doctor provide A1C and FPG values, if available. (2) At visits that are not key visits (ie, not at week 20 or week 54) patients will continue to be contacted by phone in a timeframe similar to their original study visit schedule up until the patient has reached 54 weeks from randomization (Visit 3/Day 1). Refer to section 3.2.3.16.2 for further details.
4. Consent form must be signed prior to any study specific procedures; informed consent will be obtained from the parent/legal guardian and assent will be obtained from the patient.
5. Collect serious adverse events only.
6. Male and female patients 10 to ≤14 years collect up to 5 years of relevant medical history. Male and female patients 15-17 years collect up to 7 years of relevant medical history.
7. The ECG may be done at **Visit 2 or at Visit 3,** but must be read and evaluated for study eligibility before the patient receives double-blind study medication at **Visit 3**.
8. Patients will be seen by a dietitian or qualified health professional for diet/exercise counseling at **Visit 2**.
9. The hypoglycemia assessment tool(s) will be provided as paper or as an electronic device, per site approval, and will be reviewed at each visit. The tool(s) will be dispensed at **Visit 2** and re-dispensed as needed per molality. The paper Low Blood Sugar Calendar and Notepad will be collected at each visit and a new Low Blood Sugar Calendar will be dispensed as needed during the trial. The Low Blood Sugar Calendar from the previous visit will be re-dispensed at **Visit 3**.
10. The patient and parent/guardian will be informed of the fingerstick glucose rescue threshold that is applicable until the next visit and will be instructed to call the site if the fasting fingerstick glucose (FFSG) value is greater than this threshold on 3 consecutive days. Patients and parents should be counseled that if one FFSG value is above the threshold for rescue, the FFSG has to be checked the following morning. If the FFSG value is above the threshold for rescue on two consecutive days, the FFSG has to be checked on the third day as well, and the site called if all three values are above the thresholds for rescue. After the patient/parent/guardian calls the site with FFSG values that exceed the thresholds for 3 consecutive days, and after assessing for compliance with study medication, an FPG will be performed, and the patient will be rescued if the FPG is greater than the threshold specified in Table 2-3. For reference, site personnel will record the threshold for rescue in the fingerstick glucose log book. In Phase B, the patient and parent/guardian will be instructed to call the site if the FFSG value is >130mg/dL on 2 consecutive days. After the patient/parent/guardian calls the site with FFSG values that are >130 mg/dL for 2 consecutive days, an unscheduled visit will be scheduled, and patients will be instructed to either uptitrate their background insulin or initiate insulin glargine if their FFSG and A1C meet the thresholds at the unscheduled visit.
11. Beginning at **Visit 6/Week 20** or at any visit thereafter, patients who have not been rescued in Phase A will either uptitrate their background insulin or initiate insulin glargine if their FFSG >130 mg/dL (7.2 mmol/L) and their FS A1C >7.5% at the visit. See Section 2.4.2.5.
12. At **Visit 1**, a site fingerstick A1C may be used, at the discretion of the investigator, for screening purposes; a laboratory A1C must be used to meet inclusion criteria for eligibility. At **Visit 6/Week 20**, a site fingerstick A1C must be performed as part of the assessment for uptitration of background insulin or initiation of insulin glargine. If background insulin is not uptitrated or if insulin glargine is not started at **Visit 6/Week 20**, a site fingerstick A1C must be done at all subsequent visits until the background insulin is uptitrated, or until insulin glargine is initiated or the study is completed. See Section 2.4.2.5.
13. If the patient is not fasting at **Visit 1/Screening Visit**, a fasting lipid profile, FPG, and fasting C peptide should be obtained at or prior to **Visit 2** rather than at **Visit 1**.
14. For patients who agree to continued follow-up and further data collection after discontinuing study medication, the investigator will record A1C values obtained from other sources (if available) around **Week 20** and **Week 54.**
15. Blood sample for A1C should not be collected if the **Discontinuation Visit** or **Rescue Visit** occurs prior to Week 8.
16. Samples for fasting insulin and proinsulin should not be collected on patients on insulin (background, rescue [Phase A], or glycemic therapy [Phase B]).
17. Perform only if Rescue or Discontinuation occurs prior to Visit 6/Week 20.

18. If dipstick (midstream urine specimen) is positive for blood, WBC (eg, leukocyte esterase or nitrites), or protein, then a sample for a complete urinalysis (including microscopy) should be sent to the central laboratory. Dipstick should not be performed if patient is menstruating.
19. The urine sample for microalbumin/creatinine ratio should not be collected if the patient is menstruating, has vigorously exercised within 24 hours, or has had fever or an active infection within two days of the visit.
20. Females will have a urine pregnancy test (and serum pregnancy test if required by the site's Institutional Review Board [IRB] / Ethics Committee [EC]). Patients with a positive urine pregnancy test during the double-blind treatment period will have a serum pregnancy test.
21. Serum and plasma for future biomedical research will be obtained for randomized patients who sign the FBR consent.
22. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized patients only, or at a later date as soon as the informed consent is obtained.

# 2. CORE PROTOCOL

## 2.1 OBJECTIVES AND HYPOTHESES

Section 3.1.1 presents the rationale for pooling data from the two studies.

### 2.1.1 Primary

**For MK-0431A XR P289:**

**(1) Objective**: Over 54 weeks, to assess the safety and tolerability of the addition of sitagliptin (administered as MK-0431A XR) in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**For the pooled study population (patients from MK-0431A XR P289 Phase A and MK-0431A P170 base study):**

**(2) Objective**: after 20 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to the addition of placebo on A1C in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**Hypothesis**: The addition of sitagliptin reduces A1C more than the addition of placebo after 20 weeks.

**For the pooled study population (patients from MK-0431A XR P289 Phases A+B and MK-0431A P170 base and extension studies):**

**(3) Objective:** Over 54 weeks, to assess the safety and tolerability of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

### 2.1.2 Secondary

**For the pooled study population (patients from MK-0431A XR P289 Phase A and MK-0431A P170 base study):**

**(1) Objective:** After 20 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to placebo on fasting plasma glucose (FPG) in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**(2) Objective:** After 20 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to placebo on the proportion of patients initiating glycemic rescue therapy in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**(3) Objective:** After 20 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to placebo on the proportion of patients with A1C at goal (<7.0%) in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**For the pooled study population (patients from MK-0431A XR P289 Phases A+B and MK-0431A P170 base and extension studies):**

(4) **Objective:** After 54 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) on the change from baseline in A1C in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

(5) **Objective:** After 54 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) on the change from baseline in FPG, in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

(6) **Objective:** After 54 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) on the proportion of patients with A1C at goal (<7.0%) in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

### 2.1.3 Exploratory:

**For MK-0431A XR P289:**

**(1) Objective:** After 20 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A XR) relative to placebo on the change from baseline in A1C and FPG in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**(2) Objective:** After 20 weeks and after 54 weeks, to assess the effect of the addition of sitagliptin (administered as MK-0431A XR) relative to placebo on growth velocity and Tanner Staging in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**For the pooled study population (patients from MK-0431A XR P289 Phase A and MK-0431A P170 base study):**

**(3) Objective**: After 20 weeks, to assess the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to placebo on growth velocity and Tanner Staging in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

**For the pooled study population (patients from MK-0431A XR P289 Phases A+B and MK-0431A P170 base and extension studies):**

**(4) Objective:** After 54 weeks, to assess the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to placebo on growth velocity and Tanner Staging in pediatric patients (ages 10-17 years) with T2DM with inadequate glycemic control on metformin therapy (alone or in combination with insulin).

## 2.2 PATIENT INCLUSION CRITERIA

All laboratory measurements (to determine eligibility) must be performed by the central laboratory after an overnight fast ≥10 hours in duration. A patient with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed. If the repeat value satisfies the criterion, the patient may continue in the screening process. Only the specific out-of-range value/finding should be repeated (not the entire panel).

If the period of time between the date when the screening laboratory measurements were obtained and the **Visit 3** date exceeds 28 days, patients must have all screening laboratory measurements repeated.

Patients must meet *all* of the following criteria to participate in the study.

**At Visit 1**

1. Patient has T2DM as indicated by "yes" answers to **all** of the following:

    a) Patient has diabetes diagnosed by American Diabetes Association (ADA) criteria (eg, laboratory determinations of FPG ≥126 mg/dL [7.0 mmol/L], or random plasma glucose ≥200 mg/dL [11.1 mmol/L], or two-hour oral glucose tolerance test (OGTT), plasma glucose ≥200 mg/dL [11.1 mmol/L], or A1C ≥6.5% [test performed using a method that is NGSP certified and standardized to the DCCT assay] and confirmed per ADA guidelines) documented in medical record.

    b) Patient is assessed as having a clinical profile consistent with T2DM (eg, based upon body weight, family history, presentation).

    c) Patient has BMI ≥85$^{th}$ percentile for age and sex at screening (or patient has a history of being overweight or obese at time of diagnosis of T2DM). See Appendix 6.1.

    **Note:** If patient does not have a BMI ≥85$^{th}$ percentile at the time of screening, the documentation of overweight or obesity at the time of diagnosis must be included in the source documents at the site.

2. Patient has

    i) T2DM for ≥2 years

OR

ii) T2DM for <2 years and a fasting C-peptide value >0.6 ng/mL at **Screening Visit/Visit 1**.

**Note**: All patients on background insulin (see below) should have a fasting C-peptide value >0.6 ng/mL at **Screening Visit/Visit 1** regardless of duration of T2DM

3. (a) Patient is on a stable dose of metformin (≥1500 mg/day, for ≥12 weeks) without insulin and with A1C ≥6.5% and ≤10.0%.

OR

(b) Patient is on stable doses of metformin (≥1500 mg/day, for ≥12 weeks) and insulin (of any type, variance in dose to be ≤15% of total daily dose for ≥12 weeks prior to **Screening Visit/ Visit 1**) with an A1C≥7.0% and ≤10%.

i. Patients on stable doses of metformin ± insulin ≥1000 and <1500 mg/day for ≥12 weeks can participate if there is documentation that they cannot tolerate higher doses of metformin.

ii. Patients on metformin ± insulin doses <1500 mg/day can have their metformin doses uptitrated to ≥1500 mg/day, and be eligible to participate after their dose remains stable for ≥12 weeks, if they meet all other eligibility criteria.

iii. At screening, patients on insulin doses that are not stable can have the insulin doses adjusted and be eligible to participate after their dose remains stable for ≥12 weeks, if they meet all other eligibility criteria. This stable regimen can include (1) a stable dose of basal insulin (±15%) AND/OR (2) stable prescribed doses of bolus insulin (±15%) (a) for each fingerstick glucose range for patients on sliding scale AND, if applicable, (b) for corrective doses and carbohydrate coverage.

iv. Patients currently being treated with an AHA (other than insulin) in addition to metformin cannot be included in the study after wash-off.

4. Patient is between 10 and 17 years of age (inclusive) on day of signing informed consent with randomization to occur prior to the patient's 18th birthday.

5. Patient is either a male, or patient is a female who is unlikely to conceive as indicated by at least one "yes" response to the following which will remain consistent for the projected duration of the study and for 14 days after the last dose of study medication:

a) Patient is a non-sterilized female who is currently not sexually active and agrees to follow statement "c" if heterosexual activity is initiated

OR

b) Patient agrees to abstain from heterosexual activity

**Note**: If abstinence is not a locally acceptable method of contraception, then one other adequate birth control method must be used.

OR

c) Patient agrees to use an adequate method of contraception.

**Note**: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception. Adequate methods of birth control are: hormonal contraceptive, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, or use of condom by the partner. Patients initiating hormonal contraception during the study should use one additional method during the first 2 months.

6. Parent/guardian understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to the patient's participation by giving informed written consent, and the patient has an age-appropriate understanding of the same to give informed written assent. Patients with an illiterate parent/guardian may be included if, in the opinion of the investigator, patient safety will not be compromised. Please see Section 3.2.3.11.1 for details. The parent/guardian and patient may also provide consent/assent for samples for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.

7. Patient and a family member or adult closely involved in the patient's daily activities (in the opinion of the investigator) will participate in the patient's treatment and study protocol (ie, available for telephone calls, study visits and administration of study medication as needed).

**At Visit 3/Day 1/Randomization**

8. Patient has ≥80% compliance with placebo treatment during the single-blind run-in as measured by site-performed pill count.

## 2.3 PATIENT EXCLUSION CRITERIA

All laboratory measurements (to determine eligibility) must be performed by the central laboratory after an overnight fast ≥10 hours in duration. A patient with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed. If the repeat value satisfies the criterion, the patient may continue in the screening process. Only the specific out-of-range value/finding should be repeated (not the entire panel).

If the period of time between the date when the screening laboratory measurements were obtained and the **Visit 3** date exceeds 28 days, patients must have all screening laboratory measurements repeated.

Individuals are excluded from participation in the study if they meet ***any*** of the following criteria.

**At Visit 1**

1. Patient has known type 1 diabetes mellitus or documented evidence of positive diabetes auto-antibodies (if performed when patient was diagnosed with diabetes).

2. Patient has known monogenic diabetes, secondary diabetes, or a genetic syndrome or disorder known to affect glucose tolerance other than diabetes.

3. Patient has symptomatic hyperglycemia and/or moderate to large ketonuria and/or positive test for ketonemia, requiring immediate initiation of another antihyperglycemic agent.

Specific Treatments

4. Patient has previously taken a DPP-4 inhibitor (such as sitagliptin, vildagliptin, alogliptin, saxagliptin, or linagliptin) or GLP-1 receptor agonist (such as exenatide or liraglutide).

   **Note:** Patients who have participated in single-dose studies with these agents at least 12 weeks prior to screening are eligible to participate.

5. Patient has initiated chronic treatment with a medication known to cause:

   a. weight gain within 30 days of **Visit 1**

   OR

   b. weight loss (such as orlistat) within 8 weeks of **Visit 1**

   OR

   c. increase in blood glucose within 8 weeks of **Visit 1**

      **Note (a):** Patients on a weight loss program who are not in the maintenance phase, or who have undergone bariatric surgery within 12 months prior to signing the informed consent, will be excluded.

      **Note (b):** Patients who have been treated with an anti-psychotic agent within the past 12 weeks will be excluded.

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

   **Note**: a patient who has participated in a non-interventional or placebo study may be enrolled.

7. Patient is on or likely to require treatment with ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

   **Note:** Inhaled, nasal, and topical corticosteroids are permitted.

8. Patient has undergone a surgical procedure within 4 weeks prior to signing informed consent or has major surgery planned during the study.

   **Note:** A patient who has undergone minor surgery within the prior 4 weeks and is fully recovered or a patient who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

Concomitant Conditions or Diseases of Organs and Systems

9. Patient has a history of congenital heart disease or cardiovascular disease other than hypertension.

10. Patient has a **Visit 1** systolic or diastolic blood pressure of ≥95th percentile for age, height percentile and gender (see Appendix 6.2 and 6.3) and is not considered likely to have values <95th percentile for age, height percentile and gender by **Visit 3/Day 1** with appropriate antihypertensive therapy.

    **Note:** Investigators are encouraged to maximize blood pressure control according to current guidelines. Patient may have blood pressure medications adjusted and may be enrolled if the patient's blood pressure no longer meets exclusion criteria.

11. Patient has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.

12. Patient has active nephropathy (ie, nephrotic syndrome or glomerulonephritis).

    **Note:** Patients with diabetic nephropathy will be eligible if they meet all other eligibility criteria.

13. Patient has chronic myopathy, mitochondrial disorder or a progressive neurological or neuromuscular disorder (eg, polymyositis, or multiple sclerosis).

14. Patient has human immunodeficiency virus (HIV) as assessed by medical history.

15. Patient has a clinically important hematological disorder (such as aplastic anemia, thrombocytopenia, myeloproliferative or myelodysplastic syndrome).

16. Patient is currently being treated for hyperthyroidism or patient is on thyroid hormone therapy and has not been on a stable dose for at least 6 weeks.

    **Note:** Patients under treatment for hypothyroidism with a normal TSH value may participate.

17. Patient exhibits abnormal growth patterns or is being treated with growth hormone.

18. Patient has a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer, or *in situ* cervical cancer.

    **Note (a):** A patient with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease

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

19. Patient has a history of idiopathic acute pancreatitis or chronic pancreatitis.

Other Criteria

20. Patient has a known history of recreational or illicit drug use, or of alcohol abuse or dependence (within the past year).

21. Patient has donated blood products or has had phlebotomy of >10% of estimated total blood volume within 8 weeks of signing informed consent, or intends to donate blood products or receive blood products within the projected duration of the study.

22. Patient is pregnant or breast-feeding, or is expecting to conceive or donate eggs during the study, including 14 days following the last dose of study medication.

23. Patient is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate outside of the geographic area (including attending school at a remote location) during the study, has poor mental function or parent/guardian is, in the opinion of the investigator, mentally or legally incapacitated preventing informed consent from being obtained.

24. Patient has a history or current evidence of any condition, therapy, lab abnormality or other circumstance which, in the opinion of the investigator, might pose a risk to the patient, make participation not in the patient's best interest, might confound the results of the study, or interfere with the patient's participation for the full duration of the study.

Exclusion Criteria Based on Laboratory Abnormalities

25. Patient has exclusionary laboratory values as listed in Table 2-1.

Table 2-1

Laboratory Exclusion Criteria

| Parameter[1] | Study Limit for Exclusion |
|---|---|
| Creatinine[2] | Male: ≥1.4 mg/dL (≥124 µmol/L)<br>Female: ≥1.3 mg/dL (≥115 µmol/L) |
| Estimated glomerular filtration rate (GFR)[2] | <60 mL/min/1.73m$^2$ |
| ALT | >2.5 times ULN |
| AST | >2.5 times ULN |
| TSH[3] | Outside Normal Range |
| TG[4] | >500 mg/dL (5.65 mmol/L) |
| Hemoglobin | Below Normal Range |

[1] If a screening lab is repeated, the last laboratory result should be used for to assess eligibility.
[2] Either elevated creatinine or decreased estimated GFR, as assessed by modified MDRD, meets the exclusion criteria.
[3] Patients with elevated TSH must be excluded and may be re-screened with the permission of the Merck Clinical Monitor if they have a normal TSH after they have been on a stable thyroid replacement regimen for at least 6 weeks prior to **Visit 1 with no further dose changes during the pre-randomization period**.
[4] Patients with elevated TG may be re-screened with the permission of the Merck Clinical Monitor if they have a normal TG after they have been on a stable lipid-lowering medication regimen for at least 4 weeks prior to **Visit 1 with no further dose changes during the pre-randomization period**. Refer to Section 3.2.1 for details.

**At Visit 2**

26. Patient is unable to swallow study medication (based on witnessed dose).

27. Patient has symptomatic hyperglycemia or moderate to large ketonuria or positive test for ketonemia.

28. Patient has a clinically significant ECG abnormality which, in the opinion of the investigator, exposes the patient to risk by enrolling in the study or which indicates that the patient meets **Visit 1** exclusion criterion "9", or patient has a prolonged QTc interval for age.

**At Visit 3/Randomization**

29. Patient has symptomatic hyperglycemia, and/or ketonuria and/or positive test for ketonemia, requiring immediate initiation of antihyperglycemic therapy and in the opinion of the investigator is not considered likely to respond to diet and exercise intervention.

30. Patient 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 study exclusion criterion or which, in the opinion of the investigator, exposes the patient to risk by enrolling in the study.

    **Note:** If a patient requires initiation of a new medication at **Visit 3/Day 1**, the current visit should be changed to an "**Unscheduled Visit**" and the patient should be rescheduled for a **Visit 3/Day 1** to occur 1 to 2 weeks later, except if patient needs initiation or adjustment of medications discussed in Section 3.2.1. Additional single-blind placebo run-in medication should be dispensed at this **Unscheduled Visit**.

31. Patient has a positive urine pregnancy test.

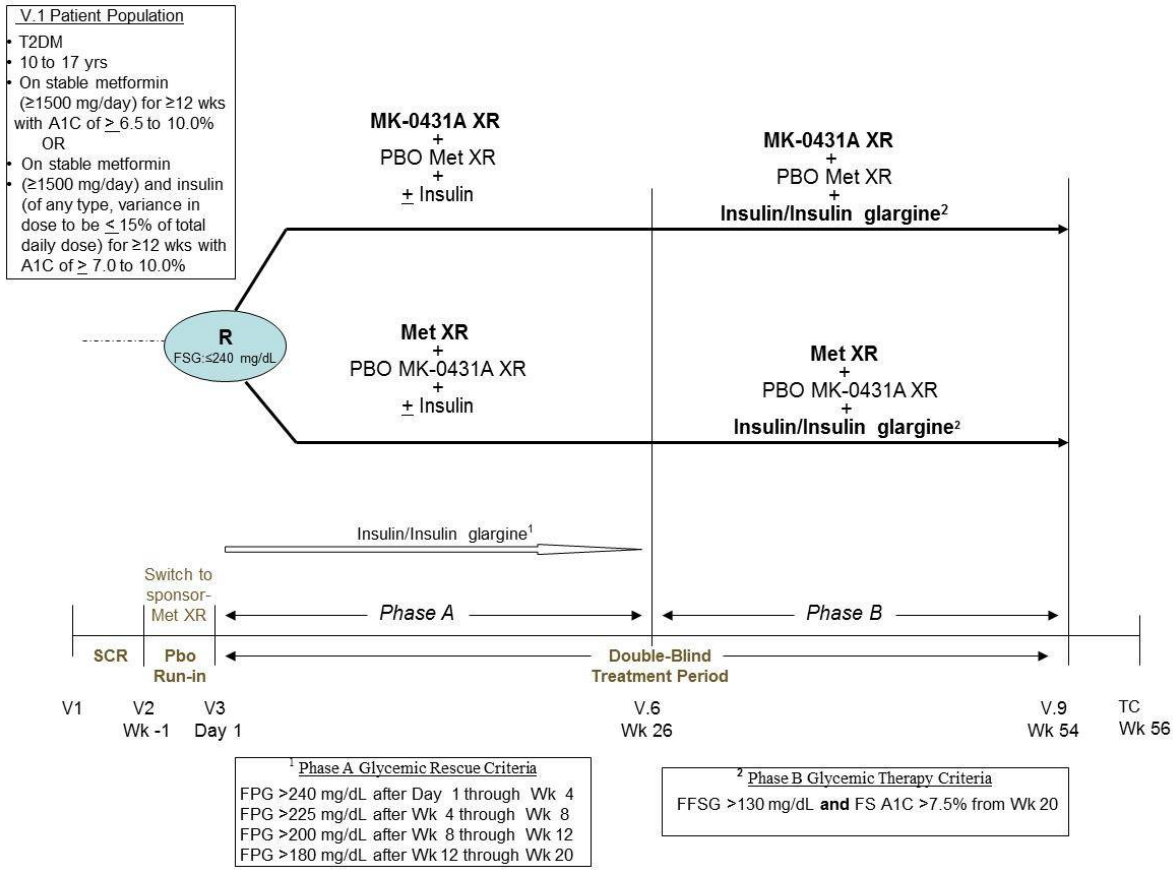
32. Patient has a site fasting fingerstick glucose (FFSG) >240 mg/dL (13.3 mmol/L).

    **Note**: If the investigator believes that the value does not reflect the patient's recent glycemic control, then the patient should not be excluded at this time. The current visit should be changed to an Unscheduled Visit and the patient should be rescheduled for **Visit 3/ Day 1**. If at the rescheduled visit, the patient meets this exclusion criterion, the patient MUST be excluded.

## 2.4 STUDY DESIGN AND DURATION

### 2.4.1 Summary of Study Design

Figure 2-1




### 2.4.2 Treatment Plan

Refer to the Study Flow Chart (Section 1.7) for the procedures to be performed at each visit. Following initial screening and evaluation of metformin dose at **Visit 1**, eligible patients will proceed to **Visit 2**. At **Visit 2/Week -1**, patients will undergo diet and exercise counseling, switch to Sponsor-supplied metformin XR at doses specified in Table 2-2 to accommodate the available doses of metformin in MK-0431A XR, and initiate MK-0431A XR placebo. Patients who enter the study on background insulin will continue on the same dose (of any type, variance of ≤15% of total daily dose) and formulation of insulin throughout the study (See Section 2.4.2.6 and 3.2.3.3 for Glycemic Rescue and Assessment and Management of Hypoglycemia).

At **Visit 3/Day 1**, patients will be randomized in a 1:1 ratio to treatment with (1) MK-0431A XR and metformin XR placebo **or** (2) metformin XR and MK-0431A XR placebo. The dose of MK-0431A XR will be determined by the dose of metformin XR at **Visit 2** (see Table 2-2). Patients will remain on a stable dose of double-blind study medication for the duration of the study. Randomization will be stratified by: 1) dose of metformin at **Visit 1,** and 2) insulin use at **Visit 1.**

Table 2-2

Study Medication Scheme

| Total Daily Dose of Metformin (IR or XR) at **Visit 1** | Total Daily Dose of Met XR and Single-Blind MK-0431A XR Placebo to be Initiated at **Visit 2** | Total Daily Dose of Double-Blind Study Medication to be Initiated at **Visit 3** |
|---|---|---|
| <1500 mg* | **Met XR**<br>**(metformin 1000 mg)**<br>• 2 tablets of Met XR 500 mg<br>• 2 tablets of MK-0431A XR 50/500 mg placebo<br>Once-a-day | **MK-0431A XR**<br>**(sitagliptin 100 mg; metformin 1000 mg)**<br>• 2 tablets of MK-0431A XR 50/500 mg<br>• 2 tablets of Met XR 500 mg placebo<br>Once-a-day<br>**-OR-**<br>**Met XR**<br>**(metformin 1000 mg)**<br>• 2 tablets of MK-0431A XR 50/500 mg placebo<br>• 2 tablets of Met XR 500 mg,<br>Once-a-day |
| 1500 mg | **Met XR**<br>**(metformin 1500 mg)**<br>• 1 tablet of Met XR 500 mg<br>• 1 tablet of Met XR 1000 mg<br>• 1 tablet of MK-0431A XR 50/500 mg placebo<br>• 1 tablet of MK-0431A XR 50/1000 mg placebo<br>Once-a-day | **MK-0431A XR**<br>**(sitagliptin 100 mg; metformin 1500 mg)**<br>• 1 tablet of MK-0431A XR 50/500 mg<br>• 1 tablet of MK-0431A XR 50/1000 mg<br>• 1 tablet of Met XR 500 mg placebo<br>• 1 tablet of Met XR 1000 mg placebo<br>Once-a-day<br>**-OR-**<br>**Met XR**<br>**(metformin 1500 mg)**<br>• 1 tablet of MK-0431A XR 50/500 mg placebo<br>• 1 tablet of MK-0431A XR 50/1000 mg placebo<br>• 1 tablet of Met XR 500 mg<br>• 1 tablet of Met XR 1000 mg<br>Once-a-day |

| Total Daily Dose of Metformin (IR or XR) at **Visit 1** | Total Daily Dose of Met XR and Single-Blind MK-0431A XR Placebo to be Initiated at **Visit 2** | Total Daily Dose of Double-Blind Study Medication to be Initiated at **Visit 3** |
|---|---|---|
| >1500 mg | **Met XR**<br>**(metformin 2000 mg)**<br>• 2 tablets of Met XR 1000 mg<br>• 2 tablets of MK-0431A XR 50/1000 mg placebo<br>Once-a-day | **MK-0431A XR**<br>**(sitagliptin 100 mg; metformin 2000 mg)**<br>• 2 tablets of MK-0431A XR 50/1000 mg<br>• 2 tablets of Met XR 1000 mg placebo<br>Once-a-day<br>**-OR-**<br>**Met XR**<br>**(metformin 2000 mg)**<br>• 2 tablets of MK-0431A XR 50/1000 mg placebo<br>• 2 tablets of Met XR 1000 mg<br>Once-a-day |
| * Patients on stable doses of metformin ≥1000 and <1500 mg/day for ≥12 weeks can participate if there is documentation that they cannot tolerate higher doses of metformin. | | |

During Phase A, those patients meeting the thresholds for rescue therapy will either uptitrate their background insulin or initiate insulin glargine. Beginning at **Visit 6/Week 20** (end of Phase A, beginning of Phase B) or at any visit thereafter, patients who have not been rescued in Phase A will either uptitrate their background insulin or initiate insulin glargine if their FFSG is >130 mg/dL (7.2 mmol/L) and their FS A1C is >7.5% at the visit. The insulin dosing will be at the discretion of the investigator (based on locally accepted, national, or international guidelines for the use of insulin). Please refer to Sections 2.4.2.5 and 2.4.2.6 for more information.

Throughout the study, glycemic endpoints (measured in the central laboratory) will remain masked to the patient and investigator. However, in order for the investigator to perform an evaluation for possible glycemic rescue with insulin in Phase A or discontinuation from the study, the central laboratory will report to the investigator in an unmasked manner any FPG laboratory value meeting rescue or discontinuation criteria (refer to Sections 2.4.2.6 and 2.4.2.7).

**Note**: The patient and family will be instructed to monitor for ketonuria/ketonemia and check fingerstick blood sugars frequently and to contact the site immediately if the patient experiences an acute intercurrent illness (eg, fever >101°F [38.5°C] and/or vomiting or abdominal pain) at any time during the study. For patients not on baseline insulin therapy, insulin therapy may be initiated during an intercurrent illness, based on the investigator's clinical judgment. For those patients on background insulin therapy, insulin can be uptitrated based on the investigator's clinical judgment. Additionally, if the patient has symptoms of dehydration, investigators may consider interrupting blinded study medication until these symptoms resolve. Patients requiring transient (ie <14 days) use of insulin or an increase in their insulin dose (>15% of the dose at screening for patients on background insulin therapy) due to an intercurrent illness will not be considered as having initiated rescue. Standard rescue criteria outlined in Section 2.4.2.6 will not apply during an acute intercurrent illness.

### 2.4.2.1 Study Visits General Information

**Fasting Prior to Scheduled Visits**

Patients should be counseled to fast (ie, no food, no drink except water, no double-blind study medication, but non-antihyperglycemic non-study medications should be taken as prescribed) for at least 10 hours prior to study **Visit 1, Visit 3, Visit 6**, **Visit 9, Rescue,** and **Discontinuation**. The Investigator should manage insulin doses appropriately for patients on insulin to prevent/ minimize the risk of hypoglycemia while fasting.

**Scheduling Visits, Visit Windows, and Study Duration**

At the end of each study visit, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule (refer to Study Flow Chart, Section 1.7), and generally, visits should be scheduled ±7 days of the designated time-point. If unavoidable, a visit may be scheduled at a time outside of this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the double-blind study period is as close as possible to 54 weeks. The interval between **Visit 2** and **Visit 3** should be a minimum of 6 days (with 100% compliance with single-blind placebo medication) and a maximum of 14 days (with ≥80% compliance with single-blind placebo medication). If a visit is scheduled at a time other than the protocol designated time, **careful consideration must be given to the amount of study medication the patient has available**. Clinic **Visit 4, Visit 5, Visit 7, and Visit 8** *may* be performed by a qualified health professional at the patient's home/location other than the site if approved by the country and local IRB/EC. These visits should be performed according to the guidelines that may exist at the participating institution, and should be consistent with the investigators usual clinical practice.

**Visit Reminders – Telephone Contacts**

Prior to each visit, patients should be contacted and reminded of:

- The date and time of appointment.
- The requirement to fast for at least 10 hours prior to clinic **Visits 1, 3, 6, 9**, **Rescue, and, Discontinuation**.
- The requirement not to take any blinded study medication at home the morning of the clinic visit (except at **Visit 2**).

  **Note:** Non-study medications that are not antihyperglycemic medications should be taken as directed by the prescribing physician.
- The requirement to bring study medication, blood glucose meter, hypoglycemia assessment tool(s), and any collected SMBG information to the clinic visit.

#### 2.4.2.2 Visit 1/Screening Visit

At **Visit 1**, written informed consent from the parent/legal guardian and written assent from the patient will be obtained. Patients will be screened according to the **Visit 1** Inclusion/Exclusion criteria and will receive a screening number. Vital signs, body weight/BMI/BMI percentile, height and fasting blood samples (as indicated in the Study Flow Chart (Section 1.7) will be obtained in patients assessed as eligible to participate in the study.

At the site, the investigator may choose to screen patients with fingerstick A1C measurements (prior to drawing blood samples for central laboratory screening measurements) to evaluate the likelihood of the patients subsequently meeting study glycemic inclusion criteria. If, based upon this fingerstick A1C value, the investigator believes the patient is an unlikely candidate for the study the patient may be excluded prior to undergoing any additional study procedures.

**Note**: Investigators should be aware that although fingerstick A1C is generally predictive of values measured in the central laboratory, modest differences can occur in individual patients. **Therefore, a fingerstick A1C cannot substitute for a central laboratory measured A1C to determine if a patient meets study A1C inclusion criteria.**

#### 2.4.2.3 Visit 2 Single-Blind Placebo Run-In

Patients who are on a stable dose of metformin IR or XR (for ≥12 weeks prior to **Visit 1**) without insulin and have a **Visit 1** A1C of ≥6.5% and ≤10.0% and who meet all other enrollment criteria will be eligible to switch from their pre-study dose of metformin to Sponsor-supplied metformin XR at doses specified in Table 2-2 above (Section 2.4.2), and enter the single-blind placebo run-in period.

Patients on stable doses of metformin and insulin (for ≥12 weeks prior to **Visit 1**) and have a **Visit 1** A1C of ≥7% and ≤10% (see inclusion criteria #2) and who meet all other enrollment criteria will switch to Sponsor-supplied metformin XR (Table 2-2), while continuing on their background insulin and enter the single blind run-in period.

**The first doses of metformin XR and single-blind placebo (MK-0431A XR placebo) should be taken as witnessed doses in the clinic *after* completion of all Visit 2 study procedures.** Patients will then take metformin XR and single-blind placebo as directed for one week prior to randomization. It is essential that all procedures be performed ***before*** the patient takes the witnessed dose for the visit.

The hypoglycemia assessment tool(s) will be dispensed at **Visit 2**. Eligible patients will have 1) diet/exercise counseling; 2) training in self-monitoring of blood glucose (SMBG) at home and checking urine or blood for ketones; 3) instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the hypoglycemia assessment tool(s).

For assessment and management of hypoglycemia, refer to Section 3.2.3.3.

#### 2.4.2.4 Visit 3/Randomization Visit to Visit 6/Week 20: Phase A Double-Blind Treatment Period

At **Visit 3**, patients who meet all study enrollment criteria will have all baseline laboratory tests and study procedures performed (refer to Study Flow Chart, Section 1.7). Assignment of a randomization number occurs only at **Visit 3/Day 1**.

At **Visit 3/Day 1,** patients will be randomized to receive:

- two tablets of MK-0431A XR (50/500 mg x 2; 50/500 mg and 50/1000 mg; or 50/1000 mg x 2) and two tablets of metformin XR placebo (matching the metformin dose in MK-0431A XR), administered once daily with a meal, preferably in the evening

OR

- two tablets of metformin XR (500 mg x 2; 500 mg and 1000 mg; or 1000 mg x 2) and two tablets of MK-0431A XR placebo (matching the metformin XR dose), administered once daily with a meal, preferably in the evening.

**The first dose of double-blind study medication will be taken as a witnessed dose in the clinic *after* completion of all procedures for the study visit.** It is essential that **all** procedures be performed ***before*** the patient takes the witnessed dose for the visit. The dose of MK-0431A XR will be determined by the dose of metformin XR at Visit 2 (see Table 2-2). Patients will then take double-blind study medications as directed for the duration of the study. Patients who meet protocol-specified glycemic rescue thresholds will either uptitrate their background insulin if they are on background insulin, or initiate insulin glargine if they are not on background insulin as described in Section 2.4.2.6.

#### 2.4.2.5 Visit 6/Week 20 through Visit 9/Week 54: Phase B Double-blind Treatment Period

Patients in both the MK-0431A XR group and the MK-0431A XR placebo group (also receiving metformin XR) will continue on their double-blind study medication. Those patients who are not on background insulin will initiate insulin glargine if their FFSG >130 mg/dL (7.2 mmol/L) and their FS A1C >7.5%. Those patients who have entered the study on background insulin will up-titrate their insulin dose if their FFSG is >130 mg/dL (7.2 mmol/L) and their FS A1C is >7.5%. Any change in insulin dose >15% of the screening dose will be considered as rescue if it is sustained for ≥14 days. The insulin dosing will be at the discretion of the investigator (based on accepted, local, national or international guidelines for the use of insulin). Patients who refuse to uptitrate their background insulin or initiate insulin glargine (or for whom it is considered inappropriate) when glycemic rescue thresholds are met will be discontinued from the study.

**The first dose of Phase B double-blind study medication will be taken as a witnessed dose in the clinic *after* completion of all procedures for the study visit. It is essential**

**that all procedures be performed *before* the patient takes the witnessed dose for the visit.**

#### 2.4.2.6 Glycemic Rescue – Phase A

After randomization, patients meeting protocol-specified glycemic rescue thresholds will be eligible for initiation of glycemic rescue therapy in Phase A (Table 2-3). When thresholds for rescue are met, patients who are not on background insulin will initiate insulin glargine and those patients who have entered the study on background insulin will uptitrate their background insulin dose. Any change in insulin dose >15% of the screening dose will be considered as rescue if it is sustained for ≥14 days. The insulin dosing will be at the discretion of the investigator (based on accepted, local, national or international guidelines for use of insulin). Patients who refuse to uptitrate their background insulin or initiate insulin glargine (or for whom it is considered inappropriate) when rescue thresholds are met will be discontinued from the study.

**Note**: Patients requiring transient (ie <14 days) use of insulin or an increase in insulin dose (>15% of dose at baseline, for patients on background insulin therapy) due to an intercurrent illness will not be considered as having initiated rescue.

The patient and parent/guardian will be (1) informed of the FFSG values that meet the threshold corresponding to the patient's duration in the study (eg, a patient has 3 consecutive FFSG >240 mg/dL [13.33 mmol/L] between **Day 1** and **Week 4**) and (2) instructed to call the site if the patient has 3 consecutive days of FFSG values that exceed the specified thresholds. Patients and parents should be counseled that if one FFSG value is above the threshold for rescue, the FFSG value has to be checked the following morning. If the FFSG value is above the threshold for rescue on the second day, the fasting glucose has to be checked on the third day as well, and the site must be called if all three values are above the thresholds for rescue. Since the glucose thresholds become lower as the study progresses, study site personnel will inform the patient and parent/ guardian of the glucose threshold (Table 2-3) at each TC (telephone contact) and clinic visit. For reference, site personnel will also record the rescue threshold level in the fingerstick glucose log book provided to the patient.

When the patient calls the site with FFSG values that exceed the rescue thresholds for 3 consecutive days, the site should schedule a clinic visit (unscheduled visit) if, in the investigator's judgment, the patient has been compliant with study medication. At the unscheduled visit, an FPG will be performed by the local and central laboratory. The value from the local laboratory can be used to assess the need for rescue (and the value from the central laboratory will be reported in the database). The patient will be rescued (by uptitration of background insulin or by initiation of insulin glargine) if the FPG is greater than the threshold specified in Table 2-3.

Insulin (background and rescue) will be sourced locally and administered subcutaneously based on instructions provided by the investigator (based on accepted local, national or international guidelines for the use of insulin). Note that for patients who are on or initiate basal insulin, prandial insulin can be added at the Investigator's discretion after at

least 6 weeks of treatment. The choice, dose, and titration of prandial insulin will be the Investigator's responsibility. Patients who refuse to uptitrate their background insulin or initiate insulin glargine (or for whom it is considered inappropriate) when glycemic rescue thresholds are met will be discontinued from the study medication (see section 2.4.2.7). Note that patients who are not compliant with study medication should be re-trained on compliance with medication and diet/exercise. The patient should be contacted a week later to assess if the FFSG values continue to meet rescue criteria and follow rescue procedures.

Table 2-3

Glycemic Rescue Criteria for Phase A

| Time in Study | FFSG Thresholds [1] | FPG Thresholds [2] |
|---|---|---|
| **Day 1** through **Week 4** | >240 mg/dL (13.33 mmol/L) | >240 mg/dL (13.33 mmol/L) |
| After **Week 4** through **Week 8** | >225 mg/dL (12.50 mmol/L) | >225 mg/dL (12.50 mmol/L) |
| After **Week 8** through **Week 12** | >200 mg/dL (11.11 mmol/L) | >200 mg/dL (11.11 mmol/L) |
| After **Week 12** through **Week 20** | >180 mg/dL (10.00 mmol/L) | >180 mg/dL (10.00 mmol/L) |

[1] The initial FFSG values would trigger repeat FFSG measurements. An FPG measurement will be triggered if 3 consecutive FFSG values meet criteria, and rescue will be initiated if the FPG is above threshold.
[2] Perform confirmatory FPG if first AM fasting fingerstick glucose (FFSG) value is greater than the defined threshold on 3 consecutive days (after assessing for study medication compliance).

**Note**: If at any time a patient has

- fingerstick glucose value >400 mg/dL (22.2 mmol/L) with or without ketonuria/ketonemia

  OR

- moderate to large ketonuria or positive test for ketonemia regardless of blood glucose levels,

The investigator should consider initiating insulin glargine for patients not on insulin treatment at screening, or should consider up-titrating insulin therapy for those patients on insulin treatment at screening.

### 2.4.2.7 Discontinuation

The SPONSOR should be immediately contacted when a patient is discontinued or study medication is interrupted because of an adverse event or a laboratory safety test abnormality. All patients will be followed up until resolution (ie, return to normal or patient's baseline, or diagnosis determined, or course of abnormalities established) for any laboratory safety test abnormality resulting in discontinuation.

#### 2.4.2.7.1 The Reason for Protocol-Specified Discontinuation From the Study is Listed Below

a) Informed consent withdrawn or patient requests discontinuation from study.

#### 2.4.2.7.2 Reasons for Protocol-Specified Discontinuation From Study Medication Are Listed Below

Note: Patients who discontinue study medication without withdrawing consent will have their diabetes managed as considered clinically appropriate by their primary doctor. Please see Section 3.2.3.16.2 for follow up of these patients. Initiation of open-label AHA will not be considered as prohibited medication in these patients.

a) Hyperglycemia: Patients will be discontinued from the study if they meet the criteria outlined below.

- In Phase A, patients meeting glycemic rescue criteria for whom: 1) the addition of open-label insulin glargine is refused by the patient or deemed clinically inappropriate by the investigator, or 2) up-titration of open-label insulin (for patients on background insulin or for those who have initiated insulin glargine at rescue) is refused by the patient or deemed clinically inappropriate by the investigator.

- In Phase B, patients meeting glycemic intensification criteria for whom: 1) the addition of open-label insulin glargine is refused by the patient or deemed clinically inappropriate by the investigator, or 2) up-titration of open-label insulin (for patients on background insulin or for those who have initiated insulin glargine at rescue) is refused by the patient or deemed clinically inappropriate by the investigator.

b) Hypoglycemia: repeated (2 or more episodes since the prior study visit) FPG or fingerstick glucose <50 mg/dL (2.78 mmol/L) with or without symptoms of hypoglycemia or ≤70 mg/dL (3.89 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity and/or skipped meal).

**Note (a)**: Patients who are on open-label insulin (background or rescue therapy) and meet these criteria can have their insulin dose reduced or interrupted at the Investigator's discretion and may continue in the study. Patients who continue to have hypoglycemia even after insulin is interrupted should discontinue study medication.

**Note (b)**: Prior to discontinuation, the investigator should check that the patient's glucose meter and test strips are functioning accurately and that the test procedure is being correctly performed by the patient.

c) Elevation in ALT (alanine aminotransferase) and/or AST (aspartate aminotransferase) ≥3-times the ULN (upper limit of normal) as specified in Appendix 6.4.

OR

Elevations in ALT and/or AST ≥3-times the upper limit of normal with concurrent total bilirubin ≥2-times the upper limit of normal and alkaline phosphatase <2-times the upper limit of normal (for age and sex) (see Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials guidance document).

d) Serum creatinine concentrations consistently ≥1.5 mg/dL (132.6 μmol/L) in males and ≥1.4 mg/dL (123.8 μmol/L) in females

OR

eGFR <60 mL/min/1.73 $m^2$.

**Note (a)**: If serum creatinine value meets the gender-specific serum creatinine discontinuation criteria, regardless of the patient's eGFR, the patient must be discontinued.

**Note (b):** A consistent value is defined as a repeat measurement performed as soon as possible (must be within 3 to 7 days of notification from the central laboratory).

e) Requirement for one of the excluded medications listed in Section 3.2.1.

f) Pregnancy

**Note:** A positive urine pregnancy test requires immediate interruption of study medication until serum βHCG can be performed and found to be negative. Patient must be permanently discontinued and followed per Sections 3.2.3.4 and 3.4.5, if pregnancy is confirmed by a positive serum pregnancy test.

g) Patient develops any condition for which metformin or sitagliptin is contraindicated according to the approved labels in the country in which the study site is located.

h) Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to risk by continuing in the study or does not allow the patient to adhere to the requirements of the protocol.

If a patient discontinues study medication, he/she should complete all **Discontinuation Visit** procedures as described in Section 3.2.3.19. Please refer to Section 3.2.3.16.2 on how to manage patients who discontinue study medication but who do not withdraw consent.

#### 2.4.2.8 Mandatory Post-study Telephone Follow-up

For all patients (except for those who withdraw consent), a post-study telephone follow-up call will be performed 14 days after the last dose of study medication (whether due to study completion or premature discontinuation from study medication) to query for SAEs. If any SAE requires a supplemental procedure, this should be performed as medically necessary. See Section 3.2.3.16 for details.

### 2.4.3 Beginning and End of Study Definition

The study begins when the first patient signs the ICF. End of Study for P289 will be declared when the last patient in both P289 and P170 (base and extension) completes the last study-related phone call (ie, 2-week post-study phone call) or Visit, withdraws from the trial, or is determined to be lost to follow up. **Note:** 56 weeks after the last patients is randomized, any patient with an outstanding status will be declared as 'lost to follow up'.

## 2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY, ETC., MEASUREMENTS

Efficacy measurements include laboratory assessments of A1C, FPG, lipid panel, and measures of beta cell function (proinsulin/insulin ratio).

## 2.6 LIST OF SAFETY MEASUREMENTS

Safety assessments will include collection of adverse events, clinical evaluation (physical examination, vital signs, body weight, BMI, assessment of growth and development), and laboratory safety assessments (blood chemistry, hematology and urine microalbumin/creatinine ratio and urinalysis).

## 2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5 of the protocol details.

All efficacy and safety endpoints at **Week 20** will be analyzed by pooling Phase A data from MK-0431A XR P289 with **Week 0** to **Week 20** data from MK-0431A P170 (base study). All endpoints at **Week 54** will be analyzed by pooling data from P289 (Phases A and B) with data from MK-0431A P170 (base and extension studies). Selected efficacy (A1C and FPG) and safety endpoints will be summarized based on data from P289 alone by treatment group.

### 2.7.1 Efficacy Analyses

The primary endpoint, primary analysis population, and statistical method that will be employed for the efficacy analysis are presented in Table 2-4.

The primary efficacy hypothesis will be evaluated in the pooled population from this study and MK-0431A P170 by comparing the addition of sitagliptin relative to placebo to metformin IR/XR on change from baseline in A1C at **Week 20** using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [62]. The model

will include terms for treatment, time, baseline metformin dose (<1500 mg, 1500 mg, or >1500 mg), study (MK-0431A P170 and MK-0431A XR P289), baseline BMI percentile, insulin use at screening (yes/no), and interactions of time by metformin dose, time by study, and time by treatment unless the model fails to converge, with a restriction of the same baseline mean across treatment groups. To ensure model convergence, the term for insulin use at screening will be removed from the model if necessary. An unstructured covariance matrix will be used to model the correlation among repeated measurements. If the total analysis sample size from 2 treatments of both studies at **Week 54** is small (ie, less than 50), then the terms for the stratification factors may be removed from the model in the order of the insulin use at screening followed by baseline metformin dose if necessary. An assessment of the poolability of the data will be performed prior to the pooling (described in Section 3.5.5.1).

Table 2-4

Summary of Analysis Strategy for Key Efficacy Endpoints

| Endpoint | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| Change from Baseline in A1C at Week 20 | cLDA | Full Analysis Set | Model-based |

### 2.7.2 Safety Analyses

Safety analyses will be performed in the All-Patients-as-Treated (APaT) population. Safety and tolerability will be assessed following a tiered approach by clinical review of all relevant parameters including adverse events, predefined limits of change (PDLCs), laboratory tests, and vital signs. For safety endpoints designated as Tier 1 [percentages of patients with symptomatic adverse events of hypoglycemia, and selected gastrointestinal (GI) events (ie, nausea, vomiting, abdominal pain or discomfort, and diarrhea)], p-values and 95% CIs for between-treatment differences will be provided using the Miettinen and Nurminen (M&N) method [63], stratified by baseline metformin dose, and study (MK-0431A XR P289 and MK-0431A P170).

### 2.7.3 Power and Sample Size

The sample size for this study is expected to be at least 90 patients, but no more than 110 patients, and the sample size for P170 (base) is expected to be at least 120 patients, but no more than 140 patients. Power calculations are based on the minimum number of expected patients from both studies.

Approximately 105 patients (pooling patients from both MK-0431A P170 and MK-0431A XR P289) will be randomized to each of the treatment groups (sitagliptin and placebo). A sample size of 105 patients per treatment will provide an effective sample size of 92 patients per treatment at **Week 20** in the power calculation for the primary hypothesis test using the cLDA model in the FAS population. An effective sample size of 92 patients per treatment will provide 86% power to detect a between-group difference

of 0.5% in A1C reduction at **Week 20** assuming the conditional standard deviation is 1.1 %. The half-width of the 95% CI is expected to be 0.35%.

### 2.7.4 Interim Analysis

No interim analyses are planned.

# 3. PROTOCOL DETAILS

## 3.1 RATIONALE

### 3.1.1 Background and Rationale for this Study

The incidence and prevalence of T2DM in the pediatric population is increasing worldwide [1 to 21]. While prevalence may vary by region, there appear to be common risk factors, including familial predisposition and sedentary lifestyle [22; 23]. Other known risk factors include race/ethnicity [5; 9 to 11], puberty [24; 25], polycystic ovarian syndrome [26], and a history of abnormal intrauterine growth [5; 27; 28]. As in adults [29], T2DM in children is characterized by insulin resistance [30 to 32], beta-cell dysfunction (with a progressive decline in beta-cell function over time) [33; 34], and overproduction of hepatic glucose [32] accompanied by elevated glucagon levels (especially following meals) [35].

T2DM in the pediatric population is associated with the development of microvascular complications, particularly nephropathy [36 to 39], as well as the presence of several cardiovascular risk factors that increase the likelihood of early macrovascular complications in this population [3; 39 to 42]. As in adults, blood glucose levels likely influence the development and progression of both the microvascular and possibly macrovascular complications of T2DM [36; 43]. Therefore, given the substantial lifelong cumulative exposure to hyperglycemia that is inevitable for this population, the availability of effective therapy for the treatment of T2DM in pediatric patients is critical.

While lifestyle modification is effective [44], it is difficult to implement and maintain, and tends to benefit a relative minority of youths with T2DM [25; 44]. Metformin is the only broadly approved oral agent for first-line therapy when lifestyle modifications fail in youths with T2DM [45 to 47]. Metformin, a biguanide, lowers glucose concentrations by decreasing hepatic glucose output and increasing insulin sensitivity in liver and muscle. Although initially effective in lowering A1C [48], studies suggest that 35-50% of pediatric patients need an additional agent within a year of diagnosis [49; 50]. Since the progression of T2DM in youths is characterized by a rapid and progressive increase in insulin resistance and decrease in insulin production, along with overproduction of hepatic glucose and excessive levels of glucagon [30; 31; 33; 51; 52], it is likely that an agent, or combination of agents, that targets each of these key defects will be necessary to be added-on to metformin to maintain glycemic control and delay progression of T2DM [53].

Sitagliptin is an orally active, selective dipeptidyl peptidase-IV (DPP-4) inhibitor that increases the levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), resulting in enhanced glucose-dependent insulin secretion and suppressed glucagon release [54].

The complementary mechanisms of action through which sitagliptin and metformin lower glucose concentrations suggest that the use of sitagliptin in combination with metformin

in pediatric patients with T2DM who have inadequate glycemic control on metformin will improve glycemic control in these patients.

This study is therefore designed to assess the safety and efficacy of MK-0431A XR (fixed-dose combination tablet of sitagliptin and extended-release metformin) relative to metformin XR for the treatment of T2DM in youths failing metformin therapy (alone or in combination with insulin).

Data from adult studies suggest that the safety and efficacy of metformin IR is similar to that of metformin XR. The safety and efficacy of metformin IR is similar in adults and children. It is anticipated that the safety and efficacy of metformin XR will be similar to metformin IR in the pediatric population. Therefore, it is reasonable to expect that the safety and efficacy of the addition of sitagliptin to on-going therapy with extended-release metformin (administered as MK-0431A XR [JANUMET XR] in MK-0431A XR P289) is likely to be similar to that of the addition of sitagliptin to on-going therapy with immediate-release metformin (administered as MK-0431A [JANUMET] in MK-0431A P170). Therefore, the data at **Week 20** from MK-0431A XR P289 (Phase A) and MK-0431A P170 (base study) will be combined for the primary analyses, with a combined sample size for both studies to be approximately 210 patients (120 patients from MK-0431A P170 and 90 patients from MK-0431A XR P289).

In addition, to provide longer term safety data, a 34-week extension to MK-0431A P170 (the current pediatric study to assess the safety and efficacy of MK-0431A [JANUMET]), which is a 20-week study (referred to as MK-0431A P170 base study) will be implemented. Data from patients who consent to participate in the extension study for MK-0431A P170 (data from the base and extension studies) will be combined with data from MK-0431A XR P289 (Phases A+B) to provide data over 54 weeks. It is anticipated that approximately 50 patients will be exposed to MK-0431A (JANUMET) or MK-0431A XR (JANUMET XR) for 54 weeks.

### 3.1.2 Rationale for Efficacy Endpoints

**Hemoglobin $A_{1c}$ (A1C)**

To assess longer-term glucose-lowering efficacy (weeks to months), A1C will be measured. Since A1C reflects 24-hour glucose concentrations - hence both fasting and post-meal glucose - this measure provides a more useful index of the glycemic efficacy of sitagliptin than FPG alone. Fasting plasma glucose will also be followed at each visit to characterize the time course of glucose control.

### 3.1.3 Rationale for Selection of Study Population

This is a study designed to assess the safety and efficacy of the fixed-dose combination of sitagliptin and extended-release metformin (MK-0431A XR) in youths with T2DM with inadequate glycemic control on a stable dose of metformin therapy (alone or in combination with insulin). Since T2DM is not prevalent in children less than 10 years of age, youths 10 to 17 years of age (inclusive) with T2DM will be enrolled in this study.

Pediatric patients 10-17 years of age with T2DM and inadequate glycemic control on metformin monotherapy are an optimal population to assess the safety and efficacy profile of the addition of a new agent in this group of patients. However, a significant proportion of pediatric patients 10-17 years of age with T2DM on metformin are being treated with insulin in addition, and despite being on insulin, have inadequate glycemic control [53, 55-57]. These patients are likely to be part of the patient population that will be treated with sitagliptin when it is approved for use in pediatric patients. The safety and efficacy of the addition of sitagliptin to patients with inadequate glycemic control on metformin and insulin has already been established in adults [58], and a similar profile is expected in pediatric patients 10-17 years of age. Therefore, including them in this clinical trial will make the clinical trial population representative of the target population, and will allow the results to be generalizable to a wide range of potential patients who could benefit from therapy with sitagliptin or sitagliptin-containing fixed-dose combination products. A stable daily dose of insulin for the purposes of this trial will be defined by a variation in the total daily dose of insulin ≤15%; for instance, a patient on a total daily dose of 35 U of insulin can have a variation in their daily dose from approximately 30 U to 40 U of insulin, a variance that is not uncommon in these significantly obese and insulin resistant patients.

### 3.1.4 Rationale for Dose Regimen

**Sitagliptin**

The sitagliptin dose for this study is based on data from MK-0431 P081 (A single-dose study to assess the pharmacokinetics, safety, and tolerability of sitagliptin in youths 10-17 years old [inclusive] with T2DM). This study evaluated single oral 50-, 100-, and 200-mg doses of sitagliptin in pediatric patients 10-17 years old (inclusive) with T2DM, and compared the pharmacokinetics of sitagliptin in this population with that in adult patients with diabetes (MK-0431 P005). The findings are described below.

Sitagliptin Pharmacokinetics (PK) and Dose Selection in Pediatric Patients:

Single oral doses of 50-, 100-, and 200-mg sitagliptin were administered in the fasted state, and were absorbed with a $T_{max}$ of ~3 hrs. Consistent with what is observed in adults, within the 50 to 200 mg dose range, sitagliptin $AUC_{0-\infty}$ increased in a dose-proportional manner, whereas sitagliptin $C_{max}$ increased in a modestly greater than dose-proportional manner and $C_{24hr}$ increased in a modestly less than dose proportional manner in pediatric patients 10-17 years old (inclusive) with T2DM. Pooled across all available doses, pediatric patients 10-17 years old (inclusive) with T2DM had an approximately 18% lower $AUC_{0-\infty}$ as compared to adult patients with T2DM (historical data from MK-0431 P005). This observed difference in $AUC_{0-\infty}$ was contained within the prespecified bounds for similarity between adults and pediatric patients 10-17 years old (inclusive) with T2DM, and was therefore not considered clinically meaningful. At the sitagliptin 200 mg dose, plasma $C_{24hr}$ levels were ~26% lower in pediatric patients 10-17 years old (inclusive) with T2DM than in adults, whereas $C_{max}$ was similar in both populations. The observed mean weighted average inhibition (WAI) of plasma DPP-4 activity over 24 hours following single oral doses of sitagliptin in pediatric patients with T2DM was

significantly different from that observed after placebo. The differences of DPP-4 WAI relative to placebo following administration of sitagliptin 50-, 100-, and 200-mg were approximately 67.2%, 73.8%, and 81.2%, respectively in pediatric patients with T2DM, and were ~10% lower than those observed in healthy adults at these doses in MK-0431 P001/002 (80.4%, 82.9%, and 91.3%, respectively). Day 1 trough (ie 24-hours postdose) DPP-4 inhibition percentages in pediatric patients with T2DM were also lower than those in healthy adults, with observed inhibitions of 54.0%, 62.8%, and 75.8% in pediatric patients 10-17 years old (inclusive) with T2DM compared to ~65%, ~75% and ~85% in healthy adult patients for the 50-, 100-, and 200-mg doses, respectively. The PK/PD relationship between sitagliptin plasma concentration and DPP-4 inhibition was similar between pediatric patients 10-17 years old (inclusive) and adult patients with T2DM. The relationship can be described by an $I_{max}$ model, with an $IC_{50}$ value for pediatric patients 10-17 years old (inclusive) of ~25.4 nM being near identical to the observed $IC_{50}$ value for adults with T2DM (25.7 nM). The differences in the extent of DPP-4 inhibition between pediatric patients 10-17 years old (inclusive) and adults with T2DM can therefore be attributed to the small differences in plasma sitagliptin concentrations between these populations. The magnitude of this difference is not expected to translate to a clinically meaningful difference in glycemic efficacy, and should not require higher doses of sitagliptin in pediatric patients (10-17 years old) compared to adults with T2DM.

Therefore, a sitagliptin dose of 100 mg/day will be used in this study (administered as fixed-dose combination tablets of 50 mg of sitagliptin and extended-release metformin [500 mg or 1000 mg] to give a total daily dose of 100 mg of sitagliptin when administered once daily).

**Metformin**

Metformin PK and Dose in Pediatric Patients:

Publicly available information indicates that after administration of a single oral metformin 500 mg tablet with food, geometric mean metformin $C_{max}$ and AUC differed less than 5% between pediatric patients (12-16 years of age) with T2DM and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function, resulting in the same doses recommended for pediatric and adult patients with T2DM (Glucophage U.S. product circular). Furthermore, in adult patients, the PK of metformin administered twice daily as an immediate-release formulation is similar to the PK of an equal dose of extended-release formulation administered once daily (Glucophage XR U.S. product circular). While there are no data regarding the use of metformin XR in pediatric patients with T2DM, the observed similarity in the PK and PD (pharmacodynamics) of metformin (immediate-release formulation) in pediatric and adult patients with T2DM suggests that pediatric and adult dosing for metformin XR will be also be similar.

Patients will enter the study on maximally tolerated doses of metformin (immediate- or extended-release formulations). The maximum daily dose of metformin, if tolerated, will be 2000 mg. Patients receiving less than 1000 mg of metformin a day will be excluded from the study.

At **Visit 2/Week -1**, patients will be switched from their pre-study dose of metformin to Sponsor-supplied metformin XR (Table 2-2). Patients whose daily dose of metformin is <1500 mg will be switched to 1000 mg of metformin XR daily. Patients whose daily dose of metformin is 1500 mg will be switched to (or maintained on) 1500 mg of metformin XR daily. Patients whose daily dose of metformin is >1500 mg will be switched to 2000 mg of metformin XR daily.

**Fixed-dose Combination of Sitagliptin and Extended-Release Metformin (MK-0431A XR)**

At **Visit 3/Day 1**, patients will be randomized to either 1) the fixed-dose combination of sitagliptin/extended-release metformin (MK-0431A XR) and metformin XR placebo **or** 2) to metformin XR and MK-0431A XR placebo. Patients will continue on the same daily dose of metformin XR initiated at **Visit 2/Week -1,** whether they are randomized to MK-0431A XR and metformin XR placebo or to metformin XR and MK-0431A XR placebo (see Table 2-2).

A Phase I trial, MK-0431A XR P296, to assess the PK and swallowability of the FDC of sitagliptin and extended-release metformin has completed. No changes to this protocol were required based on the results from study P296.

**Insulin**

Insulin is approved for use in pediatric patients with T2DM and inadequate glycemic control on metformin therapy. Use of basal insulin is associated with less hypoglycemia in patients with T2DM compared to intermediate-acting insulin [57]. Insulin glargine, a basal insulin, is widely used in pediatric patients, and is therefore used as the agent for glycemic rescue therapy in Phase A for patients not on background insulin (See Section 2.4.2.6 for glycemic rescue thresholds). The procedure and dose for initiation of insulin glargine, and for uptitration of background insulin will be at the investigator's discretion, based on local, national, or international guidelines.

At **Visit 6/Week 20** (beginning Phase B), or at subsequent clinic visits, based on a single measurement of FS A1C and FFSG (See Section 2.4.2.5 for details) patients on background insulin will uptitrate their insulin, and patients not on background insulin will initiate insulin glargine. In adults, an A1C value of 7.0% corresponds with an FPG of approximately 130 mg/dL (7.2 mmol/L) [59, 60]. A threshold of a single measurement of FFSG of >130 mg/dL (7.2 mmol/L) with a concomitant FS A1C measurement of >7.5%, was chosen to be conservative (ie, to reduce the risk of hypoglycemia) in this pediatric population, given the possible differences between the measurement of A1C via a fingerstick or at the central laboratory, and between the measurement of FFSG (capillary glucose measurements) and FPG. The procedure and dose for initiation, uptitration and continued use of insulin will be at the investigator's discretion, based on local, national, or international guidelines.

**NOTE**: After at least 6 weeks of treatment with a basal insulin, prandial insulin can be added at the Investigator's discretion. The choice, dose, and titration of prandial insulin will be the Investigator's responsibility.

### 3.1.5 Rationale for Placebo Use

The placebo control group is an essential arm in this trial, as it supports the evaluation of the safety and efficacy of sitagliptin in pediatric patients 10 to 17 years of age (inclusive) with T2DM and inadequate glycemic control on the maximally tolerated dose of metformin therapy (alone or in combination with insulin).

Glucose concentrations can change over time related to changes in diet, activity, and other factors, and hence a comparison to pretreatment baseline glucose concentrations, rather than to glucose levels in another treatment group, would not accurately characterize the glucose-lowering efficacy of the addition of sitagliptin to ongoing metformin therapy in this population. Non-placebo controlled, active-comparator studies provide important information, but the efficacy profile of the addition of an agent is best characterized by comparison to the addition of placebo, especially in the first trial of the FDC, MK-0431A XR, in the pediatric population (MK-0431A XR P289). In addition, at the present time, the only antihyperglycemic agent approved for use in pediatric patients with T2DM who have inadequate glycemic control on metformin monotherapy is insulin. Therefore, it will not be feasible to conduct a blinded active-controlled study to evaluate the safety and efficacy of MK-0431A XR. The placebo-control group in this trial will therefore support the blinded evaluation of the safety and efficacy of MK-0431A XR in this pediatric population with T2DM and inadequate glycemic control on the maximally tolerated dose of metformin

The main concern with the use of a placebo arm is the possibility of exposure to prolonged periods of hyperglycemia, which will be handled in the following manner in this study. Patients will be counseled using specially-designed material that is unique for pediatric patients with T2DM, and unlike in real-life clinical situations, will be seen in clinic and contacted by telephone very frequently. They will also monitor their fingerstick glucose and initiate glycemic rescue therapy at progressively lower glucose thresholds during the course of the study that will ensure that patients will not be exposed to hyperglycemia for prolonged periods of time. Rescue criteria included in this study (see Section 2.4.2.6) are more stringent than the criteria recommended for use in studies of adult patients with T2DM [61].

### 3.1.6 Future Biomedical Research

Merck will conduct Future Biomedical Research on blood, serum and plasma specimens collected 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 patients. 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, and/or to ensure that patients receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6.5: Collection and Management of Specimens for Future Biomedical Research.

## 3.2 STUDY PROCEDURES

Timing of laboratory specimens or specific procedures can be found in the Study Flow Chart (Section 1.7).

### 3.2.1 Concomitant Medication(s)/Treatment(s)

Patients with concomitant medical conditions (such as hypothyroidism, hypertension, and dyslipidemia) should be treated according to local guidelines.

**Note:** It is the responsibility of the investigator to ensure that patients with concomitant medical conditions are: 1) treated according to local guidelines and 2) on a stable regimen and dose of thyroid medication for at least 6 weeks prior to **Visit 1** and/or a stable dose of lipid-lowering and anti-hypertensive medications for at least 4 weeks prior to **Visit 1**.

**Note:** Medications to treat hyperthyroidism are prohibited.

**Antihyperglycemic Medications**

Double-blind study medication, open-label insulin (background or rescue therapy), and insulin glargine are the only AHA (anti-hyperglycemic agent) medications permitted in the study. Patients who discontinue study medication may be treated with antihyperglycemic medication as considered clinically appropriate.

**Lipid, Blood Pressure, and Thyroid Hormone Medications**

Concurrent lipid lowering, antihypertensive, and thyroid hormone replacement medications are permitted, as detailed above.

**Birth Control Medications**

These medications are allowed, but patients should be on a stable regimen during the placebo run-in and are expected to remain on a stable regimen during the double-blind treatment period (refer to Section 3.2.3.4 for further detail regarding contraceptive agents).

**Note**: Patients who initiate heterosexual activity during the study may begin hormonal contraception as detailed in Section 2.2.

**Corticosteroids**

Treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids (oral, injectable/parenteral) is not permitted during the study. Oral corticosteroids used for physiologic replacement therapy (ie, in patients with adrenal insufficiency) and inhaled, nasal, and topical corticosteroids are allowed.

**Note:** Use or need for use of excluded medications will require consultation with the study investigator and the Sponsor.

**Supplements**

The use of herbal supplements and other so-called "natural products" should be discouraged for the duration of the study. Patients who do not discontinue the use of such supplements should be instructed not to change the use or dose of the supplement for the duration of the study. Patients should be instructed not to initiate new supplements for the duration of the study.

### 3.2.2 Diet/Activity/Other

At **Visit 2/Week -1**, the patient and parent/guardian will receive individualized diet counseling for weight maintenance consistent with the standard guidelines of the country of the investigational site (or other similar guidelines such as those from the ADA) for pediatric patients with T2DM from a dietitian or other qualified health care professional. Detailed dietary information will not be captured in the study database. Patients and parents/ guardians will also be counseled to maintain a medically appropriate, routine exercise program; consistency and adherence to the recommended regimen of diet and exercise will be encouraged throughout the study, with monitoring of diet and exercise occurring at each scheduled study visit beginning at **Visit 3/Day 1**.

### 3.2.3 Procedures

#### 3.2.3.1 Monitoring of Glycemic Control

**Self-Monitored Blood Glucose (SMBG)**

Glucose meters will be supplied to all patients at **Visit 2/Week -1** and the patient and parent/guardian will be instructed on the procedure for performing fingerstick glucose measurements. The patient may record measurements in the fingerstick glucose log book. During both the pre-randomization and double-blind treatment periods, patients will be instructed to monitor fingerstick glucose (1) once daily (at least 2 measurements before breakfast, each week, 2) whenever they have symptoms of hypoglycemia or (2) during an intercurrent illness. For patients on insulin (as background therapy at randomization or as a rescue medication during the study), the investigator will counsel the patient and parent/guardian on the recommended frequency of home glucose monitoring based on locally accepted clinical practice guidelines.

During both the pre-randomization and double-blind treatment periods, patients and/or parents/guardians will be counseled to contact the study site (1) if patient experiences symptoms of low blood sugar or (2) for fingerstick glucose values ≤70 mg/dL (≤3.9 mmol/L) with or without symptoms (refer to Section 3.2.3.3). For patients on insulin therapy, the dose of insulin should be down-titrated or interrupted if, in the opinion of the Investigator, the hypoglycemia occurred in the absence of a readily apparent cause or precipitating factor. Further management of insulin doses will be at the investigator's discretion. In addition, patients will be counseled to contact the study site for FFSG values that meet glycemic rescue criteria (refer to Section 2.4.2.6) after randomization.

#### 3.2.3.2 Monitoring for Ketones

At **Visit 2/Week -1**, patients will be supplied with screening strips to assess for ketonuria/ketonemia and the patient and parent/guardian will be instructed on their use. Patients and parents/ guardians will be instructed to check the patient's urine for ketones in the first morning void at least once a week throughout the study. They will also check for ketones during intercurrent illnesses or if the patient's fingerstick blood glucose is ≥400 mg/dL (≥22.2 mmol/L) at any time during the study. Regardless of blood glucose levels, if urine ketones are "moderate" or "large" (as indicated on the dipstick), or blood ketones are "positive", the patient and parent/guardian will be instructed to contact the study site immediately for further assessment.

#### 3.2.3.3 Assessment and Management of Hypoglycemia

At **Visit 2/Week -1**, the site will review the symptoms of hypoglycemia with the patient and parent/guardian and advise them to promptly manage the hypoglycemia according to local clinical practice guidelines. In addition, the site will counsel the patient and parent/ guardian to immediately perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (eg, weakness, dizziness, shakiness, increased sweating, palpitations, or confusion). However, treatment of the hypoglycemic symptoms should not be delayed if a fingerstick glucose measurement cannot be performed immediately.

The patient and parent/guardian will be instructed to complete the hypoglycemia assessment tool(s) for any symptomatic episodes he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (ie, within a few minutes) after treating, the value should be recorded in the hypoglycemia assessment tool(s). In addition, patients and parents/guardians will be instructed to record any fingerstick glucose values ≤70 mg/dL (≤3.9 mmol/L) on the hypoglycemia assessment tool(s) regardless of the presence of clinical symptoms.

**Note (a):** the hypoglycemia assessment tool(s) will be available in both an electronic format and a paper format. The paper version consists of two parts: the "Low Blood Sugar Calendar" and the "Low Blood Sugar Notepad".

**Note (b):** the hypoglycemia assessment tool(s) should also be completed when the patient is away from home. If the patient is using the paper Notepad, the information should be transferred to the paper Low Blood Sugar Calendar later the same day.

Patients and parents/guardians will be instructed to contact the investigational site to report:

- any episode of possible hypoglycemia resulting in symptoms,
- any episode of hypoglycemia for which assistance was required (ie, severe hypoglycemia, details provided on the hypoglycemia assessment tool(s)),
- any episode of fingerstick glucose ≤70 mg/dL (≤3.9 mmol/L) with or without symptoms.

**Note:** As indicated, the patients will record symptoms and/or fingerstick glucose measurements that they believe are related to hypoglycemia on the hypoglycemia assessment tool(s) with the assistance of the parent/guardian. Each episode should be evaluated by the investigator and recorded on the Hypoglycemia Assessment (HA) electronic case report form (eCRF). For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (≤3.9 mmol/L), regardless of whether they are considered an adverse event, the HA eCRF must also be completed. Each episode of symptomatic hypoglycemia must be reported as an adverse event on the AE eCRF. Each episode of asymptomatic hypoglycemia considered by the investigator to be an adverse event should also be reported on the adverse event eCRF (refer to Section 3.4.7 for guidance on reporting).

**Patients on Background Insulin Therapy**

Patients on insulin should be counselled to contact the site if: a) a patient experiences 2 or more episodes of symptomatic hypoglycemia not requiring assistance within a 1-week time period; OR, b) patient experiences a single episode of hypoglycemia requiring assistance. The dose of insulin should be down-titrated or interrupted if, in the opinion of the investigator, the hypoglycemia occurred in the absence of a readily apparent cause or precipitating factor. Further management of insulin doses will be at the investigator's discretion**.**

### 3.2.3.4 Pregnancy Testing and Contraception

**Pregnancy Testing**

All females participating in the study will have a urine pregnancy test at visits indicated on the Study Flow Chart. If required by an investigational site's Institutional Review Board/Ethics Review Committee [IRB/ERC], a serum pregnancy test can also be obtained in addition to, or in place of, the urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. Patients must be discontinued and followed (refer to Section 3.4.5) if pregnancy is confirmed by a positive serum pregnancy test.

**Contraception**

Non-pregnant, non-breast-feeding females may be enrolled if they are considered unlikely to conceive. Unlikely to conceive is defined as (1) not heterosexually active for the duration of this study, or (2) heterosexually active and willing to use adequate contraception. Birth control methods can be either a barrier method and/or a hormonal method to prevent pregnancy, used throughout the study as defined in Section 2.2 and for 14 days after the last dose of study medication.

The following are considered adequate barrier methods of contraception: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, or use of condom by partner. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, vaginal, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study and agree that in order to participate in the study they **must adhere to the contraception requirement (described above) for the duration of the study.** If there is any question that a patient will not reliably comply with the requirements for contraception, she should not be enrolled into the study.

### 3.2.3.5 Anthropometric Measurements

*Body weight* will be measured (to be performed in duplicate) using a calibrated digital scale.

*Height* will be measured (to be performed in triplicate) using a wall-mounted calibrated stadiometer.

*Blood pressure* and *heart rate* will be measured (to be performed in duplicate) using an electronic blood pressure monitor.

*Waist circumference* will be measured (to be performed in duplicate).

For details on measuring techniques, refer to Appendix 6.6

### 3.2.3.6 Laboratory Monitoring

Patients should be fasting for at least 10 hours before **Visits 1, 3, 6, 9, Rescue**, and **Discontinuation**. Fasting is not required prior to other visits.

All laboratory tests outlined in the Study Flow Chart (eg, FPG, A1C, CBC, chemistry panel, lipid panel, TSH, etc.) will be performed by the central laboratory (with the exception of the site fingerstick A1C, site and patient fingerstick glucose determinations, and site dipstick urinalysis).

Glycemic endpoints (measured at the central laboratory) will be masked during the double-blind treatment period. Masking will occur after **Visit 3/Day 1**. However, in order for the investigator to perform an evaluation for possible glycemic rescue and/or discontinuation the central laboratory will report to the investigator in an unmasked manner any FPG laboratory value meeting rescue and/or discontinuation criteria (refer to Sections 2.4.2.6 and 2.4.2.7).

Laboratory test results for chemistry (eg, ALT, AST, creatinine, eGFR) will not be masked, but will be flagged by the central laboratory if they meet protocol-specified exclusion and discontinuation criteria (refer to Sections 2.3 and 2.4.2.7).

At or after **Visit 3/Day 1**, ALT and AST elevations greater than or equal to 3-times the upper limit of normal (ULN) will be flagged by the Central Laboratory and patients will be retested, according to Appendix 6.4.

### 3.2.3.7 ECG Procedures

ECGs performed at **Visit 2/Week -1**, **Visit 6/Week 20**, **Visit 9/Week 54, Discontinuation Visit** (if applicable), and **Rescue Visit** (if applicable) will be read locally, and will not be sent to a central ECG reading laboratory.

### 3.2.3.8 Assessment of Swallowing Ability

The patient's ability to swallow study medication will be assessed by collecting data from the patient using The Swallowing Ability Questionnaire and from the individual administering the witnessed dose using The Site Assessment of Swallowability Questionnaire.

The Swallowing Ability Questionnaire is a sponsor developed measure to be completed by the patient. The Swallowing Ability Questionnaire will be administered to the patients at **Visit 2/Week -1**, **Visit 3/Day 1**, **Visit 4/Week 6**, **Visit 5/Week 12**, **Visit 6/Week 20**, **Visit 7/Week 28**, **Visit 8/Week 40**, **Visit 9/Week 54**, **Discontinuation Visit** (if applicable), and **Rescue Visit** (if applicable).

The Site Assessment of Swallowability Questionnaire is a Sponsor-developed set of questions to be completed by the individual at the site administering the witnessed doses. This form captures the site personnel's assessment of the patient's ability to swallow the witnessed dose. The Site Assessment of Swallowability Questionnaire will be completed

after the witnessed dose. The Site Assessment of Swallowability Questionnaire will be completed after the witnessed dose is administered at **Visit 2/Week -1**, **Visit 3/Day 1**, and **Visit 6/Week 20.**

#### 3.2.3.9 Tanner Staging

Tanner Staging will be performed in order to assess the physical measurements of sexual development. Tanner Staging will be performed at **Visit 3/Day 1**, **Visit 6/Week 20**, **Visit 9/Week 54, Discontinuation Visit** (if applicable), or **Rescue Visit** (if applicable). Refer to Appendix 6.11 for details.

**Note:** if at any of the evaluations the patient's sexual maturation is assessed as being Tanner Stage V, no further evaluations are needed during the study.

#### 3.2.3.10 Collect Substance Use Information

The use of tobacco (pack years) and alcohol should be collected in the eCRFs.

#### 3.2.3.11 Informed Consent

The investigator must obtain documented consent from each potential patient prior to participating in a clinical trial or Future Biomedical Research.

##### 3.2.3.11.1 General Informed Consent

Consent must be documented by the patient's dated signature or by the patient's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. If the parent/guardian is illiterate, an impartial witness should be present when the entire informed consent and other written information is read and explained. The impartial witness should sign and date the informed consent indicating that the explanation of the written information was accurate, consent by the parent/guardian was given freely and the parent/guardian verbally acknowledged that they understood the information.

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

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/ERC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient'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 patient's dated signature or by the patient'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.

#### 3.2.3.11.1.1 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the patient, 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 patient.

#### 3.2.3.11.1.2 Collection of Specimens for Future Biomedical Research from Minors

Patients participating in this study should sign a separate assent form and their parents/ guardians should sign a separate consent form for the collection of future biomedical research samples.

#### 3.2.3.11.1.3 Future Biomedical Research

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

- Blood for genomics use
- Serum and plasma for future use

### 3.2.3.12 Assignment of Screening Number

A unique screening number will be assigned to all screened patients upon signing the informed consent. The screening number identifies the patients for all procedures that occur prior to randomization. Patients who are re-screened will retain the original screening number assigned at the initial screening visit.

### 3.2.3.13 Patient Identification Cards

All patients will be given a card, at **Visit 2/Week -1**, identifying them as participants in a research study. The card will contain site contact information (including direct telephone numbers) to be utilized in the event of an emergency.

### 3.2.3.14 Stratification

Randomization at **Visit 3** will be stratified by the patients' dose of metformin and insulin use at **Visit 1** into the following 6 strata: (1) <1500 mg, and insulin user; (2) 1500 mg, and insulin user; (3) >1500 mg, and insulin user; (4) <1500 mg, and non-insulin user; (5) 1500 mg, and non-insulin user; (6) >1500 mg, and non-insulin user.

### 3.2.3.15 Randomization/Allocation

A single patient cannot be assigned more than 1 randomization number.

### 3.2.3.16 Poststudy Follow-Up

#### 3.2.3.16.1 Poststudy Contact for Patients Who Have Completed the Study

Fourteen days after completion of the study, the patient will be contacted by telephone to assess for any SAEs that occurred after the administration of the last dose of study medication. The date of the telephone contact should be recorded and any SAEs that have occurred should be recorded in the Adverse Events eCRF.

If any SAE requires supplemental procedures, they should be performed as medically necessary and recorded in the Procedures eCRF.

#### 3.2.3.16.2 Follow-Up of Patients Who Have Discontinued Study Medication Prior to Study Completion

Fourteen days after discontinuation of study medication, the patient will be contacted by telephone to assess for any SAEs that occurred after the administration of the last dose of study medication.

After this 14 day post-study medication discontinuation telephone contact is made, patients who do not withdraw consent should:

1. return to the clinic for key visits (Week 20 and/or Week 54 as applicable) to have the following procedures performed: physical examination (including Tanner Staging), laboratory assessment of glycemic endpoints (A1C and FPG), and safety parameters (CBC, chemistry panel, urine microalbumin to creatinine ratio, and dipstick urinalysis), and collection of adverse events. Patients who are unable or unwilling to return to the clinic at key visits should be contacted by phone to obtain adverse events, concomitant medications and weight. For patients unable or unwilling to return to the clinic at key visits who receive their diabetes care from the study doctor, the A1C and FPG values will be obtained from their records, if available; such patients who receive their diabetes care from someone other than the study doctor should have their diabetes doctor provide A1C and FPG values, if available.,

2. be contacted by phone in a timeframe similar to their original study visit schedule at visits that are not key visits (ie, not at **Week 20** or **Week 54**), up until the patient has reached the Week 54 visit (ie, the visit that is approximately 54 weeks from randomization **Visit 3/Day 1)**. The purpose of these telephone contacts will be to assess for SAEs that occurred. The date of the telephone contact should be recorded and any serious adverse events that have occurred should be recorded in the eCRF.

Note: Study sites must make all reasonable efforts to counsel the patient to stay in the study even if they discontinued the study medication and make all reasonable efforts to contact the patient. Patients must be counseled regarding the importance of complete follow up, even when they are not continuing on study medication. Sites should make at least three attempts to make telephone contact. If telephone contacts are not successful,

sites should make at least two attempts to reach the patient via certified letter before considering the patient as lost to follow-up.

If any adverse event requires supplemental procedures, they should be performed as medically necessary and recorded in the Procedures eCRF.

The date of the telephone contact should be recorded and any SAE information and A1C values that have been obtained should be recorded in the eCRFs.

- ***Follow Up of Patients Who Have Discontinued From the Study Prior to Study Completion***

Patients who withdraw consent and discontinue from the study will not be contacted by phone for additional follow-up. Reasons for discontinuation are discussed further in Section 2.4.2.7.

### 3.2.3.17 Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations, where the investigator or delegate needs to identify the drug used by a patient and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a patient's treatment assignment, the investigator or delegate should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the patient.

Patients whose treatment assignment has been unblinded by the investigator/delegate and/or nonstudy treating physician, must be discontinued from study medication, but should continue to be monitored in the study.

Additionally, the investigator must go into the IVRS system and perform the unblinding 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 patient safety.

### 3.2.3.18 Interruption/Discontinuation/Withdrawal from Study Medication

Since patients will be receiving treatment with metformin, if a patient undergoes an imaging study requiring the use of **radiocontrast dye** (for example, an intravenous pyelogram or computerized tomography study with contrast), all study medication should be interrupted for the time of the radiocontrast dye study (refer to the Janumet XR or metformin labels). The patient's renal function should be reassessed 48 hours after the procedure: all study medication should be re-instituted (at the same dose as prior to its interruption) *only after* renal function has been evaluated and found not to have been reduced by the dye study. In a patient requiring an imaging study, if considered clinically appropriate, studies not using radiocontrast dye (eg, ultrasound, MRI with gadolinium contrast, or non-contrast CT studies) should be performed instead of radiocontrast dye studies, so as to avoid the interruption of all study medication.

The Sponsor should be immediately contacted when a patient is discontinued or study medication is interrupted because of an adverse event or a laboratory safety test abnormality.

Patients may discontinue at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a patient may be discontinued by the investigator or the SPONSOR if the patient violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a patient has been discontinued/withdrawn due to an adverse event (telephone or FAX). When a patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study 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 3.4 SAFETY MEASUREMENTS - DETAILS.

#### 3.2.3.18.1 Withdrawal from Future Biomedical Research

Patients may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Patients may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the patient'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 patient 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 (eg, if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the patient's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

#### 3.2.3.19 Discontinuation Visit Procedures

Discontinuation Visit procedures should be performed on the following patients as soon as possible after discontinuing study medication:

- All randomized patients who stop double-blind study medication but remain in the study (discontinue from study medication)
- All randomized patients who withdraw consent (discontinue from the study)

At the **Discontinuation Visit**, patients will undergo the same procedures that they would at the final study visit, **Visit 9/ Week 54**. Refer to the Study Flow Chart, Section 1.7, for details.

**Note**: the Discontinuation Visit is conducted for all patients who stop or discontinue study medication, but is only a **study** discontinuation visit for patients who are stopping study medication due to withdrawal of consent. All patients who stop study medication will be counseled and encouraged to remain in the study and to return to the site for the **Week 20** and **Week 54** visits, as applicable (described in Section 3.2.3.16.2).

#### 3.2.3.20 Collect Substance Use Information

Information regarding the use of tobacco (pack years) and alcohol should be collected.

## 3.3 EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY, ETC. MEASUREMENTS

### 3.3.1 Clinical and Laboratory Measurements for Efficacy

Efficacy measurements include laboratory assessment of: A1C, FPG, lipid parameters, and fasting insulin and proinsulin.

### 3.3.2 Medication Compliance

Adherence to treatment will be assessed by patient report which may be facilitated by tablet count as outlined in the Study Flow Chart (Section 1.7). Every effort will be made to maintain adherence as close to 100% as possible. If a patient is found to have reduced compliance (<85%), site personnel should begin frequent contacts with the patient and the parent/guardian to reinforce compliance with study medication.

## 3.4 SAFETY MEASUREMENTS

### 3.4.1 Clinical and Laboratory Measurements for Safety

- Collection and assessment of adverse events, physical examination, TS, vital signs and body weight/BMI/BMI percentile, as indicated in the Study Flow Chart (Section 1.7).

- ECG will be collected and read locally. The assessment of the ECG will be the investigator's responsibility.

- A standard instrument (the hypoglycemia assessment tools) will be provided to the patient to collect hypoglycemia information.

- Laboratory safety studies will consist of blood chemistry (including ALT, AST, creatine phosphokinase [CPK], total bilirubin, and alkaline phosphatase), hematology (including complete blood count [CBC], differential, absolute neutrophil count and platelet count), urinalysis, urine microalbumin/creatinine ratio and urine pregnancy testing (performed in all female patients).

For a complete list of laboratory measurements please refer to Appendix 6.7.

#### 3.4.1.1 Assessment of Swallowability of MK-0431A XR tablets

Swallowability of MK-0431A XR will be assessed throughout the course of the study starting at **Visit 2/Week -1** (placebo run-in).

- At **Visit 2/Week -1**, swallowability of study medication tablets will be assessed using the Swallowing Ability Questionnaire administered to the patient and by the site personnel's assessment of swallowability of the witnessed dose using the Site Assessment of Swallowability Questionnaire as well as collection of adverse events related to swallowing the witnessed dose.

- At **Visit 3/Day 1**, swallowability of double-blind study medication will be assessed using the Swallowing Ability Questionnaire administered to the patient and by the site personnel's assessment of swallowability of the witnessed dose based on using the Site Assessment of Swallowability Questionnaire as well as collection of adverse events related to swallowing the witnessed dose.

- At subsequent study visits, specified in the Study Flow Chart (Section 1.7), swallowability of double-blind study medication will be assessed using the Swallowing Ability Questionnaire administered to the patient and the collection of adverse events related to swallowing the tablets.

### 3.4.2 Data Monitoring Committee

#### 3.4.2.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) consists of members of the Sponsor's Senior Management. The EOC will receive and decide upon any recommendations made by the external Data Monitoring Committee (eDMC) regarding the trial.

#### 3.4.2.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an eDMC will monitor the interim safety data from this trial. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The eDMC will include 2 clinicians experienced in pediatric endocrinology and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The eDMC will make recommendations to the EOC regarding steps to ensure both patient safety and the continued ethical integrity of the trial. Also, the eDMC will review interim trial results, consider the overall risk and benefit to trial participants and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team, meeting facilitation; the trial governance structure, and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the eDMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter. The eDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both patient safety and the continued ethical integrity of the trial.

### 3.4.3 Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable 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 (ie, 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 randomization must be reported by the investigator if they cause the patient 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 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 3.4.6. The investigator will make every attempt to follow all patients with non-serious adverse events for outcome.

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

### 3.4.4 Definition of an Overdose for This Protocol

An overdose must be reported if any of the following occur during the conduct of the study:

1. Administration of MK-0431A XR/matching placebo tablets that would result in *more than or equal to* 200 mg of sitagliptin per day for more than 1 day.

2. Administration of MK-0431A XR/matching placebo tablets that would result in *more than* 200 mg of sitagliptin per day.

3. Administration of MK-0431A XR/matching placebo or metformin XR/matching placebo tablets that would result in *more than* 3000 mg of metformin per day.

For recommended management of acute overdose for MK-0431A XR, please refer to the Investigator's Brochure (IB).

**Note**: Any overdose meeting above criteria whether or not associated with an adverse event must be reported to headquarters' personnel within 24 hours.

#### 3.4.4.1 Reporting of Overdose to SPONSOR

If an adverse event(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other criteria for serious are met.

If a dose of test drug 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).

### 3.4.5 Reporting of Pregnancy to 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 patient (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before randomization must be reported by the investigator if they cause the patient 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 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).

### 3.4.6 Immediate Reporting of Adverse Events to the SPONSOR

#### 3.4.6.1 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 3-1 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the patient 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 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 patients with serious adverse events must be followed up for outcome.

#### 3.4.6.2 Selected Nonserious Adverse Events

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 randomization, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the patient 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 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:

- an overdose of Sponsor's product, as defined in Section 3.4.4 - Definition of an Overdose for This Protocol, that is not associated with clinical symptoms or abnormal laboratory results.

- 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 Administrative Binder, or equivalent).

### 3.4.7 Guidance on Adverse Events Related to Glycemia

#### 3.4.7.1 Hyperglycemia

An adverse event of hyperglycemia requires that a patient have one or more symptoms (eg, increased thirst, polyuria) typically associated with an increased glucose level. At the discretion of the investigator, this may be captured as an adverse event of "hyperglycemia". This diagnosis may be supported by, but does not require, results from a glucose meter or the study central laboratory. Further, at the discretion of the investigator, an elevated blood glucose value without associated symptoms that is considered to be an adverse event may be reported as an adverse event of "increased blood glucose". General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (refer to Section 3.4.8).

### 3.4.7.2 Hypoglycemia

#### 3.4.7.2.1 Documentation

Regardless of whether an episode is considered an adverse event, the HA eCRF ***must*** be completed for the following:

- all episodes determined by the investigator to be hypoglycemia (symptomatic or asymptomatic)
- all glucose values ≤70 mg/dL (≤3.9 mmol/L)

#### 3.4.7.2.2 Guidance

All episodes considered as likely to represent symptomatic hypoglycemia by the investigator must be captured as an adverse event of "hypoglycemia". This diagnosis may be supported by, *but does not require*, confirmatory blood glucose results (such as those measured using a fingerstick or from a clinical laboratory sample). Further, at the discretion of the investigator, an asymptomatic blood glucose value ≤70 mg/dL (3.9 mmol/L) may be reported as an adverse event of "asymptomatic hypoglycemia". General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (refer to Section 3.4.8).

### 3.4.8 Evaluating Adverse Events

Refer to Table 3-1 for instructions in evaluating adverse events.

Table 3-1
An investigator, who is a qualified physician, will evaluate all adverse events as to:

| | | |
|---|---|---|
| **Maximum Intensity** | **Mild** | awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated) |
| | **Moderate** | discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong) |
| | **Severe** | incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities) |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose 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 experience 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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)** | |
| | **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 experience 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 test drug to be discontinued? | |
| **Relationship to test drug** | Did the test drug cause the adverse event? The determination of the likelihood that the test drug 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.<br>**The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to the test drug 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 test drug?<br>Is the time of onset of the AE compatible with a drug-induced effect? |
| | **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 test drug (continued)** | **The following components are to be used to assess the relationship between the test drug and the AE: (continued)** | |
| | **Dechallenge** | Was the dose of test drug discontinued or reduced?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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 test drug; or (3) the study is a single-dose drug study.) |
| | **Rechallenge** | Was the subject reexposed to the test drug in this study?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study.)<br>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE. |
| | **Consistency with Study Drug Profile** | Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug 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 drug relationship).** |
| **Yes, there is a reasonable possibility of drug relationship.** | | There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause.<br>**Depending on data collection method employed, drug relationship may be further graded as follows:** |
| | **Definitely related** | There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class. |
| | **Probably related** | There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. |
| | **Possibly related** | There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive. |
| **No, there is not a reasonable possibility of drug relationship** | | Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)<br>**Depending on data collection method employed, drug relationship may be further graded as follows:** |
| | **Probably not related** | There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous. |
| | **Definitely not related** | The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE. |

### 3.4.9 SPONSOR Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

## 3.5 STATISTICAL ANALYSIS PLAN (SAP)

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, along with an explanation as to why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate SAP will be issued for this study.

### 3.5.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the SPONSOR. This study will be conducted as a double-blind study under in-house blinding procedures.

After all patients remaining in the study have completed **Week 54** (or discontinued prior to **Week 54**) of Phase B of this study and the MK-0431A P170 extension study, and medical and scientific reviews of the data have been completed, the analysis will be conducted and a CSR will be created to summarize the results of this study. The results of the pooled P289 and P170 (base and extension) studies will be summarized in a separate report.

### 3.5.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

### 3.5.3 Analysis Endpoints

Safety and efficacy endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

The baseline value will be defined as the **Visit 3/Day 1** (randomization) measurement. If this measurement is not available, the last available pre-treatment value will be used as the baseline value. If no pre-treatment measurement is available, the baseline value will be treated as missing. The primary time point of the study is **Week 20**.

The analysis for efficacy and safety endpoints at **Week 20** in Phase A will be performed by pooling data from MK-0431A XR P289 and MK-0431A P170. Data from Phases A+B of P289 will be pooled with data from the base and extension (Weeks 0-54) studies of MK-0431A P170.

### 3.5.3.1 Efficacy Endpoints

The descriptions of the efficacy measurements and time points at which they are measured are described in Section 3.3 and Section 1.7, respectively. The efficacy endpoints to be analyzed are listed in Table 3-2. All of these endpoints will be analyzed at the **Week 20** and **Week 54** time points (unless otherwise stated) in the report that will be written after the study is complete. **Week 20** is the primary time point for efficacy analysis.

Parameters that are derived from more than 1 measurement, such as non-HDL-C, will be calculated based on the measurements taken on the same visit.

Day range definitions for the efficacy endpoints are provided in Appendix 6.8.

Table 3-2

Efficacy Endpoints

| **Endpoint Accessing Primary Hypothesis** |
|---|
| Change from baseline in A1C at Week 20 |
| **Secondary Endpoints** (assessed at Weeks 20 and 54 or as indicated) |
| Change from baseline in A1C at Week 54<br>Proportion of patients meeting A1C goal (<7.0%, <6.5%) at Week 20 and Week 54<br>Change from baseline in FPG at Week 20 and Week 54<br>Proportion of patients initiating glycemic rescue therapy by Week 20<br>Proportion of patients initiating insulin glargine at/after Week 20 |
| **Other Endpoints** |
| Change from baseline in fasting endpoints at Week 20 and Week 54:<br>• Insulin<br>• Proinsulin<br>• Proinsulin/insulin ratio<br>• Homeostatic Model Assessment of β-cell function (HOMA-β)<br>• Homeostatic Model Assessment of insulin resistance (HOMA-IR)<br>Time to initiation of glycemic rescue therapy at Week 20 and Week 54<br>Percent change from baseline in lipid panel at Week 20 and Week 54<br>• Triglycerides (TG)<br>• LDL-C<br>• HDL-C<br>• Non-HDL-C<br>• Total cholesterol (TC) |

### 3.5.3.2 Safety Endpoints

The descriptions of the safety measurements and time points at which they are measured are described in Section 3.4.1 and Section 1.7 respectively.

Part of the assessment of laboratory safety will be accomplished by defining limits of change for particular tests such that occurrences of patient values beyond these bounds are considered abnormal. Limits of change criteria are provided in Appendix 6.9. These

criteria are based upon the laboratory normal ranges and abnormalities considered to be potentially clinically meaningful.

#### 3.5.3.3 Derivation of Efficacy Endpoints

Computational details for efficacy endpoints listed in Table 3-2 are provided below:

- HOMA-β = 20×fasting insulin (in mcIU/mL) ÷ {[FPG (in mg/dL)/18] – 3.5}
- HOMA-IR = fasting insulin (in mcIU/mL) × FPG (in mg/dL) / (22.5×18)

NOTE: HOMA-β and HOMA-IR will not be calculated for patients on background insulin because fasting insulin will not be measured in these patients.

Day range definitions for the efficacy endpoints are provided in Appendix 6.8.

### 3.5.4 Analysis Populations

#### 3.5.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) populations will serve as the primary populations for the analysis at **Week 20** and **Week 54** with pooled populations of this study and P170 (base+extension).

Two populations will be defined for efficacy analyses, the **Week 20** Full Analysis Set (FAS) that will include all randomized patients who took at least one dose of study medication in the **Week 0** to **Week 20** period of P289 (ie, Phase A) or of P170 (ie, base study) regardless of whether they continued beyond that period of the study, and the **Week 54** FAS that will include only those patients from each study who received at least one dose of study medication beyond **Week 20** (ie, the Phase B of P289 and extension study of P170). For analyses using the longitudinal data analysis (LDA) model, both FAS populations further require that those patients have at least one measurement of the relevant analysis endpoint, either at baseline or post-baseline. For analyses that use the analysis of covariance (ANCOVA) model, both FAS populations further require that those patients have a baseline measurement.

The **Week 20** FAS will be considered the primary efficacy analysis population. The Phase A+B analyses will also be performed using the **Week 54** FAS population as a secondary analysis.

The time-to-insulin initiation analysis will include all randomized patients.

For all efficacy analyses, patients will be counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial.

Details on the approach to handling missing data are provided in Section 3.5.5, Statistical Methods.

### 3.5.4.2 Safety Analysis Populations

Two populations will be defined for safety analyses, the **Week 20** All Patients as Treated (APaT) population consisting of all randomized patients who took at least one dose of study medication in the **Week 0** to **Week 20** period of P289 (ie, Phase A) or of P170 (ie, base study) regardless of whether they continued beyond that period of the study, and the **Week 54** APaT that will include only those patients from each study who received at least one dose of study medication beyond **Week 20** (ie, Phase B of P289 and extension study of P170).

Patients will be included in the treatment group to which they were randomized, except for any patients who took incorrect study treatment for the entire treatment period. Such patients 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.

### 3.5.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 3.5.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 3.5.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical tests will be conducted at $\alpha$=0.05 level (2-sided).

Analyses will be performed for Phase A (**Week 0** to **Week 20**) and Phases A+B (**Week 0** to **Week 54**). Data from Phase A of P289 will be pooled with data from MK-0431A P170 (base study), and Phases A+B from P289 will be pooled with data from MK-0431A P170 (base and extension studies). Supportive efficacy and safety analyses will also be provided by summary statistics by treatment group for selected efficacy endpoints (FPG, A1C) and safety endpoints for P289 alone. Data on swallowability will be presented without pooling because these data are being collected only in P289.

### 3.5.5.1 Statistical Methods for Efficacy Analyses

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

There will be two estimands for the analysis of A1C, Treatment Effect (TE) and Treatment Policy (TP). The primary hypothesis will be tested using the TE estimand with the TP estimand providing a supplemental analysis, except where regulatory practice

requires the TP estimand, the TP estimand will constitute the test of the primary hypothesis and the TE estimand will be a supplemental analysis.

The TE estimand consists of the following elements:

- Target population: Pediatric patients (age 10 to 17 years, inclusive) with T2DM who have inadequate glycemic control
- Endpoint: Mean change from baseline in A1C at Week 20 as if all patients remained on treatment
- Intercurrent event: data obtained after discontinuation of treatment or after taking rescue medication are not relevant to this estimand
- Measure of intervention effect: difference in endpoint means comparing randomized treatments (MK-0431A and MK-0431A XR versus metformin IR/XR)

The TP estimand consists of the following elements:

- Target population: Pediatric patients (age 10 to 17 years, inclusive) with T2DM who have inadequate glycemic control
- Endpoint: Mean change from baseline in A1C at Week 20
- Intercurrent event: regardless of whether study medication or rescue medication was taken up to Week 20
- Population level-summary: difference in endpoint means comparing the effect of being randomized to treatment (MK-0431A and MK-0431A XR versus metformin IR/XR)

Accordingly, analyses corresponding to the TE estimand will exclude data after the last dose of study medication (plus a 5-day offset) as well as data after the initiation of rescue medication. Analyses corresponding to the TP estimand will include all available data at the Week 20 timepoint, including data after the last dose of study medication in any patient who remains in the study after discontinuing study medication.

**20-Week Pooled Data (Phase A from P289 and MK-0431A P170 Base Study)**

*Primary Endpoint: TE Estimand*

To address the primary hypothesis using the TE estimand, the mean change from baseline in A1C produced by MK-0431A and MK-0431A XR at **Week 20** will be compared to that of metformin IR/XR using the least-squares (LS) means of the MK-0431A IR/XR and metformin IR/XR treatment groups as estimated via a longitudinal data analysis (LDA) method. The model will include terms for treatment, time, baseline metformin dose (<1500 mg, 1500 mg, or >1500 mg), study (MK-0431A XR P289 and MK-0431A P170), baseline BMI percentile, insulin use at screening (yes/no), and the interactions of time by metformin dose, time by study, and time by treatment, unless the model fails to

converge. For the **Week 20** analysis, the LDA model will further assume a common baseline mean across treatment groups within each combination of study/baseline metformin dose/insulin use (which is valid due to randomization) and a different mean for each treatment at each of the post-baseline time points. This LDA model is called constrained LDA (cLDA), proposed by Liang and Zeger [62]. To ensure model convergence, the term for insulin use at screening will be removed from the model if necessary. 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 treatment difference in terms of mean change from baseline to a given time point will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The poolability of two studies will be assessed in a preliminary cLDA model at **Week 20** which includes terms for treatment, study, time, treatment by time interaction, and treatment by study interaction. The interaction between treatment and study will be tested for significance at $\alpha$=0.05 level to determine the heterogeneity of treatment effect across studies. If $p < 0.05$, then further analyses will be conducted to examine the nature of the interaction, quantitative or qualitative. Unless qualitative interaction is confirmed, the cLDA model for the primary hypothesis will be performed by pooling populations from the two studies. If the **Week 20** analyses are based on the pooled populations, then the **Week 54** analyses will be based on the pooled populations as well.

For the cLDA model, the Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. An unstructured covariance matrix will be used to model the correlation among repeated measurements and hence avoids the potential bias that could result from the use of specific structured covariance models. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can substantially overestimate or underestimate the true variance. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion.

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 within each combination of study/baseline metformin dose/insulin use. 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 patients who are missing

either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes are given in Appendix 6.10.

*Primary Endpoint: TP Estimand*

The primary endpoint of A1C will be analyzed using analysis of covariance (ANCOVA) to evaluate the TP estimand. The ANCOVA model will include terms for treatment, baseline metformin dose, study (MK-0431A P170 and MK-0431A XR P289), and insulin use at screening (yes/no), and covariates for baseline BMI percentile, and baseline A1C value. Any terms dropped from the cLDA model due to convergence issues will also be dropped from the ANCOVA model. A retrieved-dropout (RD) approach for missing data imputation will be used if feasible. The RD approach will assume that missing Week 20 data for patients who discontinued study medication can be represented by the observed Week 20 data for patients in the same arm who discontinued study medication but remained in the study.

The RD analysis will use patients who discontinued from study medication but had Week 20 A1C measurement as reference group to impute the missing Week 20 data for patients who were in the same arm and discontinued the study medication and had no Week 20 data.

The following steps will be taken to perform the RD analysis:

1. All patients who did not adhere to study medication prior to Week 20 will be classified according to their pattern of protocol deviation (from the assigned treatment plan) defined by the time of discontinuation from study medication, and a separate A1C profile will be assumed for each deviation pattern for each treatment group. There will be four possible deviation patterns by last dose of study medication (A: Week 20; B: 12 to <20 weeks; C: 6 to <12 weeks; D: 0 to <6 weeks).
2. Assume that the repeated A1C measures follow a multivariate normal distribution with a different mean profile and common variance covariance matrix for each deviation pattern and each treatment group.
3. For each deviation pattern and each treatment group, assume that the distribution of missing values is same as the distribution of observed values among patients who did not adhere to study medication but remained in the study and had an observed A1C value at Week 20.
4. Based on the assumptions and the non-informative prior distributions for the mean profiles and variance-covariance matrix described above, the imputed Week 20 values for each patient will be drawn from the posterior distribution of missing values.
5. A set of $K$ ($K$=100) 'complete' datasets will be created from the imputation. An ANCOVA model as presented previously will be used to analyze each of the 'complete' datasets and perform the final inference, combining the resulting parameter estimates and standard errors following Rubin's rule.

In order to perform the RD analysis, there must be at least one subject in each of the 8 reference groups (four deviation patterns × two treatment groups).

In these studies, patients were not required to return for clinic visits when discontinued from study medication until the implementation in September 2015 of amendments P170-11 (base study), and P289-07. Thus, the RD analysis may not be feasible due to insufficient observed Week 20 data post discontinuation of study medication. In that case, the primary analysis will use the Return-to-Baseline (RTB) approach for missing data imputation. The RTB analysis assumes patients who discontinued the study medication prematurely would have a 'washout' of any potential effect of the assigned study medication.

The RTB analysis will include all patients with a baseline A1C measurement. Missing A1C values at Week 20 will be imputed from a normal distribution with the expected value set to the subject's baseline value plus a shift and standard deviation computed based on the root mean squared error from the ANCOVA model described above. For subjects with missing data at Week 20, one hundred imputations will be performed based on the distribution specified previously. Each of the 100 resulting datasets will contain the original non-missing A1C data and the imputed data for the missing values at Week 20. The 100 datasets will be analyzed using the ANCOVA model described above. The 100 ANCOVA-based estimates of the treatment difference will be combined using PROC MIANALYZE based on Rubin's rule which accounts for between and within imputation variability.

*Secondary Endpoints*

All other continuous efficacy endpoints except triglycerides will be analyzed using the above cLDA model. For analyses of lipid endpoints, the response vector consists of log-transformed baseline and post-baseline values. The treatment difference in terms of mean percent changes from baseline to a given time point will be estimated and tested from this model through back-transformations.

Triglycerides will be analyzed using a nonparametric method: an ANCOVA based upon Tukey's normalized ranks [68] on the percent change from baseline. This model will have the same terms as the ANCOVA model described above. For this analysis, within-treatment effects will be estimated using medians, and between-treatment effects will be estimated using the Hodges-Lehmann estimate [69] with a corresponding distribution-free 95% confidence interval (CI) based on Wilcoxon's rank sum test. The standard deviation of the median will be computed as (Q3-Q1)/1.075, where Q3 and Q1 represent the $75^{th}$ and $25^{th}$ percentiles, respectively. Missing values will be imputed from the last observed post-baseline measurement, if available.

Analyses of the percentages of patients at the A1C goals of <7.0% and <6.5% at **Week 20** will be conducted using the Miettinen and Nurminen (M&N) method [63], an unconditional, asymptotic method, stratified by, study (MK-0431A XR P289 and MK-0431A P170), insulin use at screening (yes/no), and baseline A1C (> or ≤ median). However, if necessary due to small number of patients within the stratum, the insulin use

at screening will be removed from the model. The differences in percentages along with the corresponding 95% CIs will be provided. The multiple imputation (MI) method will be used to determine whether a patient has met the goal when the A1C result at **Week 20** is not available. 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. The seed for the random number generator will be 0431170289. Patients with missing **Week 20** data will be categorized as at or not at the A1C goals (<7.0% or <6.5%) at **Week 20** after imputation. To estimate the within-group response rates and between-group rate difference, each of the 10 imputed data sets will be summarized to obtain the proportion of responders within each group. The estimated proportions of responders from the 10 imputed data sets will be combined using standard multiple imputation techniques to yield an overall estimate of response rate and associated variance for each group [66]. The estimated response rates and adjusted effective sample sizes [67] will then be used to obtain the confidence intervals for between-group rate difference via the M&N method. In addition, as a sensitivity analysis the Cochran-Mantel- Haenszel method (CMH) will be used to analyze the percentages of patients at the A1C goals of < 7.0% and <6.5% at **Week 20** in the 'all patients randomized' population, with missing data imputed as 'not at goal'. Furthermore, an additional sensitivity analysis for A1C < 7.0% goal will be performed for patients with a baseline A1C ≥ 7.0%.

A time-to-event analysis will be performed for the initiation of glycemic rescue therapy in Phase A. The proportion of patients initiating glycemic rescue therapy in Phase A in each treatment group will be summarized. Plots of the Kaplan-Meier estimate of the distribution of the time-to-initiation of glycemic rescue therapy in Phase A will be provided for each treatment arm and log-rank tests, stratified by study, comparing the time-to-initiation distribution of sitagliptin versus placebo will be conducted. In this analysis, patients will be censored at the time of discontinuation from study medication.

Table 3-3 summarizes the analysis strategy for all efficacy endpoints in Phase A.

Table 3-3

Analysis Strategy for Efficacy Variables in Phase A

| Endpoint/Variable | Approach | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Endpoints Assessing Primary Hypothesis** | | | | |
| Change from baseline in A1C at Week 20 | P (TE)<br>P (TP)<br>S | cLDA<br>ANCOVA<br>Summary Statistics | FAS<br>FAS<br>FAS/All Data* | Model-based<br>RD/RTB<br>Data as Observed |
| **Other Endpoints** | | | | |
| Change from baseline in FPG at Week 20 | P<br><br>S | cLDA<br><br>Summary Statistics | FAS<br><br>FAS/All Data* | Model-based<br><br>Data as Observed |
| Proportion of patients with A1C at Goals (<7.0%, <6.5%) at Week 20 | P<br>S<br>S | M&N<br>CMH<br>M&N | FAS<br>ASR<br>FAS/Subgroup‡ | Multiple Imputation<br>"not at goal"<br>Multiple Imputation |
| Percent change from baseline in lipid parameters (other than triglycerides) at Week 20 | P | cLDA | FAS | Model-based |
| Percent change from baseline in triglycerides at Week 20 | P | Non-parametric method | FAS | LOCF |
| Change from baseline in Insulin, Proinsulin and Proinsulin / Insulin Ratio | P | cLDA | FAS | Model-based |
| Change from baseline in HOMA-β and HOMA-IR | P | cLDA | FAS | Model-based |
| Time to initiation of glycemic rescue therapy during Phase A | P | Kaplan-Meier | ASR | N/A |
| Proportion of patients initiating glycemic rescue therapy during Phase A | P | Summary | ASR | N/A |

ASR = All patients randomized; P=Primary approach; RD=Retrieved dropout; RTB=Return-to-baseline; S=Secondary approach; TE=Treatment effect; TP=Treatment policy.
‡ Subgroup=patients with baseline A1C ≥7.0% (applicable to A1C goal <7.0% analysis).
* Includes data following initiation of rescue therapy as well as data collected after discontinuation of study medication.

## 54-Week Pooled Data (Phases A+B from P289 and MK-0431A P170 base and extension studies)

The statistical models for the analyses at **Week 54** will be analogous to those in Phase A unless noted otherwise below. No between-group comparisons will be provided for **Week 54**.

The analysis of (percent) change from baseline in continuous efficacy endpoints in the **Week 54** FAS population using the longitudinal data analysis model will not assume a common mean across treatment groups at baseline. If the total analysis sample size from 2 treatments of both studies at **Week 54** is small (ie, less than 50), then the terms for the stratification factors may be removed from the model in the order of the insulin use at screening followed by baseline metformin dose if necessary.

Analyses of the percentages of patients at the A1C goals of <7.0% and <6.5%at **Week 54** will be analogous to those at Week 20.

For triglycerides, within-treatment effects will be estimated using medians, and between-treatment effects will not be estimated. The standard deviation of the median will be computed as (Q3-Q1)/1.075, where Q3 and Q1 represent the 75$^{th}$ and 25$^{th}$ percentiles, respectively. Missing values will be imputed from the last observed post-baseline measurement.

Table 3-4 summarizes the strategy for Phases A+B efficacy analyses.

Table 3-4

Analysis Strategy for Efficacy Variables in Phases A+B

| Endpoint/Variable | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| Change from baseline in A1C at Week 54 | LDA[†]<br>Summary | FAS<br>FAS/All Data[‡] | Model-based<br>Data as Observed |
| Change from baseline in FPG at Week 54 | LDA[†]<br>Summary | FAS<br>FAS/All Data[‡] | Model-based<br>Data as Observed |
| Proportion of patients with A1C at goals (<7.0%, <6.5%) at Week 54 | M&N<br>M&N | FAS<br>FAS/Subgroup[§] | MI<br>MI |
| Percent change from baseline in lipid parameters (other than triglycerides) at Week 54 | LDA[†] | FAS | Model-based |
| Percent change from baseline in triglycerides at Week 54 | Summary | FAS | LOCF |
| Proportion of patients initiating insulin glargine | Summary | FAS | N/A |

[†] The analyses will be performed in the Week 54 FAS population.
[‡] Includes data following initiation of rescue therapy as well as data collected after discontinuation of study medication.
[§] Patients with baseline A1C ≥7.0% for A1C goal <7.0% analysis.

### 3.5.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, BMI, vital signs, growth velocity and Tanner Staging data, and urine microalbumin/creatinine ratio, and patient reported outcomes.

Per the trial design, patients who discontinued study medication prior to **Visit 9/Week 54** and agreed to continue follow-up and further data collection will be contacted every 8-12 weeks up until the patient has reached 54 weeks from randomization, **Visit 3/Day 1**, to collect any SAEs that occurred after the discontinuation of the study medication.

For the pooled populations, safety analyses will be conducted for **Week 0** to **Week 20** (P289 Phase A and P170 base study) and **Week 0** to **Week 54** (P289 Phases A+B and P170 base and extension studies). For P289 alone, the safety analyses will be conducted

for Phase A (**Week 0** to **Week 20**) and Phases A+B (**Week 0** to **Week 54**). All safety endpoints will be analyzed for the time frame consisting of the Treatment Period + 14 day-post treatment follow up, and for SAEs, an additional analysis including data from all post-randomization follow-up will be performed. For Phase A analyses, the 14-day post-Treatment Period window will exclude the Phase B Treatment Period for patients who enter Phase B; ie, events that occur during the first 14 days of Phase B will not be counted.

All safety endpoints, except hypoglycemia, will be summarized regardless of the initiation of insulin glargine. Summaries of hypoglycemia endpoints will exclude data measured following the initiation of insulin glargine.

The analysis of safety results will follow a tiered approach (see Table 3-5). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) and PDLC in laboratory, vital signs that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse events and PDLC 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, and not a formal method for assessing the statistical significance of the between-group differences in adverse events and PDLCs.

Continuous measures such as changes from baseline in laboratory parameters 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.

Swallowability data collected from the Swallowing Ability Questionnaire and the Site Assessment of Swallowability Questionnaire will also be summarized by treatment group for this study alone.

Adverse events of symptomatic hypoglycemia and selected gastrointestinal (GI) adverse events (ie, nausea, vomiting, abdominal pain or discomfort [including abdominal pain, abdominal discomfort, stomach discomfort], diarrhea) are Tier 1 endpoints.

In addition, the AE categories consisting of the percentage of patients 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 will be considered Tier 2 endpoints. The p-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method [63], stratified by baseline metformin dose, and study (MK-0431A P170 and MK-0431A XR P289). The CMH weighting scheme will be used for stratification factors in the analysis. For continuous Tier 2 safety parameters, change from baseline or percent change from baseline will be analyzed using the same LDA models described in Section 3.5.5.1. Only 95% confidence interval for between-group difference will be provided.

The continuous endpoints of waist circumference and BMI will be considered Tier 2 safety parameters. Changes from baseline in laboratory parameters, vital signs and urine parameters that are not prespecified as Tier-1 or Tier-2 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format. Mean change from baseline over time will be plotted with the corresponding standard errors for endpoints designed to be collected at multiple time points post randomization.

Table 3-5 summarizes the analysis strategy for safety endpoints.

Table 3-5

Analysis Strategy for Safety Parameters

| Tier | Safety Endpoint | p-Value | 95% CI for Treatment Comparison | Descriptive Statistics |
|---|---|---|---|---|
| Tier 1 | Any AE of symptomatic hypoglycemia | X | X | X |
| | Selected (GI) events (diarrhea, nausea, abdominal pain/discomfort, vomiting) | X | X | X |
| Tier 2[†] | AE summary measures | | X | X |
| | Specific AEs[‡], SOCs, and PDLCs | | X | X |
| | Any AE of hypoglycemia | | X | X |
| | AEs of severe hypoglycemia<br>Any<br>Requiring medical assistance<br>Not requiring medical assistance | | X | X |
| | Change from baseline in BMI, and waist circumference | | X | X |
| Tier 3 | All endpoints listed after Tier 2 (above) that have incidence <4 patients in all treatment groups | | | X |
| | Additional hypoglycemia adverse event endpoints | | | X |
| | Change from baseline results (laboratory measurements and vital signs, urine microalbumin/creatinine ratio) | | | X |
| | Swallowing Ability Questionnaire (patient) | | | X |
| | Site Assessment of Swallowability Questionnaire | | | X |
| | Growth velocity and Tanner Staging | | | X |

[†] Endpoints listed here will qualify for Tier 2 only if the incidence is ≥4 patients in at least one of the treatment groups.
[‡] Among those endpoints not pre-specified as Tier 1 endpoints.
SAE=Serious adverse event; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

## Analysis of Hypoglycemia

Separate analyses of hypoglycemia will be performed for patients on a background insulin and for patients not on a background of insulin at screening.

The Tier 1 analysis for hypoglycemia will include the numbers and percentages of patients experiencing one or more adverse event of symptomatic hypoglycemia, regardless of fingerstick glucose value.

The Tier 2 analysis for hypoglycemia will include the numbers and percentages of patients experiencing one or more of each the following, regardless of fingerstick glucose value:

- Adverse events of hypoglycemia (symptomatic or asymptomatic)
- Adverse events of severe hypoglycemia, defined as adverse events of symptomatic hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained. These events will be further sub-classified as:

- Those that required medical assistance. Adverse events of symptomatic hypoglycemia that included a markedly depressed level of consciousness, loss of consciousness, or seizure will be classified as having required medical assistance, whether or not medical assistance was obtained

- Those that did not require medical assistance (ie, those episodes that required non-medical assistance to treat).

The Tier 3 summary of hypoglycemia will include the following, based on episodes classified by the investigator as adverse events:

- The numbers and percentages of patients with each of the following, overall and by lowest reported glucose category (<50 mg/dL [<2.8 mmol/L], ≤70 mg/dL [≤3.9 mmol/L], >70 mg/dL [>3.9 mmol/L], or unknown). A patient's lowest glucose category will be classified as unknown only if no glucose measurements are available for that patient.

  1. any episodes (symptomatic or asymptomatic)
  2. symptomatic episodes
  3. asymptomatic episodes

- The numbers and percentages of patients with episodes having precipitating factors, overall and separately by factor

- The number of episodes per patient

- The number of each of the following (summed across all patients). The overall summary will include an indication of whether precipitating factors were present.

  1. all episodes (symptomatic or asymptomatic)
  2. symptomatic episodes
  3. asymptomatic episodes

Exposure-adjusted incidence rates (ie, number of patients with ≥1 event, per 100 patient-years) may also be provided for selected endpoints defined above.

A summary of patients with episodes that were reported on the hypoglycemia assessment (HA) eCRF but were not classified by the investigator as adverse events will also be provided. If a substantial number of patients had episodes that were not classified as adverse events, then additional summaries may be provided for the Tier 3 endpoints above, including all episodes reported on the HA eCRF (ie, not restricted to adverse events). It is expected that all symptomatic hypoglycemia episodes will be classified by the investigator as adverse events and, thus, that any episodes that are not classified as adverse events will be asymptomatic episodes.

#### 3.5.5.3 Summaries of Baseline Characteristics and Demographics

Summaries will be provided based on the pooled data from both studies, MK-0431A XR P289 and MK-0431A P170, as well as on P289 alone. The comparability of the treatment groups at baseline for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical tests will be performed on these characteristics. The number and percentage of patients screened, randomized, the primary reasons for screen failure, and the primary reason for discontinuation will be displayed. Medical history and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. In addition, 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, standard deviation [SD], median, range and proportion will be provided.

- Continuous baseline demographic variables: age (years), weight (kg), height (cm), body mass index (BMI; $kg/m^2$), and BMI percentile for age and sex.
- Categorical baseline demographic variables: gender (male, female), and race (White, Black, Asian or Other), ethnicity (Hispanic/Latino or not)
- Baseline A1C, and distribution of A1C at baseline (A1C levels <8%, ≥8% and <9%, ≥9%)
- Baseline FPG
- Metformin dose level at **Visit 1** (<1500 mg, 1500 mg, >1500 mg)
- Time since diagnosis of diabetes mellitus (> or ≤1 year)
- Baseline substance use (tobacco/alcohol)
- Insulin use at screening (yes/no)

### 3.5.6 Multiplicity

There is a single efficacy hypothesis for one primary endpoint, change from baseline in A1C at **Week 20**, consisting of a comparison of 2 treatments. Therefore, no multiplicity adjustment is necessary to control the overall Type I error at 0.05 (2-sided) for efficacy hypotheses.

### 3.5.7 Sample Size and Power Calculations

#### 3.5.7.1 Sample Size and Power for Efficacy Analyses

The sample size for this study is expected to be at least 90 patients, but no more than 110 patients, and the sample size for P170 base is expected to be at least 120 patients, but no more than 140 patients. Power calculations are based on the minimum number of expected patients from both studies.

Approximately 105 patients (pooling patients from MK-0431A XR P289 and MK-0431A P170) will be randomized to each of the treatment groups (MK-0431A and MK-0431A XR versus metformin IR/XR). A sample size of 105 patients per treatment group will be equivalent to an effective sample size of approximately 92 per treatment at **Week 20** in the power calculation for the primary hypothesis test using the cLDA model in the FAS population. An effective sample size of 92 per treatment will provide 86% (96%) power to detect a between-group difference of 0.5% (0.6%) in A1C reduction at **Week 20** assuming the conditional standard deviation is 1.1%. The half-width of the 95% CI is expected to be 0.35%. These calculations were based upon the following assumptions:

- Cumulative attrition rates at Weeks 6, 12, and 20 are 0.10, 0.15, and 0.20, respectively
- A conditional correlation matrix at Weeks 6, 12, and 20 is

$$\begin{pmatrix} 1 & 0.87 & 0.74 \\ 0.87 & 1 & 0.93 \\ 0.74 & 0.93 & 1 \end{pmatrix}$$

The correlation matrix assumptions above are based on data from MK-0431 P036.

Table 3-6 shows the power for succeeding in the test of the primary hypothesis of the combined studies, for two treatment differences (0.5% and 0.6%) and standard deviations of 1.1 of change from baseline of A1C, using $\alpha$=0.05 (two-sided) with t-statistics. Previously observed between-group differences (sitagliptin minus placebo) in change from baseline in A1C in adults for metformin add-on studies range from -0.51 to -1.02% after 18 to 24 weeks of treatment. The observed treatment differences in adults for metformin add-on studies with the similar A1C entry criteria as the current study ranges from -0.51 to -0.65%. Therefore, the power calculations are provided at treatment difference 0.5% or 0.6%. The observed standard deviation in adults for metformin add-on studies with the similar A1C entry criteria ranges from 0.65 to 1.09%. Unpublished internal analyses suggest that the SD may be higher in a younger population. Therefore, the assumed SD for this study is 1.1% for A1C change from baseline.

Table 3-6

Power for Superiority in Change from Baseline in A1C (%)
92 Evaluable Patients Per Group and $\alpha$ = 0.05 (two-sided)

| Difference (%) | Standard Deviation (%) | Power (%) |
|---|---|---|
| 0.6 | 1.1 | 96% |
| 0.5 | 1.1 | 86% |

It is anticipated that approximately 50 patients will be exposed to MK-0431A XR (from MK-0431A XR P289, Phase A+B) or MK-0431A (from MK-0431A P170 base and extension studies) for 54 weeks.

### 3.5.7.2 Sample Size and Power for Safety Analyses

If no adverse events are observed in a treatment group from pooling data of MK-0431A XR P289 and MK-0431A P170 in which 105 patients are enrolled in the treatment group, the upper bound of the 95% confidence interval for the within-group incidence rate is 3.4 %.

### 3.5.8 Subgroup Analyses

To assess whether the treatment effect at **Week 20** is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables by pooling MK-0431A XR P289 and MK-0431A P170 with a minimum of 8 patients per treatment group in each subgroup:

- Baseline A1C: ≥ or < median
- Gender
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age: ≤14 or >14
- Metformin dose level at **Visit 1**: <1500 mg, 1500 mg, or >1500 mg
- Baseline BMI percentile: ≥ or <median
- Time since diagnosis of diabetes at baseline: > or ≤ 1 year

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. The RMANCOVA model will adjust for baseline value for A1C, baseline metformin dose (<1500 mg, 1500 mg, or >1500 mg), subgroup, study, insulin use at screening (yes/no), and treatment-by-subgroup interaction for all subgroups listed above except the background insulin therapy. For the analysis of background insulin therapy, the term of insulin use at screening (yes/no) will be removed from the RMANCOVA model. However, for the analysis of other subgroups, the term for insulin use at screening will be eliminated if necessary due to sparse cells. In the analysis model, 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. For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once. Treatment effects and nominal 95% confidence intervals 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 trial 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.

### 3.5.9 Interim Analyses

No interim analyses of efficacy are planned for this trial. The external DMC (see Section 3.4.2.2) will monitor interim data to ensure both patient safety and continued ethical integrity of the trial. Analyses of efficacy data from Phase A will not be conducted until the final database (including data through Week 54) is unblinded.

### 3.5.10 Compliance (Medication Adherence)

The computation of compliance will be based on the study medication case report form from P289 alone and the pooled population from MK-0431A XR P289 and MK-0431A P170. A day within the Double-blind Treatment Period will be considered a compliant day if the patient reports taking the required number of tablets encompassing both the assigned treatment(s) and any matching placebo tablets defined as follows:

For P289 alone:

1) MK-0431A XR or matching placebo: 2 tablets

2) Metformin XR or matching placebo: 2 tablets

For the pooled population:

1) MK-0431A (IR or XR) or matching placebo: 2 tablets

2) Metformin (IR or XR) or matching placebo: 2 tablets

If the study medication eCRF indicates general compliance problems with any double-blinded therapy, the patient will be considered non-compliant for that day regardless of the number of tablets for the assigned treatment(s) and any matching placebo reported.

For a patient who is followed for the entire study period, the "Number of Days in Double-blind Treatment Period" is the total number of days from the first dose of double-blind study medication to the last scheduled day for treatment administration for that patient. For a patient who discontinues from the study prematurely, the "Number of Days in Double-blind Treatment Period" is the total number of days from the first dose of double-blind study medication to the date of the last dose of study medication. The “Number of Days in the Study” is the total number of days from Day 1 to the day of study completion or study discontinuation.

For each patient, the compliance rate, based on time until study medication discontinuation, and the adherence rate, based on time until study discontinuation, will be calculated, using the following formula

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

$$\text{Adherence rate (\%)} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Study}} \times 100.$$

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

### 3.5.11 Extent of Exposure

The extent of exposure to 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 (sitagliptin and placebo) from the pooled studies MK-0431A XR P289 and MK-0431A P170, and from P289 alone.

## 3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

### 3.6.1 Patients and Replacement Information

Clinical supplies will be packaged to support randomization of up to approximately 110 patients. Randomized patients who discontinue study medication will not be replaced.

Clinical supplies will be packaged according to a component schedule generated by the SPONSOR.

### 3.6.2 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-7.

Table 3-7

Product Descriptions

| Product Name & Potency | Dosage Form | Comments |
|---|---|---|
| MRT[1] MK-0431A 50 mg / 500 mg | Tablet | Protect from moisture |
| MRT MK-0431A 50 mg / 500 mg Placebo | Tablet | Protect from moisture |
| MRT MK-0431A 50 mg / 1000 mg | Tablet | Protect from moisture |
| MRT MK-0431A 50 mg / 1000 mg Placebo | Tablet | Protect from moisture |
| Metformin XR 1000 mg | Tablet | N/A |
| Metformin XR 1000 mg Placebo | Tablet | N/A |
| Metformin XR 500 mg | Tablet | N/A |
| Metformin XR 500 mg Placebo | Tablet | N/A |
| [1]Modified release tablet | | |

All placebos will be created by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in the image of the active product.

Other clinical supplies, such as open-label insulin and insulin glargine will be supplied by the investigator or by the site as needed. The investigator or designee will record the lot number, expiration date, and drug dispensed.

### 3.6.3 Primary Packaging and Labeling Information

Supplies will be packaged in HDPE bottles as described in Table 3-8 below.

Table 3-8

Packaging of Clinical Supplies

| Interval ID/ Container ID | Product Name & Potency | Fill Count | Dosing Instructions |
|---|---|---|---|
| A | MK-0431A 50 mg/ 500 mg Placebo | 28 | Once daily with a meal, preferably in the evening. |
| B | MK-0431A 50 mg / 1000 mg Placebo | 28 | Once daily with a meal, preferably in the evening |
| C | Metformin XR 500 mg | 28 | Once daily with a meal, preferably in the evening |
| D | Metformin XR 1000 mg | 28 | Once daily with a meal, preferably in the evening |
| E | MK-0431A 50 mg / 500 mg or Placebo | 35 | Once daily with a meal, preferably in the evening |
| F | MK-0431A 50 mg / 1000 mg or Placebo | 35 | Once daily with a meal, preferably in the evening |
| G | Metformin XR 1000 mg or Placebo | 35 | Once daily with a meal, preferably in the evening |
| H | Metformin XR 500 mg or Placebo | 35 | Once daily with a meal, preferably in the evening |

Container label text may include the following:

| | |
|---|---|
| • Packaging Control #/ Packaging Lot ID #<br>• Space for baseline #<br>• Randomization # or Component ID #<br>• Space for Randomization #<br>• Fill Count & Dosage Form<br>• Container ID<br>• Interval ID<br>• Re-evaluation date | • Dosing Instructions<br>• Storage Conditions<br>• Compound ID - Protocol #<br>• Country regulatory requirements<br>• SPONSOR address (If applicable)<br>• Translation Key (If applicable) |

### 3.6.4 Clinical Supplies Disclosure

**IVRS studies**

The IVRS should be used in order to unblind patients and to unmask drug identity. The SPONSOR will not provide disclosure envelope with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the clinical monitor. Any unblinding that occurs at the site must be documented.

### 3.6.5 Storage and Handling Requirements

The storage conditions will be indicated on the label.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

### 3.6.6 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (ie, when counting returns). The CRA should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

U.S. sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping.

For sites outside of the United States, the local country SPONSOR personnel will provide appropriate documentation that needs to be completed for drug accountability.

### 3.6.7 Comparator Statement

At the close of the study after unblinding, a letter is to be sent by the investigator to those patients who received placebos in the image of the competitor's product to provide the following advice:

"You have participated in a study conducted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This is to advise you that you were among those who received a look-alike tablet created by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., to resemble the drug GLUCOPHAGE XR (Metformin XR) as much as possible. You did not receive the active drug GLUCOPHAGE XR (Metformin XR) as manufactured by Merck KGaA and its Subsidiaries".

## 3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

## 3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

# 4. ADMINISTRATIVE AND REGULATORY DETAILS

## 4.1 CONFIDENTIALITY

### 4.1.1 Confidentiality of Data

***For Studies Conducted Under the U.S. IND***

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

***For All Studies***

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, 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 study 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.

### 4.1.2 Confidentiality of Patient Records

***For All Studies***

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

***For Studies Conducted Under the U.S. IND***

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time ("HIPAA").

### 4.1.3 Confidentiality of Investigator Information

***For All Studies***

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

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

***For Multicenter Studies***

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

## 4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/ Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

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

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (eg, thorough understanding of clinical trial methods, appropriate enrollment of patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study 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 site's IRB/IEC.

## 4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to

subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## 4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

## 4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

## 4.6 PUBLICATIONS

This study 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 study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), 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.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single 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 should meet conditions 1, 2, and 3. Significant contributions to study 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 study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend 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 study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

# 5. LIST OF REFERENCES

1. Rapaport R, Silverstein JH, Garzarella L, Rosenbloom AL. Type 1 and type 2 diabetes mellitus in childhood in the United States: practice patterns by pediatric endocrinologists. J Pediatr Endocrinol Metab 2004;17:871-7.

2. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 1996;128(5, Part 1):608-15.

3. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, et al. Type 2 diabetes among north American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 2000;136(5):664-72.

4. Pavkov ME, Hanson RL, Knowler WC, Bennett PH, Krakoff J, Nelson RG. Changing patterns of type 2 diabetes incidence among Pima Indians. Diabetes Care 2007; 30(7):1758-63.

5. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ. Increasing prevalence of type II diabetes in American Indian children. Diabetologia 1998; 41:904-10.

6. Moore KR, Harwell TS, McDowall JM, Helgerson SD, Gohdes D. Three-year prevalence and incidence of diabetes among American Indian youth in Montana and Wyoming, 1999 to 2001. J Pediatr 2003;143:368-71.

7. SEARCH for Diabetes in Youth Study Group. The burden of diabetes mellitus among US youth: prevalence estimates from the search for diabetes in youth study. Pediatrics 2006;118(4):1510-8.

8. SEARCH. Incidence of diabetes in youth in the United States. JAMA 2007;297:2716-24.

9. Lobstein T, Jackson-Leach R. Estimated burden of paediatric obesity and co-morbidities in Europe. Part 2: numbers of children with indicators of obesity-related disease. Int J Pediatric Obesity 2006;1:33-41.

10. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005;146(5):693-700.

11. Haines L, Wan KC, Lynn R, Barrett TG, Shield JPH. Rising incidence of type 2 diabetes in children in the U.K. Diabetes Care 2007;30:1097-101.

12. Bell RA, Mayer-Davis EJ, Beyer JW, D'Agostino RB Jr, Lawrence JM, Linder B, et al. Diabetes in Non-Hispanic White youth - Prevalence, incidence, and clinical characteristics: the SEARCH for diabetes in youth study. Diabetes Care 2009; 32(Suppl 2):S102-S111.

13. Dabelea D, DeGroat J, Sorrelman C, Glass M, Percy CA, Avery C, et al. Diabetes in Navajo youth prevalence, incidence, and clinical characteristics: the SEARCH for diabetes in youth study. Diabetes Care 2009;32(Suppl 2):S141-S147.

14. Invitti C, Guzzaloni G, Gilardini L, Morabito F, Viberti G. Prevalence and concomitants of glucose intolerance in European obese children and adolescents. Diabetes Care 2003;26(1):118-24.

15. Lawrence JM, Mayer-Davis EJ, Reynolds K, Beyer J, Pettitt DJ, D'Agostino RBJr, et al. Diabetes in Hispanic American youth prevalence, incidence, demographics, and clinical characteristics: the SEARCH for diabetes in youth study. Diabetes Care 2009;32(Suppl 2):S123-S132.

16. Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Dolan LM, Dabelea D, et al. Type 1 and Type 2 Diabetes in Asian and Pacific Islander - U.S. youth The SEARCH for diabetes in youth study. Diabetes Care 2009;32(Suppl 2):S133-S140.

17. Mayer-Davis EJ, Beyer JW, Bell RA, Dabelea D, D'Agostino RB Jr, Imperatore G, et al. Diabetes in African American youth prevalence, incidence, and clinical characteristics: the SEARCH for diabetes in youth study. Diabetes Care 2009; 32(Suppl 2):S112-S122.

18. Open database: Supplemental Tables. Diabetes Care. c2009. 2009.

19. Reinehr T, Andler W, Kapellen T, Kiess W, Richter-Unruh A, Schönau E, et al. Clinical characteristics of type 2 diabetes mellitus in overweight European Caucasian adolescents. Exp Clin Endocrinol Diabetes 2005;113:167-70.

20. Weigand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Grüters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity – a problem that is no longer restricted to minority groups. Eur J Endocrinol 2004;151:199-206.

21. Harron KL, Feltbower RG, McKinney PA, Bodansky HJ, Campbell FM, Parslow RC. Rising rates of all types of diabetes in south Asian and non-south Asian children and young people aged 0-29 years in West Yorkshire, U.K., 1991-2006. Diabetes Care 2011;34(3):652-4.

22. Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. Pediatrics 2005;116:473-80.

23. Lee S, Gungor N, Bacha F, Arslanian SA. Racial differences in adiponectin in youth. Diabetes Care 2006;29(1):51-6.

24. Jacobson-Dickman E, Levitsky L. Oral agents in managing diabetes mellitus in children and adolescents. Pediatr Clin N Am 2005;52:1689-703.

25. American Diabetes Association. Type 2 diabetes in children and adolescents. Diabetes Care 2000;23(3):381-9.

26. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and risk of cardiovascular disease. J Clin Endocrinol Metab 2001;86(1):66-71.

27. Desai M, Gayle D, Babu J, Ross MG. Programmed obesity in intrauterine growth-restricted newborns: modulation by newborn nutrition. Am J Physiol Regul Interg Comp Physiol 2005;288:R91-R96.

28. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 1999;22(6):944-50.

29. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667-87.

30. Weiss R, Dziura JD, Burgert TS, Taksali SE, Tamborlane WV, Caprio S. Ethnic differences in beta cell adaptation to insulin resistance in obese children and adolescents. Diabetologia 2006;49:571-9.

31. Caprio S. Insulin resistance in childhood obesity. J Pediatr Endocrinol Metab 2002; 15:487-92.

32. Druet C, Tubiana-Rufi N, Chevenne D, Rigal O, Polak M, Levy-Marchal C. Characterization of insulin secretion and resistance in type 2 diabetes of adolescents. J Clin Endocrinol Metab 2006;91(2):401-4.

33. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. β-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005; 54:1735-43.

34. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. Diabetes Care 2005;28(4):902-9.

35. Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. Diabetes Care 1999;22(2):345-54.

36. Bogdanovic R. Diabetic nephropathy in children and adolescents. Pediatr Nephorol 2008;23:507-25.

37. Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC. Incidence of Retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. Diabetes Care 2003;26(1):76-81.

38. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006;296(4):421-6.

39. Eppens MC, Vraig ME, Cusumano J, Hing S, Chan AKF, Howard NJ, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006;29(6):1300-6.

40. Petitti DB, Imperatore G, Palla SL, Daniels SR, Dolan LM, Kershnar AK, et al. Serum lipids and glucose control. Arch Pediatr Adolesc Med 2007;161:159-65.

41. Sanders BH, Lubsch LM, West DS. Prevalence and treatment of metabolic syndrome in adolescents with type 2 diabetes. Ann Phamacother 2006;40:1517-21.

42. Gungor N, Thompson T, Tyrrell KS, Janosky J, Arslanian S. Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. Diabetes Care 2005; 28(5):1119-221.

43. DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353(25):2643-53.

44. Urakami T. How should we treat type 2 diabetes in youth? Pediatric Endocrinology Reviews 2005;3(1):33-9.

45. Pinhas-Hamiel O, Zeitler P. Clinical presentation and treatment of type 2 diabetes in children. Ped Diabetes 2007;8(Suppl 9):16-27.

46. Bobo N, Evert A, Gallivan J, Imperatore G, Kelly J, Linder B, et al. Commentaries: An update on type 2 diabetes in youth from the National Diabetes Education Program. Pediatrics 2004;114(1):259-63.

47. Canadian Diabetes Association. Type 2 diabetes in children and adolescents. Clin Pract Guidelines 2003:S91-S93.

48. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes. Diabetes Care 2002;25:89-94.

49. Kadmon, PM, Gruppuso PA. Glycemic control with metformin or insulin in adolescents with type 2 diabetes mellitus. J Pediatr Endocrinol Metab 2004;17:1185-1193

50. Farrah SE, Wals KT, Friedman IB, Pisacano MA, DiMartino-Nardi J. Prevalence of retinopathy and microalbuminuria in pediatric type 2 diabetes mellitus. J Pediatr Endocrinol Metab 2006;19:937-942

51. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, et al. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet 2003;362: 951-7.

52. Yeckel CW, Taksali SE, Dziura J, Weiss R, Burgert TS, Sherwin RS, et al. The normal glucose tolerance continuum in obese youth: evidence for impairment in β-cell function independent of insulin resistance. J Clin Endocrinol Metab 2005; 90(2):747-54.

53. Zuhri-Yafi M, Brosnan PG, Hardin DS. Treatment of type 2 diabetes mellitus in children and adolescents. J Pediatr Endocrinol Metab 2002;15(Suppl 1):541-6.

54. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterol 2007;132:2131-57.

55. Silverstein JH, Rosenbloom AL. Treatment of type 2 diabetes mellitus in children and adolescents. J Pediatr Endocrinol Metab 2000;13:1403-9.

56. Kaufman FR. Type 2 diabetes mellitus in children and youth: a new epidemic*. J Pediatr Endocrinol Metab 2002;15:737-44.

57. Klingensmith G, Connor CG, Ruedy K, Beck RW, Kollman C, Haro H, et al. Presentation of youth with type 2 diabetes in the pediatric diabetes consortium. Pediatric Diabetes 2016;17:266-273

58. Ramachandran A, Riddle MC, Kabali C, Gerstein HC on behalf of the ORIGIN investigators. Relationship between A1C and fasting plasma glucose in dysglycemic or type 2 diabetes. An analysis of baseline data from the ORIGIN trial. 2012;35:749-753.

59. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia with insulin glargine. A meta-analysis comparing insulin glargine with human NPH in type 2 diabetes. Diabetes Care 2005;28:950-55.

60. van'T Riet E, Alssema M, Rijkelijkhuizen JM, Kostense PJ, Nijpels G, Dekker JM. Relationship between A1C and glucose levels in the general Danish population. The new Hoorn study. Diabetes Care;2010:33:61-66.

61. Hodges JL, Lehmann EL. The efficiency of some nonparametric competitors of the ttest. Ann Math Statist 1956;27:324-35.

62. De Onis M Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World Health Organization 2007;85:660-667.

63. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report in the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatr 2004;114(2):555-76.

# 6. APPENDICES

## 6.1 BMI-FOR-AGE CHARTS

Sites should follow their approved country-specific BMI-for-age percentile charts, if available (eg, sites within the United States will refer to the Centers for Disease Control charts). If an approved BMI-for-age percentile chart is not available, refer to the World Health Organization charts shown in Figures 1 and 2 below.

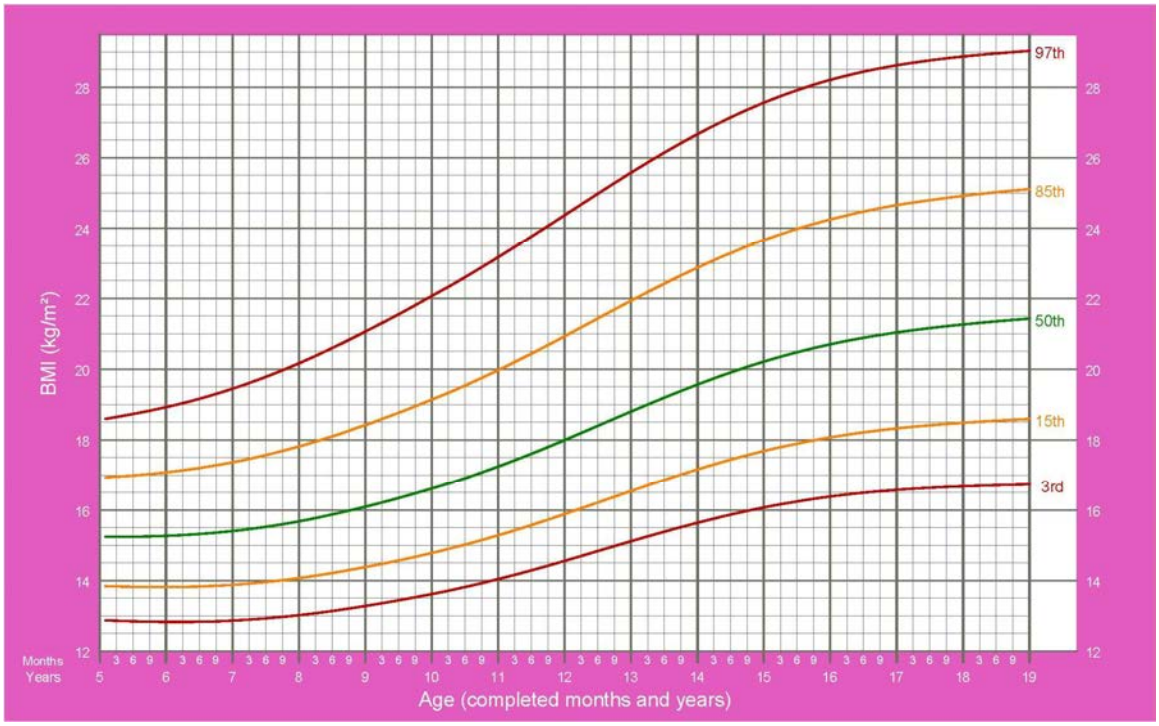
**Instructions for obtaining the body mass index-for-age percentile:**

- Find the child's age on the horizontal axis
- Find the BMI measurement on the vertical axis.
- The body mass index-for-age percentile will be at the intersection of the child's age and BMI measurement.

World Health Organization

Figure 1

BMI-for-Age—Girls, 5 to 19 Years (Percentiles)



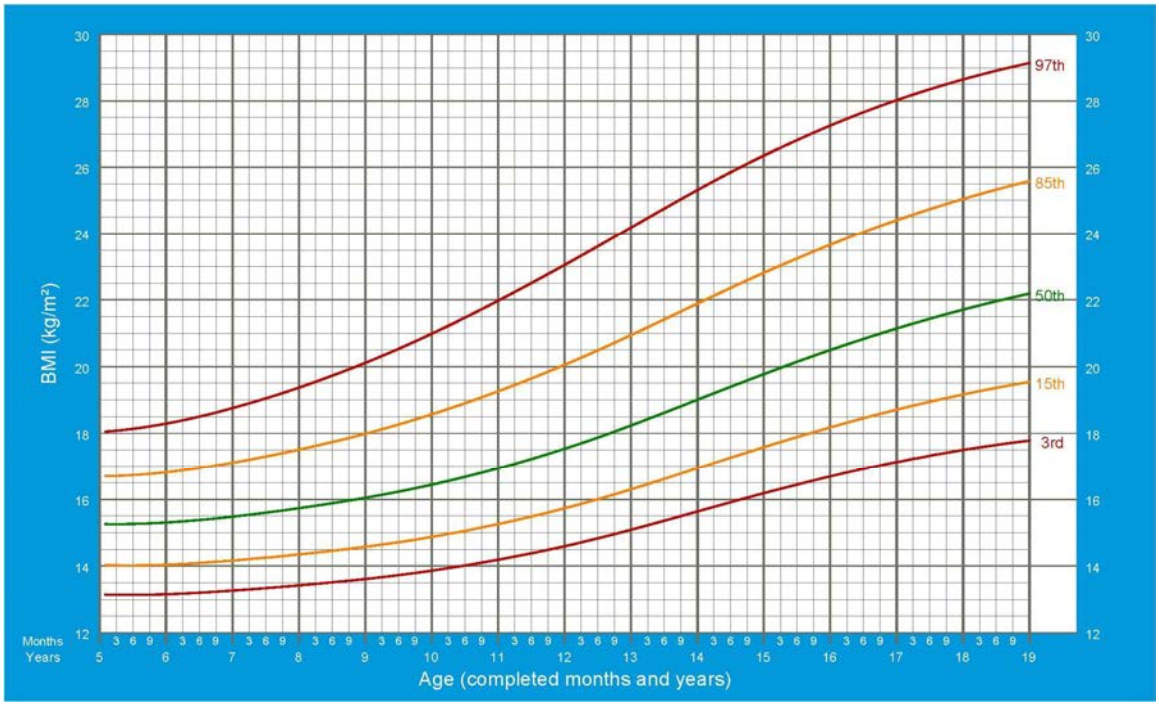

2007 WHO Reference

Ref: [62]

World Health Organization

Figure 2

BMI-for-Age—Boys, 5 to 19 Years (Percentiles)




2007 WHO Reference

Ref: [62]

## 6.2 BLOOD PRESSURE TABLE FOR GENDER/AGE/HEIGHT FOR BOYS AGE 10-17

| Years of Age (Years) | Blood Pressure Percentile | Systolic Blood Pressure by Percentile of Height (mmHg) | | | | | | | Diastolic Blood Pressure by Percentile of Height (mmHg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 10 | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 99th | 122 | 123 | 125 | 127 | 128 | 130 | 130 | 85 | 86 | 86 | 88 | 88 | 89 | 90 |
| 11 | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 124 | 125 | 127 | 129 | 130 | 132 | 132 | 86 | 86 | 87 | 88 | 89 | 90 | 90 |
| 12 | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 99th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 86 | 87 | 88 | 89 | 90 | 90 | 91 |
| 13 | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 130 | 131 | 133 | 135 | 136 | 137 | 87 | 87 | 88 | 89 | 90 | 91 | 91 |
| 14 | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 87 | 88 | 89 | 90 | 91 | 92 | 92 |
| 15 | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 134 | 135 | 136 | 138 | 140 | 142 | 142 | 88 | 89 | 90 | 91 | 92 | 93 | 93 |
| 16 | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| | 99th | 136 | 137 | 139 | 141 | 143 | 144 | 145 | 90 | 90 | 91 | 92 | 93 | 94 | 94 |
| 17 | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |
| | 99th | 139 | 140 | 141 | 143 | 145 | 146 | 147 | 92 | 93 | 93 | 94 | 95 | 96 | 97 |
| Note: country-specific Blood Pressure norms may be used; otherwise, these guidelines should be used. | | | | | | | | | | | | | | | |

Ref: [63]

## 6.3 BLOOD PRESSURE TABLE BY GENDER/AGE/HEIGHT FOR GIRLS AGE 10-17

| Years of Age (Years) | Blood Pressure Percentile | Systolic Blood Pressure by Percentile of Height (mmHg) | | | | | | | Diastolic Blood Pressure by Percentile of Height (mmHg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 10 | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 99th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 84 | 84 | 85 | 86 | 86 | 87 | 88 |
| 11 | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 125 | 125 | 126 | 128 | 129 | 130 | 131 | 85 | 85 | 86 | 87 | 87 | 88 | 89 |
| 12 | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 127 | 127 | 128 | 130 | 131 | 132 | 133 | 86 | 86 | 87 | 88 | 88 | 89 | 90 |
| 13 | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 129 | 130 | 132 | 133 | 134 | 135 | 87 | 87 | 88 | 89 | 89 | 90 | 91 |
| 14 | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 130 | 131 | 132 | 133 | 135 | 136 | 136 | 88 | 88 | 89 | 90 | 90 | 91 | 92 |
| +15 | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 131 | 132 | 133 | 134 | 136 | 137 | 138 | 89 | 89 | 90 | 91 | 91 | 92 | 93 |
| 16 | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 132 | 133 | 134 | 135 | 137 | 138 | 139 | 90 | 90 | 90 | 91 | 92 | 93 | 93 |
| 17 | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 133 | 133 | 134 | 136 | 137 | 138 | 139 | 90 | 90 | 91 | 91 | 92 | 93 | 93 |

Note: country-specific Blood Pressure norms may be used; otherwise, these guidelines should be used.

Ref: [63]

## 6.4 STANDARD OPERATING PROCEDURES FOR LIVER ENZYME ELEVATIONS

Every increase in ALT, and/or AST, above the limits described in the protocol is defined as clinically significant (ie, 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 (for age and sex),** *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 (see Section 3.4.6.2).* Alkaline phosphatase reference ranges for age and sex are listed below.

Alkaline Phosphatase Reference Ranges by Age and Sex [1]

| Age Range (years) | Reference Ranges for Females (U/L) | Reference Ranges for Males (U/L) |
|---|---|---|
| 10 - 12 | 51 - 332 | 42 – 362 |
| 13 - 15 | 50 - 162 | 74 - 390 |
| 16 - 17 | 47 - 119 | 52 - 171 |
| ≥18 | 30 – 115 | 43 - 115 |

[1] If testing is performed by a local laboratory, then reference ranges from that local laboratory should be used.

**<u>For patients with ALT or AST increases (either ALT or AST ≥3-times the ULN)</u>** but who <u>*do not*</u> 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 (see Section 3.4.6.2).

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

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 (eg, 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); and (c) Hepatitis C (antibody).

**B. <u>Actions</u>**

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 study medication 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 study medication therapy interrupted immediately.

Once interrupted, reinstatement of therapy must occur only after consultation with a Merck Clinical Monitor.

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 Merck Clinical Monitor 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 Merck Clinical Monitor.

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.

## 6.5 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

### 6.5.1 Scope of Future Biomedical Research

The DNA, serum, and plasma, specimens collected in the current trial will be used to study various causes for how patients may respond to a drug. The DNA, serum and plasma specimens will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

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, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

### 6.5.2 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 response.[2]

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 6.5.3 Summary of Procedures for Future Biomedical Research

a. Patients for Enrollment

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

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[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.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all patients or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the patients on **Visit 1**. If delayed, present consent at next possible Patient Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Patients are not required to participate in the Future Biomedical Research sub-study in order to participate in the main trial.

Consent forms signed by the patient will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Patients who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

### 6.5.4 Confidential Patient 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 patient clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing patient characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

At the clinical 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 patient identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

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

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

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

### 6.5.5 Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (eg, a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

### 6.5.6 Withdrawal From Future Biomedical Research

Patients may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Patients may withdraw consent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact MERCK using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. Subsequently, the patient's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MERCK to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the patient 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 study data and results. No new analyses would be generated after the request is received.

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

### 6.5.7 Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency 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 site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

### 6.5.8 Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (eg, ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-study will not be used for any other purpose.

### 6.5.9 Reporting of Future Biomedical Research Data to Patients

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

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

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

### 6.5.10 Gender, Ethnicity, and Minorities

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

### 6.5.11 Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the patient 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 study.

Merck has developed strict security, policies and procedures to address patient 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.

It is necessary for patient-related data (ie, ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be reassociated to double coded specimens at the time of data analysis. These patient data will be kept in a separate, secure Merck database, and all specimens will be stripped of patient identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual patient.

### 6.5.12 Self-Reported Ethnicity

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

### 6.5.13 Questions

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

## 6.6 BLOOD PRESSURE AND ANTHROPOMETRIC MEASUREMENTS

**Blood Pressure**

Ensure patient has not had any caffeine or tobacco within 30 minutes. BP should be measured in the sitting position. The patient will remain in the sitting position for at least 5 minutes before any blood pressure readings are recorded. The same arm, preferably the non-dominant arm, should be used for all blood pressure determinations at each visit. **Systolic and diastolic BP will be determined by obtaining two measurements, 1 to 2 minutes apart. The consecutive systolic BP readings should be within 5 mm Hg of each other and the consecutive diastolic BP readings should be within 5 mm Hg of each other. The final BP measurement must be recorded.**

**Body Mass Index**

The Body Mass Index will be calculated using the following equation:

$$\text{BMI} = \frac{\text{Body weight in Kilograms}}{(\text{Height in meters})^2}$$

Note:
1 kg = 2.2 pounds
1 m = 3.28 feet

**Weight**

Weight will be taken on the same calibrated digital scale throughout the study, after voiding and while wearing only a gown and underwear (no street clothes, no shoes or socks). Patients should step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. **Patients should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.**

**Weight (to the nearest 0.2 kg) will be measured after voiding. Measurements will be collected until 2 consecutive measurements do not differ by more than 0.2 kg from each other. The final weight measurement must be recorded. The same digital scale must be used throughout the study.**

The SPONSOR will provide a scale and/or 10-kg weight to study sites that do not have one. **The scale must be calibrated according to the manufacturer's instructions at set-up and when it is transferred or moved. Additional calibrations should be performed according to the manufacturer's instructions.**

**Height**

**Standing height will be measured without shoes using a stadiometer.**

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows should be moved or removed from the top of the head before the measurement is taken.

A fixed stadiometer with vertical backboard, fixed floorboard and movable headboard must be used. Patients should stand with the heels of their feet against the vertical backboard with feet pointing outward at approximately a 60-degree angle. Body weight should be distributed evenly with both feet flat on the floor. The examiner should check several contact points with the vertical backboard, including heels, buttocks, shoulder blades, and the back of the head. This may be difficult for patients with certain body shapes. However, the head should be in the Frankfort plane (an imaginary line from the ear canal to just below the lower orbit of the eye should be parallel to the floor). Patient should be looking straight ahead, and be asked to take a deep breath and stand tall. Once the patient is positioned, the headboard will be placed on top of the head, with sufficient pressure to compress the hair. The measurement is recorded in cm, to the nearest mm. **Measurements will be collected until 3 consecutive measurements do not differ by more than 1.0 cm from each other. The final height measurement must be recorded.** Some patients may have physical conditions that may limit the ability to measure height accurately (eg, kyphosis). In such cases, height should be measured to the best of the examiner's ability, a note should be made of the condition and measurements should be repeated in the same manner for the rest of study.

**The stadiometer must be calibrated when mounting it to the wall, and according to the manufacturer's instructions thereafter.**

**Waist Circumference**

**The tape measure used should be non-stretching, non-metallic, retractable tape.**

The tape is placed around the patient's trunk at the appropriate level for waist measurement. The tape's "zero line" is aligned alongside of the tape graduations on the Metric side of the tape. The zero end of the tape is held in the left hand above the remaining part of the tape held by the right hand. The measurement is read next to the tape's "zero line" and recorded in centimeters to the nearest millimeter.

Waist circumference will be measured according to the National Health and Nutrition Examination Survey (NHANES) III protocol. The measuring tapes may be provided by the Sponsor. **It is advisable that the patient's waist measurement be obtained by the same study personnel at each visit in order to provide consistency.** Waist circumference will be measured after voiding, in gown, underwear and socks but without shoes.

To define the level at which waist circumference is measured, a bony landmark is located and marked. The patient stands and the examiner, positioned at the right of the patient, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn using a black pen, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at the end of normal minimal respiration (in duplicate). **Measurements will be collected until two consecutive measurements do not differ by more than 1 cm.** The average of these two measurements will be reported.

## 6.7 LABORATORY EVALUATIONS

**Fasting plasma glucose (FPG) test (Visits 1, 3, 6, 9, Rescue, and Discontinuation)**

**Whole blood hemoglobin $A_{1c}$ (A1C) test (Visits 1, 3, 4, 5, 6, 7, 8, 9, Rescue, and Discontinuation)**

**Note:** Do not collect A1C at **Rescue or Discontinuation Visit**s if the visit occurs before **Visit 4/Week 6.**

**Fasting insulin and proinsulin tests (Visits 3, 6, Rescue, and Discontinuation)**

Do not collect samples for fasting serum insulin and proinsulin on patients on insulin (background, rescue [Phase A] or glycemic therapy [Phase B]).

**Fasting serum C-peptide test (Visit 1)**

Only obtained for patients with a diagnosis of T2DM < 2 years.
(In South Africa and India, C-peptide will be measured in all patients.)

**Diabetes Autoantibody Panel (Only for India--Visit 1)**

Glutamic acid decarboxylase 65- kDa autoantibody (GAD65-Ab)
Insulinoma-associated protein-2 autoantibody (IA2 Ab)

**Lipid Analyses (Visits 1, 3, 6, 9, Rescue, and Discontinuation)**

Total cholesterol
Triglycerides (TG)
HDL cholesterol
LDL cholesterol-calculated
Non-HDL cholesterol – calculated

**Hematology (Visits 1, 3, 5, 6, 7, 9, Rescue, and Discontinuation)**

Hemoglobin, hematocrit, and red blood cell count
Mean corpuscular hemoglobin concentration and mean corpuscular volume
White blood cell count and differential
Platelet count
Absolute neutrophil count

**Blood Chemistry (Visits 1, 3, 5, 6, 7, 9, Rescue, and Discontinuation)**

Serum sodium test
Serum potassium test
Serum chloride test
Serum bicarbonate test
Serum calcium test

Serum phosphorus test
Serum albumin test
Serum alkaline phosphatase test
Serum uric acid test
Total serum protein test
Serum alanine aminotransferase test (ALT)
Serum aspartate aminotransferase test (AST)
Serum creatine phosphokinase test (CPK)
Total serum bilirubin test
Serum blood urea nitrogen test
Serum creatinine test

**Urine Pregnancy Test (Visits 1, 3, 4, 5, 6, 7, 8, 9, Rescue, and Discontinuation)**
performed for all females at the investigator's site

Serum beta-human chorionic gonadotropin (β-hCG) test in all randomized patients with a positive urine pregnancy test.

**Dipstick Urinalysis (Visits 1, 3, 6, 9, Rescue, and Discontinuation)**

If dipstick urinalysis (midstream) is positive for blood, leukocyte esterase, nitrites, or protein, then a complete urinalysis (dipstick and microscopy) must be sent to the central laboratory. Dipstick urinalysis should not be performed if the patient is menstruating.

**Urine microalbumin/creatinine ratio (Visits 3, 6, 9, Rescue, and Discontinuation)**

This urine sample should not be collected if the patient is menstruating, has vigorously exercised within 24 hours, or had fever or an active infection within two days of the visit.

**Thyroid Function Test (Visit 1)**

Serum thyroid-stimulating hormone (TSH) test

**Future Biomedical Research (FBR) Samples (Visits 3, 6, 9, Rescue, and Discontinuation)**

Serum (SST) and Plasma (EDTA) Samples
Blood (DNA) for FBR **(Visit 3 only)**

## 6.8 MAPPING OF RELATIVE DAY RANGES TO WEEKS

The following rules will be used to map the relative day ranges to weeks for A1C, vitals, and laboratory parameters for summaries and analyses that are based on individual time points. If a patient has multiple observations within a day range, the observation that is closest to the target day (calculated as target week ×7) will be used in the analyses. For summaries and analyses that are not based on individual time points (eg, AEs and PDLCs), all results will be included without mapping to individual time points.

| Required Phase | Relative Day Range | Week |
|---|---|---|
| | ***Day Relative to Start of Trial***[†] | |
| Baseline/Treatment | Day ≤1 | 0 |
| A | 2≤ Day ≤63 | 6 |
| A | 64≤ Day ≤112 | 12 |
| A | Day ≥113 | 20 |
| | ***Day Relative to Start of Phase B***[‡] ***(Visit 6)*** | |
| B | Day ≤98 | 28 |
| B | 99≤ Day ≤189 | 40 |
| B | Day ≥190 | 54 |

[†] Start of Phase A is defined as first dose of Phase A study medication for all treated patients and the randomized day for patients who did not take any dose of study medication.
[‡] Start of Phase B is defined as first dose day of Phase B study medication or Visit 6 day for patients who entered Phase B off study medication.

The following rules will be used to map the relative day ranges to weeks for FPG, Tanner Staging, growth velocity, lipids, ECG, waist circumference, urine microalbumin/creatinine ratio, and insulin-related parameters.

| Required Phase | Relative Day Range | Week |
|---|---|---|
| | ***Day Relative to Start of Trial***[†] | |
| Baseline/Treatment | Day ≤1 | 0 |
| A | Day ≥70 | 20 |
| | ***Day Relative to Start of Phase B***[‡] ***(Visit 6)*** | |
| B | Day >119 | 54 |

[†] Start of Phase A is defined as first dose of Phase A study medication for all treated patients and the randomized day for patients who did not take any dose of study medication.
[‡] Start of Phase B is defined as first dose day of Phase B study medication or Visit 6 day for patients who entered Phase B off study medication.

For the additional analysis that includes data collected after discontinuation of study medication, the same day ranges will be applied, regardless of trial phase. If a patient does not have a **Week 20** visit, the **Week 20** date will be imputed as 140 days after randomization prior to applying the day ranges in Phase B for the additional data beyond **Week 20**.

## 6.9 PREDEFINED LIMITS OF CHANGE (PDLC)

The following predefined limits of change will be assessed in the statistical analysis, as described in Section 3.5.

| Laboratory Test | Predefined Limits of Change† Criterion | Categories Assessed for Each Criterion | |
|---|---|---|---|
| | | At Least One Value | Last On-Treatment Value |
| **Laboratory – Hematology** | | | |
| Hemoglobin (g/dL) | 1. Decrease ≥1.5 g/dL | N | Y |
| WBC Count ($10^3$/microL) | 1. Decrease ≥50% and value < LLN | Y | Y |
| | 2. Increase ≥20% and value > ULN | Y | Y |
| Neutrophil Count ($10^3$/microL) | 1. Decrease ≥20% and value < LLN | Y | Y |
| | 2. Increase ≥20% and value > ULN | Y | Y |
| Lymphocyte Count ($10^3$/microL) | 1. Decrease ≥20% and value < LLN | Y | Y |
| | 2. Increase ≥20% and value > ULN | Y | Y |
| Platelet Count ($10^3$/microL) | 1. Decrease ≥25% and value < LLN | Y | Y |
| | 2. Increase ≥100% and value > ULN | Y | Y |
| **Laboratory – Chemistry** | | | |
| BUN (mg/dL) | 1. Increase ≥50% and value > ULN | N | Y |
| Serum Creatinine (mg/dL) | 1. Increase ≥0.3 mg/dL | N | Y |
| Total Bilirubin (mg/dL) | 1. Value ≥2×ULN | Y | Y |
| AST (IU/L) | 1. Value ≥3×ULN | Y | Y |
| | 2. Value >5×ULN | Y | Y |
| | 3. Value >10×ULN | Y | Y |
| | 4. Value >20×ULN | Y | Y |
| ALT (IU/L) | 1. Value ≥3×ULN | Y | Y |
| | 2. Value >5×ULN | Y | Y |
| | 3. Value >10×ULN | Y | Y |
| | 4. Value >20×ULN | Y | Y |
| AST (IU/L) or ALT (IU/L) | 1. Value ≥3×ULN | Y | Y |
| | 2. Value >5×ULN | Y | Y |
| | 3. Value >10×ULN | Y | Y |
| | 4. Value >20×ULN | Y | Y |
| AST (IU/L) or ALT (IU/L)+ Total Bilirubin (mg/dL) | 1. ALT≥3×ULN or AST≥3×ULN with Bilirubin ≥2×ULN | Y | Y |
| Alkaline Phosphatase (IU/L) | 1. Value >1.5×ULN | Y | Y |
| Serum Uric Acid (mg/dL) | 1. Increase ≥50% and value > ULN | Y | Y |
| Serum Sodium (mEq/L) | 1. Decrease ≥10 mEq/L and value < LLN | N | Y |
| | 2. Increase ≥10 mEq/L and value > ULN | N | Y |
| Serum Potassium (mEq/L) | 1. Decrease ≥1.0 mEq/L and value < LLN | N | Y |
| | 2. Increase ≥1.0 mEq/L and value > ULN | N | Y |
| Serum Calcium (mg/dL) | 1. Increase ≥1.0 mg/dL and value > ULN | N | Y |
| | 2. Decrease ≥1.0 mg/dL and value < LLN | N | Y |

† Increases and decreases are relative to baseline.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, LLN = Lower limit of normal; ULN = Upper limit of normal; WBC = white blood cell.

## 6.10 CONSTRAINED LONGITUDINAL DATA ANALYSIS (CLDA) METHOD (WITH ADJUSTMENT FOR BASELINE VALUES) – TECHNICAL DETAILS FOR MODEL SPECIFICATION, ASSUMPTIONS, AND SAS IMPLEMENTATION CODES

**Model**

Let $Y_{ijt}$ be the response for patient $i$, with treatment assignment $j$, at time $t$. The marginal mean responses of the cLDA model can be formulated as

$$E(Y_{ij0}) = \gamma_0, \quad t = 0,$$

and

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt}, \quad j = 0,1, \quad t = 1,2,...,T.$$

The mean response $\gamma_0$ at $t$=0 is constrained to be the same for both treatment groups due to randomization. The effect $\gamma_{jt}$ denotes the change from baseline for treatment $j$ at time $t$. The cLDA model assumes that baseline and post-baseline values have a joint multivariate normal distribution. An unstructured covariance matrix can be specified in the mixed model to account for within patient correlation at times $t \geq 0$ (including baseline).

The treatment difference for the mean change from baseline at time point $t$, $t = 1,2,...,T$ is defined as:

$$\eta_t = \gamma_{1t} - \gamma_{0t}.$$

At each time point $t$, $t = 1,2,...,T$, the mean change from baseline (LSMEANS) for test drug and control are $\gamma_{1t}$ and $\gamma_{0t}$, respectively, as defined in the cLDA model above.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, missing at random [MAR] or missing completely at random [MCAR]). This missing data mechanism requires that the probability of a data point being missing does not depend on the missing data after adjusting for the observed data.

The LDA model assumes that the mechanism for any missing data is missingness at random (MAR), which means that missingness is caused by data that have already been observed, rather than by data that have not been observed. Any missingness that is caused by treatment is MAR, because treatment is an observed variable. Missingness that is the result of hyperglycemia-related discontinuation is also MAR, because it depends only on observed glycemic measurements. Other potential reasons for discontinuation include laboratory safety measurements outside acceptable limits, clinical or laboratory adverse events, relocation, withdrawal of consent, and violation of the protocol. Missingness due to some of those reasons (such as relocation) is likely to be completely at random (a

special case of MAR), and for the other reasons is likely to be MAR. It is not expected that non-MAR mechanisms will account for a substantial amount of missing data.

**Model Convergence**

If the unstructured covariance model fails to converge with the default algorithm, then Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased.

**SAS Code**

SAS code for fitting the full likelihood cLDA model is provided below.

```
**********************************************************************;
** data step necessary prior to running SAS PROC MIXED;
**********************************************************************;
DATA long; SET long;
ARRAY T{4} t0-t3; * time indicator variables;
ARRAY TT{8} tt0-tt7; * time by treatment indicator variables;
** define week times treatment indicator variables;
DO i = 1 to 4;
DO j = 1 to 2;
T{i} = (time=(i-1));
TT{i+4*(j-1)} = T{i}*(trt=j);
END;
END;
DROP i j;
RUN;
**********************************************************************;
** fitting the cLDA model using SAS PROC MIXED;
**********************************************************************;
PROC MIXED DATA=long;
CLASS subjid dosestrat typestrat time;  ** subj is the subject id number **;
MODEL y=dosestrat  typestrat time dosestrat*time typestrat*time tt5 tt6 tt7;
REPEATED time / SUBJECT=subjid TYPE=UN;
ESTIMATE 'MK-431A  vs. metformin ' tt7;
ODS OUTPUT Estimates=outm1;
RUN;
```

## 6.11 TANNER STAGING

**Tanner Stages of Maturation**

In male patients, Tanner Staging will be assessed by testicular volume and pubic hair distribution as denoted in the listings below. An orchidometer (Prader) will be used to evaluate testicular volume. The testes will be palpated with a gloved hand and the wooden ball of the orchidometer that most closely matches the testicular size is determined. For each male patient, Tanner Staging will be recorded for both pubic hair and testicular volume.

In female patients, Tanner Staging will be evaluated by the stage of breast development and pubic hair distribution as denoted in the listings below. If breast development is asymmetrical, the development should be characterized using the more advanced stage. Additionally, each female patient will be asked at each visit if menarche has occurred and this information will be captured at each visit. For each female patient, Tanner Staging will be recorded for both pubic hair and breast.

**Pubic hair (both male and female)**

- Tanner I -- none (prepubertal state)
- Tanner II -- small amount of long, downy hair with slight pigmentation at the base
- Tanner III -- hair becomes more coarse and curly, and begins to extend laterally
- Tanner IV -- adult-like hair quality, extending across pubis but sparing medial thighs
- Tanner V -- hair extends to medial surface of the thigh

**Genitals (male)**

- Tanner I -- prepubertal (testicular volume less than 1.5 ml; small penis)
- Tanner II -- testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged
- Tanner III -- testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen
- Tanner IV -- testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length and circumference
- Tanner V -- testicular volume greater than 20 ml; adult scrotum and penis

**Breasts (female)**

- Tanner I -- no glandular tissue; areola follows the skin contours of the chest (prepubertal)
- Tanner II -- breast bud forms, with small area of surrounding glandular tissue; breast bud within area of areola; areola begins to widen
- Tanner III -- breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
- Tanner IV -- increase breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
- Tanner V -- breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla

### 6.12 List of Prior Amendments

Amendment 01 dated 10Oct2012, Country-specific Brazil.

Amendment 02 dated 10Oct2012, Country-specific Brazil.

Amendment 03 dated 24Jun2013, Country-specific, South Africa.

Amendment 04 dated 09Apr2014, Global.

Amendment 05 dated 12Jan2015, Global.

Amendment 06 dated 04Feb2015, Country-specific, Saudi Arabia.

Amendment 07 dated 31Aug2015, Global.

Amendment 08 dated 20Oct2015, Country-specific, Saudi Arabia.

Amendment 09 – Not released.

# 7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff

**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.

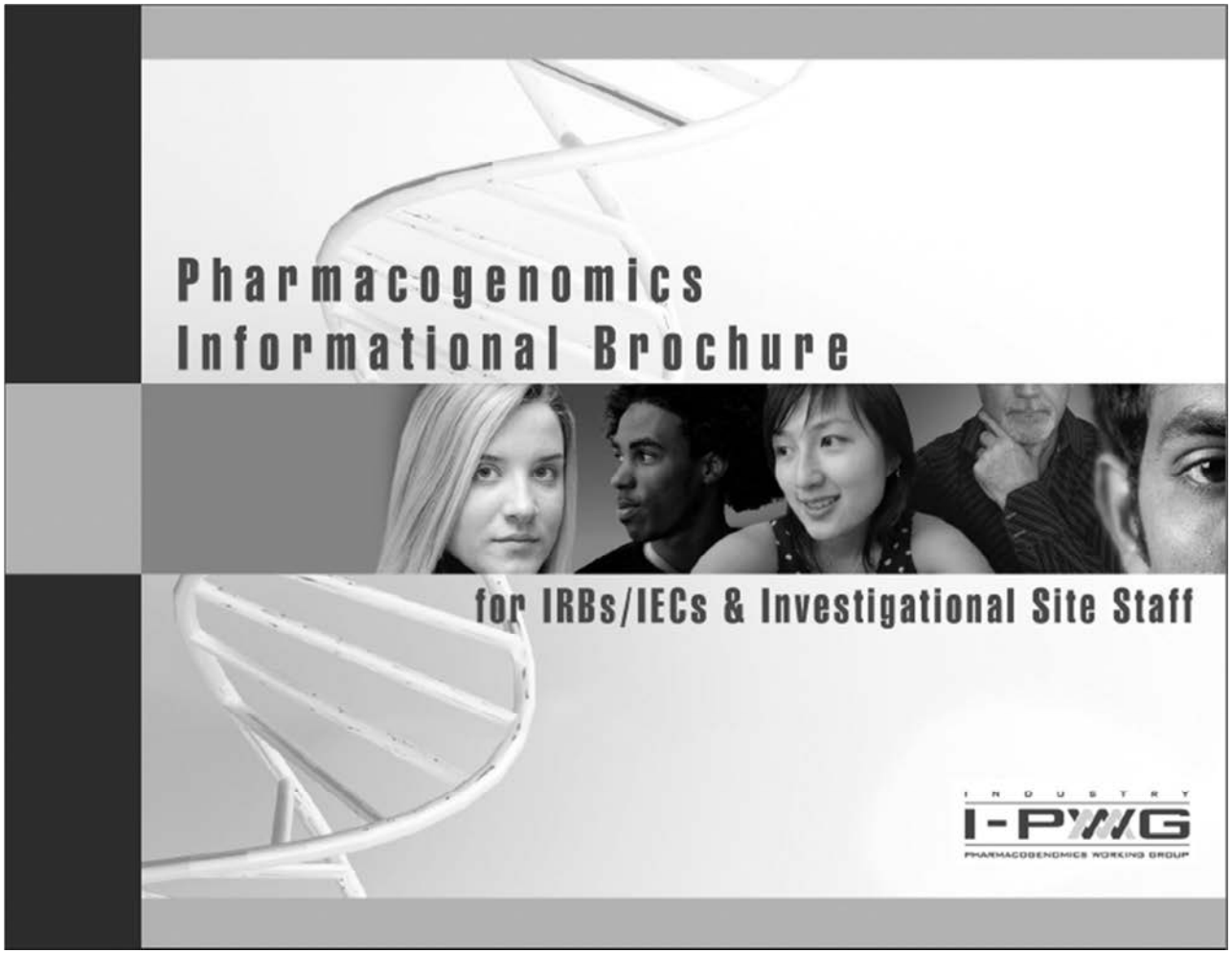
**C. Funding for Travel and Other Requests**

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".


Pharmacogenomics
Informational Brochure
for IRBs/IECs & Investigational Site Staff
INDUSTRY
I-PWG
PHARMACOGENOMICS WORKING GROUP

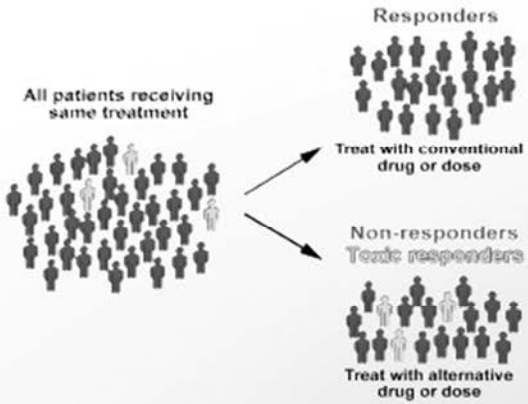
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

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

## What is DNA and What is Pharmacogenomics?

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

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




## Why is Pharmacogenomics Important?

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

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

## How is Pharmacogenomics Being Used in Drug Development?

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

PGx research is currently being used in drug development to:

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

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## Pharmacogenomics Already a Reality in Drug Labels

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

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

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

For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

## DNA Samples from Clinical Trials An Invaluable Resource

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

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

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

## Informed Consent

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

## Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

## Privacy, Confidentiality, and Patient Rights

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

**i) Sample Labeling**

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

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Table adapted from ICH Guidance E15

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

**ii) Separation of Data and Restricted Access**

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

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

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iii) Legislation on Genetic Discrimination

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

## Country-Specific Laws and Regulations on DNA Collection

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

## Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

## Where to Get More Information

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

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

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

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## Glossary

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

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

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

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

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

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

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## References

1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

2. Anderson DC, Gomez-Mancilla B, Spear BB, et al. Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group. Pharmacogenomics Journal 2002;2(5):284-92.

3. ICH E6(R1) - Guideline for Good Clinical Practice. June 1996. (Accessed at: http://www.ich.org/LOB/media/MEDIA482.pdf)

4. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006;20(1):24-36.

5. Genetic Information Nondiscrimination Act (GINA): 2007-2008. (Accessed at: http://www.genome.gov/24519851)

6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.

7. EMEA CHMP Reflection Paper on Pharmacogenomics in Oncology - Draft. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)

8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.tga.health.gov.au/docs/pdf/euguide/emea/307001en.pdf)

9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12851706enfin.pdf)

10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings. November 2006. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/2022704en.pdf)

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11. EMEA CHMP Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/20191405en.pdf)

12. EMEA CHMP Reflection Paper on the Use of Genomics in Cardiovascular Clinical Intervention Trials. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/27878906enfin.pdf)

13. EMEA CHMP Biomarkers Qualification: Guidance to Applicants. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf)

14. EMEA CHMP Understanding Terminology Used in Pharmacogenetics July 2004. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/384204en.pdf)

15. FDA Companion Guidance - Pharmacogenomic Data Submissions - draft. August 2007. (Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)

16. FDA. FDA Guidance - Pharmacogenetic Tests and Genetic Tests for Heritable Markers. June 2007. (Accessed at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm)

17. FDA Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)

18. EMEA FDA - Processing Joint FDA EMEA VGDSs within the framework of the Confidentiality Arrangement May 2006. (Accessed at : http://www.emea.europa.eu/pdfs/general/direct/pr/FDAEMEA.pdf)

19. Rittenhouse P. Framing DNA collection in the clinic. Biocentury, The Bernstein Report on BioBusiness March 2006:A13-5.



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http://www.i-pwg.org

# 8. SIGNATURES

## 8.1 SPONSOR'S REPRESENTATIVE

| TYPED NAME | SIGNATURE | DATE |
|---|---|---|
| | | |

## 8.2 INVESTIGATOR

I agree to conduct this clinical study 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); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study 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 the SAFETY MEASUREMENTS section of this protocol. 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 study 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 | SIGNATURE | DATE |
|---|---|---|
| | | |