

Official Protocol Title:	A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control
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TITLE:

A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control

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SUMMARY OF CHANGES

Note: Protocol amendment P083-15 was not implemented. The changes listed in the Summary of Changes Section of amendment P083-16 are the same as those included in amendment P083-15.

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 when post-study reporting activities have been initiated.
3.5.1	Responsibility for Analyses/ In-House Blinding	Updated to include 2 database locks.	Database will be locked in stages to accommodate submission to regulatory agencies.
3.5.5.1	Statistical Methods for Efficacy Analyses	<ul style="list-style-type: none"> • Provided clarification on analysis using the treatment effect estimand. • Added analyses using the treatment policy estimand, including the ‘retrieved dropout’ (RD) and ‘return-to-baseline’ approaches for handling missing data. • Added 2 sensitivity analyses 	<ul style="list-style-type: none"> • To define estimands as recommended by ICH E9 (R1). • To comply with regulatory request. • 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. This change was part of a protocol clarification letter (PCL).
1.6	Dosage/Dosage Form, Route, and Dose Regimen	<ul style="list-style-type: none"> • Clarified the definition for stable dose of background insulin. • Down-titration of metformin was updated in the content of the blister pack and dose regimen during Phase B table. 	<ul style="list-style-type: none"> • To provide additional details for different types of insulin (basal and bolus) administration. This change was part of a PCL. • To provide additional details on down-titration of metformin.
1.7	Study Flow Chart	<ul style="list-style-type: none"> • Dispensation of the patient identification card was moved from Visit 1 to Visit 2. • Clarified that dental sub-study procedures do not apply to Brazil and Serbia. 	<ul style="list-style-type: none"> • Consistency with Section 3.2.3.16 - Patient Identification Cards. This change was part of a PCL. • Brazil and Serbia are not participating in the dental sub-study. The text in the protocol will allow us to proceed without creating country specific amendments for Brazil and Serbia.
2.2	Patient Inclusion Criteria	<ul style="list-style-type: none"> • Clarified the definition for stable dose of background insulin. • Clarified that the screening laboratory assessments must be repeated if the duration between the Screening Visit and Visit 3 is >28 days. 	<ul style="list-style-type: none"> • To provide additional details for different types of insulin (basal and bolus) administration. This change was part of a PCL. • To ensure patient laboratory results for eligibility assessment are recent.

Section Number	Section Title	Description of Change	Rationale
2.3	Patient Exclusion Criteria	<ul style="list-style-type: none"> • Clarified that the screening laboratory assessments must be repeated if the duration between the Screening Visit and Visit 3 is >28 days. • Clarified that the results of the antibody screen for anti-GAD or ICA-512 must be available and evaluated before the patient can be randomized at Visit 3. 	<ul style="list-style-type: none"> • To ensure patient laboratory results for eligibility assessment are recent. • To align the protocol requirements with laboratory turn-around times.
2.4.1	Summary of Study Design	The number of patients per group was removed from the Study Design figure.	Simplify figure.
2.4.2.1	Study Visits General Information	<ul style="list-style-type: none"> • Clarified that patients should fast ≥ 10 hours prior to Rescue and Discontinuation Visits. • Window between Visit 2 and Visit 3 was added 	<ul style="list-style-type: none"> • To clarify instructions outlined in Section 1.7 Study Flow Chart. This change was part of a PCL. • To clarify the duration of the placebo run-in period and to harmonize with the current guidance to investigators.
2.4.2.3	Visit 2 Single-Blind Placebo Run-in	<ul style="list-style-type: none"> • Emphasized completion of procedures before dosing. • Clarified that the results of the antibody screen for anti-GAD or ICA-512 must be available and evaluated before the patient can be randomized at Visit 3. 	<ul style="list-style-type: none"> • To ensure that results from procedures are not affected by administration of study medication. This change was part of a PCL. • To align the protocol requirements with laboratory turn-around times.
2.4.2.4	Visit 3/Randomization Visit	Emphasized completion of procedures before dosing.	To ensure that results from procedures are not affected by administration of study medication. This change was part of a PCL.

Section Number	Section Title	Description of Change	Rationale
2.4.2.5	Visit 3/Day 1 through Visit 11/Week 54	<ul style="list-style-type: none"> • Emphasized completion of procedures before dosing. • At visit 8, patients participating in the Meal Tolerance Test (MTT) will have the witnessed dose administered 30 minutes prior to ingesting the standard meal. 	<ul style="list-style-type: none"> • To ensure that results from procedures are not affected by administration of study medication. This change was part of a PCL. • For consistency with Appendix 6.7.
2.4.2.6.1	Rescue Step 1 (Blinded)	<ul style="list-style-type: none"> • Glycemic Rescue Criteria Table was updated. • Down-titration of metformin was updated 	<ul style="list-style-type: none"> • For consistency with the Study Design figure. • To provide additional details on down-titration of metformin.
2.7	Statistical Analysis Plan	Clarified that details of the statistical analysis plan for the supplemental dental data sub-study will be provided in a separate document	For consistency with the SAP description in Section 3.5.
2.7.3	Power and Sample Size	Power and sample size were updated.	To reflect revised sample size.
3.1.7	Supplemental Dental Data Sub-Study	<ul style="list-style-type: none"> • Reviewer information was updated. • Clarified that dental sub-study procedures do not apply to Brazil and Serbia. 	<ul style="list-style-type: none"> • Dental data will be assessed by an independent pediatric dentist reviewer. • Brazil and Serbia are not participating in the dental sub-study. The text in the protocol will allow us to proceed without creating country specific amendments for Brazil and Serbia.
3.2.3.6	Laboratory Monitoring	<ul style="list-style-type: none"> • Clarified fasting labs should be collected during Visits 1, 3, 8, 11, Rescue, and Discontinuation. • Clarified that CD26 values will remain masked to both patient and investigator throughout the study. 	<ul style="list-style-type: none"> • To clarify instructions outlined in Section 1.7 Study Flow Chart. This change was part of a PCL. • Clarification

Section Number	Section Title	Description of Change	Rationale
3.2.3.12	Bone Age Assessment Procedures	Reference of Independent review charter was added.	For additional detailed description of bone age assessments.
3.2.3.19	Post-Study Follow-Up	Clarified that dental photos will be taken only for patients who consent to the dental substudy.	Clarification.
3.2.3.20	Blinding/Unblinding	Text on unblinding of patients was updated.	To reflect protocol template updates.
3.5	Statistical Analysis Plan	Data analysis plan for the dental substudy was removed.	Analyses of data from the dental substudy will be described in a separate document.
3.5.3.1	Efficacy Endpoints	<ul style="list-style-type: none"> • Added hemoglobin A1C at Week 14. • Endpoints involving proinsulin will not be analyzed as AUC. 	<ul style="list-style-type: none"> • Regulatory agency requirement. • Proinsulin is collected at a single time point and therefore AUC cannot be derived.
3.5.3.3	Derivation of Efficacy Endpoints	Clarified definition of composite index of insulin sensitivity.	Clarification.
3.5.3.4	Derivation of Safety Endpoints	Section was added.	To clarify how endpoints will be derived during analyses.
3.5.4.1	Efficacy Analysis Populations	<ul style="list-style-type: none"> • Completers population was removed. • Handling of patients randomized twice and patients with incorrect assignment was added. 	<ul style="list-style-type: none"> • The population is not related to the study's estimands. • To document handling of data.
3.5.5.1	Statistical Methods for Efficacy Analyses	<ul style="list-style-type: none"> • Included Treatment Effect estimand and Treatment Policy estimand and their corresponding analyses. • Removal of analysis of covariance (ANCOVA)/last observation carried forward (LOCF). • Summary statistics will be provided using observed data for change from baseline in 2-hour PMG, AUC endpoints, and endpoints derived from 9-point MTT at Week 20. 	<ul style="list-style-type: none"> • To comply with regulatory request. • ANCOVA/LOCF is not consistent with the study's estimands. • There will be insufficient participants with MTT data for model-based statistical analyses.

Section Number	Section Title	Description of Change	Rationale
3.5.5.2	Statistical Method for Safety Analyses	Changed safety analyses approach – primary approach will include data after rescue except for hypoglycemia endpoints.	Simplification of analysis approach.
3.5.5.3	Summaries of Baseline Characteristics, Demographics, and Other Analyses	<ul style="list-style-type: none"> • Description of variables was updated. • Removal of demographic baseline characteristics summary for patients who continue to Phase B. 	<ul style="list-style-type: none"> • Simplification. • No separate analysis for this group is planned.
3.5.7	Sample Size and Power Calculations	Updated sample size information.	To reflect revised sample size.
3.5.8	Subgroup Analyses	Description of subgroups was updated.	Simplification.
3.5.9	Interim Analyses	Emphasized that the first database lock for the primary efficacy analysis is not an interim analysis.	Clarification.
3.5.10	Medication Adherence	Adherence definition was added.	To reflect compliance based on time in study.
3.6.1	Product Descriptions	<ul style="list-style-type: none"> • Corrected product description. • Blister card table was added. 	Correction.
5	List of references	List of references was updated.	Deleted references that are no longer applicable.
6.11	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 (new)	Patient Randomized Twice	Appendix added to define handling of patient randomized twice.	To document handling of data.
6.14	Supplemental Dental Data Sub-study	Clarified that dental sub-study procedures do not apply to Brazil and Serbia.	Brazil and Serbia are not participating in the dental sub-study. The text in the protocol will allow us to proceed without creating country specific amendments for Brazil and Serbia.
6.14.2	Sub-Study Design and Procedures	Dental data will be assessed by an independent pediatric dentist reviewer.	Reviewer information was updated.

Section Number	Section Title	Description of Change	Rationale
6.14.7	Sub Study Statistical Analysis Plan	Section was deleted.	The statistical plan for the dental substudy will be presented in a separate document.
6.15	List of Prior Amendments	List was updated.	Update.
	Throughout the document	<ul style="list-style-type: none">• The word 'subject' was replaced with 'patient'.• 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 Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control.

1.2 INDICATION

For the treatment of pediatric patients (10 to 17 years of age, inclusive) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control.

1.3 SUMMARY OF RATIONALE

This study (MK-0431 P083) is designed to assess the safety and efficacy of sitagliptin, relative to placebo, as initial oral therapy for the treatment of T2DM in pediatric patients (10 to 17 years of age, inclusive) with inadequate glycemic control.

1.4 SUMMARY OF STUDY DESIGN

P083 is a multinational, two Phase, double-blind, parallel-group study of approximately 56 weeks duration, including a screening period of up to 1 week [**Visits 1 to 2**], a 1-week single-blind placebo run-in period [**Visits 2 to 3**], a 20-week placebo-controlled, double-blind treatment period [**Visits 3 to 8; Phase A**] and a 34-week double-blind active-controlled treatment period [**Visits 8 to 11; Phase B**] during which patients randomized to the placebo arm who have not initiated glycemic rescue therapy with metformin during Phase A will receive metformin (in a blinded manner) as shown in [Table 1-1](#), [Table 1-2](#) and [Figure 2-1](#). 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) to assess for any serious adverse events (SAEs).

At **Visit 2**, eligible patients will undergo diet and exercise counseling and initiate sitagliptin-placebo and metformin-placebo. Eligible patients will be randomized (1:1) at **Visit 3/Day 1** to either sitagliptin or placebo. Patients meeting progressively stricter glycemic thresholds will be eligible to initiate glycemic rescue therapy (Step 1 and Step 2, Section 2.4.2.6) in both Phase A and Phase B. Except for Step 2 rescue and Step 2 treat-to goal, study medication will be managed through the Interactive Voice Response System (IVRS) using blister packs. The content of the blister pack and the dose regimen for study medication, including Step 1 and Step 2 rescue, are described in [Table 1-1](#) (for the placebo run-in and Phase A) and [Table 1-2](#) (for Phase B).

A supplemental dental data sub-study has been added to the protocol via amendment; the rationale for the sub-study is provided in Section 3.1.7. Procedures specific to the supplemental dental data sub-study amendment are outlined in Appendix 6.14 and apply to all randomized patients who took at least one dose of study medication, i.e., those who are new to P083, those ongoing (on or off study medication) in P083, and those who have completed P083 (on or off study medication). Patients who have withdrawn consent from

P083 are not eligible. Appendix 6.14 outlines the definition of new, ongoing, and completed patients.

Note: Patients currently enrolled in MK-0431 P351 (a non-interventional follow-up study to MK-0431 P083) are also eligible to be contacted to participate in this sub-study.

Consent will be required to participate in this sub-study (see Section 3.2.3.13.4).

1.5 SAMPLE

At least 190, but no more than 220 patients 10 to 17 years of age (inclusive) with T2DM who have inadequate glycemic control are eligible to participate if they meet ONE of the following enrollment criteria:

- not on treatment with an antihyperglycemic agent (AHA) for ≥ 12 weeks prior to Visit 1 and have inadequate glycemic control (hemoglobin A1c [A1C] of $\geq 6.5\%$ and $\leq 10.0\%$ at Visit 1)

OR

- on a stable dose (variance in dose to be $\leq 15\%$ of total daily dose) of insulin (without any other antihyperglycemic agents) for at least 12 weeks prior to Screening Visit/Visit 1 and have inadequate glycemic control (A1C of $\geq 7\%$ and $\leq 10.0\%$ at Visit 1). This stable regimen can include (1) a stable dose of basal insulin ($\pm 15\%$) AND/OR (2) stable prescribed doses of bolus insulin ($\pm 15\%$) (a) for each fingerstick glucose range for patients on sliding scale AND, if applicable, (b) for corrective doses and carbohydrate coverage.

At least 30% of randomized patients will be 10 to 14 years of age and at least 20% of patients will be recruited from European Union (EU) member states or countries with ethnicity and life-style similar to those in EU countries. Further, at least 1/3 and not more than 2/3 of the patients in each age subset (10 to 14, 15 to 17 years) will be female.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Sitagliptin (100 mg), metformin (500 mg) and their matching placebos will be supplied as oral tablets in blister packs. The dose regimen for the study is shown in [Table 1-1](#) and [Table 1-2](#).

Background insulin and open-label insulin for Step 2 rescue and Treat-to-Goal Step 2 will be sourced locally and administered subcutaneously based on instructions provided by the investigator (based on accepted local, national or international guidelines for the indication and use of insulin).

Doses of background insulin should remain stable (variance in dose to be $\leq 15\%$ of total daily dose) for the duration of the trial (See Section 2.4.2.6, Section 2.4.2.6.1 for up-titration, Section 3.2.3.3 for down-titration, and Section 1.5 for stable regimen).

Any open-label alternate glycemic rescue medication (other than metformin, or a DPP-4 inhibitor, or a GLP 1 receptor agonist) used for Step 2 rescue for patients ≥ 18 years of age will be sourced locally by subsidiary or designee, investigator site, or by prescription.

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.

Table 1-1

Content of the Blister Pack and Dose Regimen in Phase A

Treatment Phase	Treatment Arm	
	Sitagliptin	Placebo
Placebo Run-In	1 tablet of sitagliptin-placebo prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals.	
Phase A (From Visit 3 through Visit 8)	1 tablet of sitagliptin prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals ^{1,2}	1 tablet of sitagliptin-placebo prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals ^{1,2}
¹ Step 1 Rescue for patients in both treatment arms: All patients who require glycemic rescue therapy (including patients on background insulin) will be rescued with metformin. The patients' study medication kit (with the blister packs) will be replaced with a new one in which the metformin-placebo has been replaced by active metformin in a blinded fashion (starting at 500 mg/day and up-titrated by 500 mg every week to a final dose of 1000 mg bid.). ² Step 2 Rescue for patients in both treatment arms: Patients who continue to require glycemic rescue therapy after Step 1 Rescue will initiate open-label insulin. Patients on background insulin therapy should have the dose of their background insulin up-titrated for Step 2 rescue. Refer to Section 2.4.2.6 for further details.		

Table 1-2

Content of the Blister Pack and Dose Regimen during Phase B

Treatment Phase	Treatment Arm	
	Sitagliptin	Placebo
Phase B (From Visit 8 through Visit 11)	Patients who have not initiated glycemic rescue therapy in Phase A will continue to receive 1 tablet of sitagliptin prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals. ^{1,3}	Patients who have not initiated glycemic rescue therapy in Phase A will receive 1 tablet of sitagliptin-placebo prior to the morning meal, and metformin-placebo in the blister pack will be replaced by active metformin in a blinded fashion (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg bid.). Patients who are not able to tolerate a higher dose of metformin (or matching placebo) will have their dose reduced at an unscheduled visit and should continue on the maximal tolerated dose for the duration of the study. ^{2,3}
<p>¹ Step 1 Rescue for patients in the sitagliptin arm: All patients who require glycemic rescue therapy (including patients on background insulin) will be rescued with metformin. The patients' study medication kit (with the blister packs) will be replaced with a new one – the new blister pack will contain active sitagliptin, and the metformin-placebo will have been replaced by active metformin in a blinded fashion (starting at 500 mg/day and uptitrated by 500 mg every week to a final dose of 1000 mg bid.). Patients who are not able to tolerate a higher dose of metformin (or matching placebo) will have their dose reduced at an unscheduled visit and should continue on the maximal tolerated dose for the duration of the study.</p> <p>² Step 1 Rescue for patients in the placebo arm who have switched to metformin: All patients who require glycemic rescue therapy (including patients on background insulin) will be rescued with sitagliptin. The patients' study medication kit (with the blister packs) will be replaced with a new one – the new blister pack will contain active metformin, and the sitagliptin-placebo will have been replaced by active sitagliptin in a blinded fashion.</p> <p>³ Step 2 Rescue for patients in both treatment arms: Patients who continue to require glycemic rescue therapy after Step 1 Rescue will initiate open-label insulin. Patients on background insulin therapy should have the dose of their background insulin up-titrated for Step 2 rescue. Refer to Section 2.4.2.6 for further details.</p>		

1.7 STUDY FLOW CHART

	Screening	Single-Blind Placebo Run-In	Randomization	Double-Blind Treatment Phase A					Double-Blind Treatment Phase B			Rescue Step 1/ or Treat to Goal Step 1 or Discontinuation ¹	Rescue Step 2 Or Treat to Goal Step 2 ¹	2-Week Post-Study Phone Contact	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Rescue ¹ / D/C ² Visit			
		Week -1	Week 0/ Day 1	Week 2 TC	Week 4	Week 8	Week 14	Week 20	Week 30	Week 42	Week 54			Week 56 OR 14 days post D/C	
Study Procedures															
Obtain informed consent and assent ^{3,4}	X														
Dispense patient identification card		X													
Obtain informed consent and assent for Future Biomedical Research ⁵			X												
Evaluate Inclusion/Exclusion criteria ⁴	X	X	X												
Monitor for Adverse Events ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁷
Collect medical history ⁸	X														
Review prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Perform physical exam			X					X			X	X	X		
Perform Tanner staging			X					X			X	X			
Visual oral examination (including inspection of teeth) ⁴			X					X			X	X			
Measure vital signs (HR, BP measured twice)	X	X	X		X	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 ⁹						X			X	X			
X-ray of Left Hand and Wrist (for bone age / central vendor)			X ¹⁰					X ¹¹			X	X			
Pediatric Quality of Life Questionnaire (PedsQL™)			X ¹²												
Diet/exercise counseling ¹³		X													
Diet/exercise monitoring			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Hypoglycemia Assessment Tool(s) ¹⁴		X				X		X	X	X					
Instruct on hypoglycemia symptoms and management		X	X	X	X	X	X	X	X	X					
Review the 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) and screening kit for ketones		X													
Review rescue criteria ¹⁵			X	X	X	X	X	X	X	X					
Witnessed Dose		X	X					X ¹⁶							
Dispense single-blind placebo medication		X													

	Screening	Single-Blind Placebo Run-In	Randomization	Double-Blind Treatment Phase A					Double-Blind Treatment Phase B			Rescue Step 1/ or Treat to Goal Step 1 or Discontinuation ¹	Rescue Step 2 Or Treat to Goal Step 2 ¹	2-Week Post-Study Phone Contact			
				Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Rescue ¹ / D/C ² Visit		
					Week -1	Week 0/ Day 1	Week 2 TC	Week 4	Week 8	Week 14	Week 20	Week 30	Week 42	Week 54			Week 56 OR 14 days post D/C
Assess for single-blind medication compliance			X														
Dispense double-blind study medication			X		X	X	X	X	X	X		X ²					
Assess for double-blind medication compliance				X	X	X	X	X	X	X	X	X	X				
Review SMBG measurements			X	X	X	X	X	X	X	X	X	X	X				
Monitoring and Central Laboratory Procedures																	
Site finger stick A1C ¹⁷	X																
Fasting plasma glucose (FPG) ¹⁸	X		X					X			X	X	X				
A1C	X		X			X	X	X	X	X	X	X ¹⁹					
Site finger stick glucose			X														
Fasting C-peptide ¹⁸	X																
Diabetes Autoantibody Panel	X																
Complete Blood Count (CBC)/Differential	X		X		X			X			X	X	X				
Fasting insulin and proinsulin ²⁰			X					X			X	X	X				
Chemistry panel	X		X		X			X	X	X	X	X	X				
Lipid panel ¹⁸	X		X					X			X	X	X				
TSH	X																
Meal Tolerance Test (MTT) 9 point: -10, 0, 10, 20, 30, 60, 90, 120, 180 ²¹			X					X			X	X	X				
Dipstick Urinalysis ²²	X	X	X					X			X	X	X				
Urine microalbumin/creatinine ratio ²³			X					X			X	X	X				
Urine Pregnancy test (for all females) ²⁴	X		X		X	X	X	X	X	X	X	X ¹	X ¹				
CD26 assay ²⁵			X					X			X	X ²⁵					
IGF-1 and IGF-BP3			X					X			X	X	X				
Biochemical Markers of Bone Turnover and calcitonin ²⁶			X					X			X	X	X				
Blood sample (serum) for Future Biomedical Research ²⁷			X					X			X	X	X				
Blood sample (plasma) for Future Biomedical Research ²⁷			X					X			X	X	X				
Blood for Future Biomedical Research (for DNA) ²⁸					X												

CD= cluster of differentiation; D/C= discontinuation visit; DNA= deoxyribonucleic acid; EC= ethics committee; ECG= electrocardiogram; IGF= Insulin-like growth factor; IRB= institutional review board; TC= Telephone call; WBC= White blood cells.

NOTE: Visits (with the exception of **Visits 1, 3, 8, 11, Step-1 rescue, Treat-to-target Step-1, or Discontinuation visits**) *may* be performed, if approved by the country and local IRB/EC, by a qualified health professional at the patient's home or location other than the site.

- 1 All rescue procedures should be performed prior to the initiation of rescue therapy Step 1 or Step 2 or treat-to-goal Step 1/Step 2. If the rescue visit (Step 1 or Step 2 or treat-to-goal Step 1/Step 2) occurs on a regular scheduled visit, all procedures for that visit should be performed. If the rescue Step 1 or treat-to-goal Step 1 or Discontinuation visit is performed as an unscheduled visit within 4 weeks of **Visit 3 or Visit 8**, do not perform: physical examination, X-ray procedure, Tanner staging, visual oral examination, height measurement, waist circumference measurement, ECG, complete blood count/differential, chemistry panel, lipid panel, MTT, dipstick urinalysis, urine microalbumin/creatinine ratio, biochemical samples of bone turnover and calcitonin, CD 26, FBR sampling, and IGF-1 and IGF-BP3. For the Rescue or Discontinuation visits, the urine pregnancy test is needed only if the prior visit is more than 4 weeks apart. 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 3.2.3.19).
- 2 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 for key visits and 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 (i.e., not at week 20 and 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 3.2.3.19 for further details.
- 3 Consent form must be signed prior to any study specific procedures; informed consent will be obtained from parent/legal guardian and assent will be obtained from the patient.
- 4 See Appendix 6.14 for the supplemental dental data sub-study flow charts and other details. Note: Procedures for the Supplemental Dental Data Substudy do not apply to Brazil and Serbia.
- 5 Future Biomedical Research consent from the parent/legal guardian and assent should be obtained prior to collecting the blood (DNA), plasma and serum samples.
- 6 Collect information about intercurrent illnesses.
- 7 Collect serious adverse events only.
- 8 For male and female patients 10 to ≤ 14 years, collect up to 5 years of relevant medical history. For male and female patients 15 to 17 years, collect up to 7 years of relevant medical history.
- 9 The ECG may be done at **Visit 2 or Visit 3** but must be read and evaluated for study eligibility before the patient receives double-blind study medication at **Visit 3**.
- 10 The baseline X-ray must be performed after **Visit 2** and prior to dispensation of study medication at **Visit 3**. The baseline X-ray will be read upon receipt at the Central Vendor; if there is a status of "skeletal maturity," then no further X-rays are required during the study. For additional details on X-ray procedure timing refer to Section 3.2.3.12.
- 11 The **Visit 8** X-ray will be read upon receipt at the Central Vendor; if there is a status of "skeletal maturity," then no further X-rays are required during the study.
- 12 The Peds QL™ will be administered to patients and their parents in countries where local validated translations of the questionnaire are available. **Note:** The Peds QL will not be administered to illiterate parents and their children.
- 13 Patients will be seen by a dietician or qualified health professional for diet/exercise counseling at **Visit 2**.
- 14 The Hypoglycemia Assessment Tool(s) will be provided in paper or as an electronic device, per site approval. The Tool(s) will be reviewed at each visit, and re-dispensed as required per the modality in use. The electronic device (if used) should be dispensed at Visit 2. The Low Blood Sugar Calendar and Notepad in paper will be collected and reviewed at each visit. A new Low Blood Sugar Calendar will be dispensed at **Visit 2, Visit 6, Visit 8, Visit 9, and Visit 10**. The Low Blood Sugar Calendar from the previous visit will be re-dispensed at **Visit 3, Visit 5, and Visit 7**.
- 15 The patient and parent/guardian will be informed of the finger stick glucose rescue threshold that is applicable until the next visit and will be instructed to call the site if the fasting finger stick glucose value is greater than this threshold on 3 consecutive days. Patients and parents should be counseled that if one fasting finger stick glucose value is above the threshold for rescue, the fasting finger stick glucose value has to be checked the following morning. If the fasting finger stick glucose value is above the threshold for rescue on two consecutive days, the fasting finger stick glucose has to be checked on the third day as well, and the site called if all three values are above the threshold for rescue. After the patient calls the site with fasting finger stick glucose values that exceed the thresholds for 3 consecutive days, and after assessing for compliance with study medication (refer to Section 2.4.2.6) an FPG will be performed, and the patient will be rescued if the FPG is greater than the threshold specified in [Table 2-2](#). For reference, site personnel will record the threshold for rescue in the finger stick glucose log book.
- 16 Patients who participate in the MTT at **Visit 8/Week 20** will be contacted by the site the day after the visit to collect the date and time that study medication was taken.
- 17 Site finger stick A1C may be used, if available, at the discretion of the investigator, for screening purposes only; laboratory A1C must be used to meet inclusion criteria for eligibility.
- 18 If the patient is not fasting at **Visit 1/Screening Visit**, a fasting lipid profile, fasting C-peptide and FPG should be obtained at or prior to **Visit 2** rather than at **Visit 1**.
- 19 Blood sample for A1C should not be collected if the **Discontinuation or Rescue Visit** occurs prior to **Week 8**.
- 20 If a patient is undergoing the MTT, then do not obtain separate samples for fasting insulin and proinsulin as these samples are obtained as part of the MTT. Do not perform fasting insulin and proinsulin on patients with background insulin therapy.

- 21 MTT will be performed only in patients who agree to undergo this procedure. Do not perform MTT on patients with background insulin therapy.
- 22 If dipstick (midstream urine specimen) is positive for blood, WBC (e.g., 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.
- 23 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.
- 24 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.
- 25 The parent/legal guardian should not schedule the patient for an immunization 2-4 weeks prior to **Visits 3, 8 and 11**. If the **Rescue Visit** occurs prior to **Visit 8**, a sample for the CD26 assay should be obtained at that time instead of at **Visit 8/Week 20**. For patients who have not received rescue therapy in Phase B, if a sample for CD26 was not obtained or analyzed at **Visit 8**, it can still be obtained at or prior to **Visit 9**.
- 26 Biochemical markers of bone turnover include urine (second AM void) N-terminal cross-linking telopeptide of bone collagen (NTX) and creatinine; and serum bone-specific alkaline phosphatase (Ostase assay).
- 27 Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for plasma and serum are collected. The plasma and serum samples for FBR should be collected at **Visit 3** (pre-dose), **Visit 8, Visit 11, Rescue** (if applicable) and/or **Discontinuation**. If FBR consent is obtained at a later time in the study, then FBR plasma and serum samples should be obtained only at the remaining scheduled time points.
- 28 Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for DNA are collected. The FBR sample for DNA should be obtained pre-dose, at **Visit 5**, at the same time as other blood collections, and as the last sample drawn. If FBR consent is obtained at a later date, then the FBR sample for DNA can be obtained at the same time as a remaining scheduled blood collection.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

In pediatric patients (ages 10 to 17 years) with T2DM with inadequate glycemic control:

1. **Objective:** After 20 weeks, to assess the effect of treatment with sitagliptin compared with placebo on A1C.

Hypothesis: Sitagliptin reduces A1C more than placebo after 20 weeks of treatment.

2. **Objective:** To assess the safety and tolerability of sitagliptin.

2.1.2 Secondary

In pediatric patients (ages 10 to 17 years) with T2DM with inadequate glycemic control, after 20 weeks:

1. **Objective:** To assess the effect of treatment with sitagliptin compared with placebo on fasting plasma glucose (FPG).
2. **Objective:** To assess the effect of treatment with sitagliptin compared with placebo on the proportion of patients requiring glycemic rescue therapy.
3. **Objective:** To assess the effect of treatment with sitagliptin compared with placebo on the proportion of patients at goal (A1C <7.0%).
4. **Objective:** To assess the effect of treatment with sitagliptin compared with placebo on body mass index (BMI).
5. **Objective:** To assess the effect of treatment with sitagliptin compared with placebo on fasting measures of beta cell function by assessing change from baseline in HOMA- β and proinsulin/insulin ratio as well as on 2-hour post-meal glucose (PMG) and indices of insulin secretion derived from C-peptide, insulin, and glucose profiles with a standard meal challenge.
6. **Objective:** To summarize data on the following:
 - Growth velocity
 - Change from baseline in Tanner staging
 - Skeletal maturation (Δ Bone age/ Δ Chronologic age)
 - Percentage change from baseline in IGF-1 and IGF-BP3
 - Change from baseline in markers of bone turnover and calcitonin
 - Percentage change from baseline in CD26 expression
 - Change from baseline in measures of dentition

In pediatric patients (ages 10 to 17 years) with type 2 diabetes mellitus (T2DM) with inadequate glycemic control, after 54 weeks:

1. **Objective:** To assess the effect of treatment with sitagliptin (change from baseline) on A1C, FPG, the proportion of patients requiring glycemic rescue therapy, BMI, fasting measures of beta cell function by assessing change from baseline in HOMA- β and proinsulin/insulin ratio as well as on 2-hour PMG and indices of insulin secretion derived from C-peptide, insulin, and glucose profiles with a standard meal challenge.
2. **Objective:** To assess change from baseline in the placebo group (for patients in the placebo group who switched to metformin at the end of Phase A) in A1C, FPG, proportion of patients requiring glycemic rescue therapy, BMI, fasting measures of beta cell function by assessing change from baseline in HOMA- β and proinsulin/insulin ratio as well as on 2-hour PMG and indices of insulin secretion derived from C-peptide, insulin, and glucose profiles with a standard meal challenge.
3. **Objective:** To assess the effect of treatment with sitagliptin on the proportion of patients at goal (A1C <7.0%).
4. **Objective:** To summarize data on the following:
 - Growth velocity
 - Change from baseline in Tanner staging
 - Skeletal maturation (Δ Bone age/ Δ Chronologic age)
 - Percentage change from baseline in IGF-1 and IGF-BP3
 - Change from baseline in markers of bone turnover and calcitonin
 - Percentage change from baseline in CD26 expression
 - Change from baseline in measures of dentition

2.2 PATIENT INCLUSION CRITERIA

All laboratory measurements (to determine eligibility) are to be performed after an overnight fast ≥ 10 hours in duration. Patients with screening values outside the ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed by the central laboratory. If the repeat value satisfies the criterion they may continue 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.

For the supplemental dental data sub-study, inclusion criteria for participation in the sub-study are found in Appendix 6.14.

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 by American Diabetes Association (ADA) criteria (e.g. 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 $\geq 6.5\%$ [test performed using a method that is NGSP certified and standardized to the DCCT assay], and confirmed per ADA guidelines).
- b) Patient is assessed as having a clinical profile consistent with T2DM (e.g., based upon body weight, family history, presentation).
- c) Patient has Body Mass Index (BMI) percentile $\geq 85^{\text{th}}$ percentile at screening (or patient has a history of being overweight or obese at time of diagnosis of T2DM). The body mass index-for-age charts from the WHO can be found in Appendix 6.9.

Note: If patient does not have a BMI $\geq 85^{\text{th}}$ percentile at the time of screening, the documentation of overweight or obesity at the time of diagnosis of T2DM must be included in the source documents at the site.

d) Patient has a fasting C-peptide value >0.6 ng/mL at **Screening Visit/Visit 1**.

2. Patient either:

a) Has not received treatment with any AHA during the 12 weeks prior to the **Screening Visit/Visit 1**. However, patients who have had no more than a total of 10 days of treatment with an oral AHA (i.e., metformin, sulfonylureas, meglitinides or alpha-glucosidase inhibitors) during the 12 weeks prior to the **Screening Visit/Visit 1** are eligible.

Note: For patients who have received treatment with an oral AHA for more than a total of 10 days within the 12 weeks prior to the **Screening Visit/Visit 1**, therapy should not be stopped (washed-off) to make them eligible for the study.

OR

b) Is on a stable dose (variance in dose to be $\leq 15\%$ of total daily dose) of insulin (without any other AHA) for at least 12 weeks prior to **Screening Visit/Visit 1**. This stable regimen can include (1) a stable dose of basal insulin ($\pm 15\%$) AND/OR (2) stable prescribed doses of bolus insulin ($\pm 15\%$) (a) for each fingerstick glucose range for patients on sliding scale AND, if applicable, (b) for corrective doses and carbohydrate coverage.

Note: At screening, patients on insulin doses that are not stable can have their insulin doses adjusted and be eligible to participate after their dose remains stable for ≥ 12 weeks, if they meet all other eligibility criteria. In India, only patients on stable doses of insulin will be eligible.

3. Patient has an A1C of $\geq 6.5\%$ and $\leq 10.0\%$.

Note: Patients on insulin have an A1C $\geq 7.0\%$ and $\leq 10.0\%$.

4. Patient is between 10 and 17 years of age (inclusive) on the 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable 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 two 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. If the parent/guardian is illiterate, please see Section 3.2.3.13.1 for details. In addition, the parent/guardian may also consent to have the child participate in Future Biomedical Research (FBR) by signing a separate consent. **Note:** otherwise eligible patients will be able to participate in the main study even if they opt to not participate in FBR.
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 (i.e., available for telephone calls, study visits and administration of study medication as needed).

At Visit 3/Day 1/Randomization

8. Patient has $\geq 80\%$ compliance with placebo treatment during the single-blind run-in as measured by site-performed tablet count.

2.3 PATIENT EXCLUSION CRITERIA

All laboratory measurements (to determine eligibility) must be performed after an overnight fast ≥ 10 hours in duration. Patients with screening values outside the ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed by the central laboratory. If the repeat value satisfies the criterion, the patient may continue 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

Glucose Metabolism and Therapy Criteria

1. Patient has a history of type 1 diabetes mellitus, autoimmune diabetes mellitus or has a positive antibody screen for anti-GAD or ICA-512.

Note: The results of the antibody screen for anti-GAD or ICA-512 must be available and evaluated before the patient can be randomized at Visit 3.

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 antihyperglycemic therapy.

Specific Treatments

4. Patient has previously taken a DPP-4 inhibitor (such as sitagliptin, vildagliptin, alogliptin, or saxagliptin) 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. Based on past experience, patient has hypersensitivity or contraindication (according to the product circular in the country of the investigational site) to metformin.

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

-weight gain within 30 days of **Visit 1**; OR

-weight loss (such as orlistat) or increase blood glucose within 8 weeks of **Visit 1**.

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

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

7. Patient is currently participating in or has participated in another study with an investigational compound or device within the prior 12 weeks of signing the informed consent (including patients who have participated in single-dose studies with these agents) and does not agree to refrain from participating in any other study while participating in this study.

8. 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.

9. Patient has undergone a surgical procedure within the prior 4 weeks or has major surgery planned during the study.

Note: Patients who have undergone minor surgery within the prior 4 weeks and are fully recovered or patients who have planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

Concomitant Conditions or Diseases of Organs and Systems

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

11. Patient has a **Visit 1** systolic or diastolic blood pressure of ≥ 95 th percentile for age, height percentile and gender (see Appendix 6.2 and 6.3) and is not considered likely to have values < 95 th 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 be enrolled if repeat blood pressure measurement no longer meets exclusion criteria.

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

13. Patient has active nephropathy (i.e., nephrotic syndrome or glomerulonephritis).

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

14. Patient has chronic myopathy, mitochondrial disorder, or a progressive neurological or neuromuscular disorder (e.g., polymyositis, or multiple sclerosis).

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

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

17. Patient is under treatment for hyperthyroidism.

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

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

19. Patient has a history of malignancy or clinically important hematologic disorder.

Exception: (1) patients with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate; and (2) patients with other malignancies which have been successfully treated >5 years prior to screening, where in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of screening. **However, patients with a history of leukemia, lymphoma, malignant melanoma, or renal cell carcinoma are ineligible for the study regardless of the time since treatment, and in such cases, no exceptions will apply.**

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

Other Criteria

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

22. 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.

23. Patient is pregnant, has a positive urine pregnancy test at **Screening Visit/Visit 1**, is expecting to conceive within the projected duration of the study, or is breast-feeding.

24. Patient is unlikely to adhere to the study procedures and appointment schedule, 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.
25. 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 Lab Abnormalities

26. Patient has exclusionary laboratory values as listed in [Table 2-1](#) below.

Table 2-1

Laboratory Exclusion Criteria

Parameter ¹	Study Limit for Exclusion
eGFR ²	<55 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
ALT= alanine amino transferase; AST= aspartate aminotransferase; eGFR= estimated glomerular filtration rate; TSH= thyroid stimulating hormone; TG= triglycerides; ULN= upper limit of normal. ¹ If screening laboratory values are repeated, the last laboratory draw/result should be used for inclusion. ² As assessed by modified MDRD. ³ Patients with abnormal 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

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 "10", or patient has a prolonged QTc interval for age.

At Visit 3/Randomization

29. Patient has symptomatic hyperglycemia, and/or ketonuria or positive test for ketonemia requiring immediate initiation of AHA 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 run-in which meets any previously described study exclusion criterion.

Note: If a patient requires initiation of a new medication (other than single-blind study medication) at **Visit 3**, the current visit should be changed to an "Unscheduled Visit" and the patient should be rescheduled for a **Visit 3** 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.

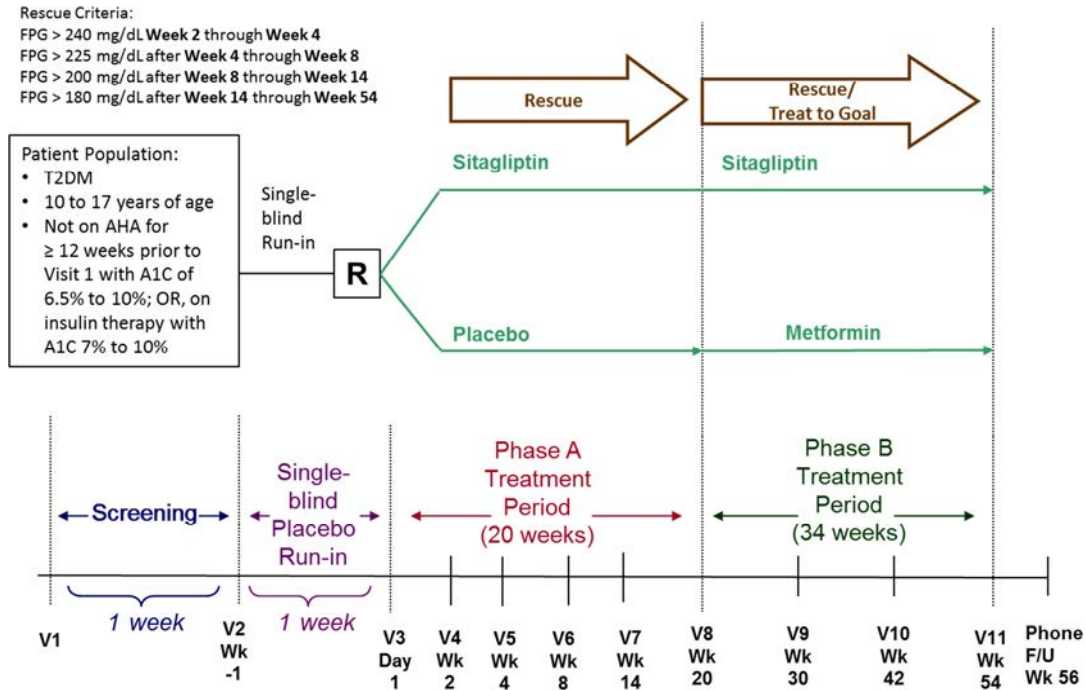
31. Patient has a positive urine pregnancy test.
32. Patient has a site fasting fingerstick glucose (FFSG) >240mg/dL (13.3 mmol/L). **Note:** If the investigator believes that the value does not reflect the patient's recent glycemic control, then the patient should not be excluded at this time. The current 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

Study Design



Refer to Appendix 6.14 for the supplemental dental data sub-study details.

2.4.2 Treatment Plan

Refer to the Study Flow Chart (Section 1.7) for the procedures to be performed at each visit (**Note:** Refer to the Flow charts in Section 6.14.5 for the procedures to be performed at each visit for the Supplemental Dental Data Sub-Study). Following initial screening and evaluation at **Visit 1** eligible patients will proceed to **Visit 2/Week -1**. At **Visit 2**, patients will undergo diet and exercise counseling and initiate sitagliptin- and metformin-placebos provided in blister packs ([Table 1-1](#)). Patients who enter the study on background insulin will continue on the same dose (variance of $\leq 15\%$ of total daily dose) and formulation of insulin throughout the study unless they meet criteria for Rescue Step 2 or Treat to Goal Step 2 or downtitrate their dose due to hypoglycemia.

At **Visit 3/Day 1**, patients will be randomized (1:1) to either sitagliptin OR placebo (Phase A period).

At **Visit 8/Week 20** (start of Phase B), patients in the sitagliptin group who have not initiated glycemic rescue therapy in Phase A will continue to receive sitagliptin and placebo to metformin. Patients in the placebo group who have not initiated glycemic rescue therapy in Phase A will receive sitagliptin-placebo and initiate metformin (refer to [Table 1-2](#)).

Throughout the study, glycemic endpoints, including A1C and FPG will remain masked to the patient and investigator. 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 (and/or A1C value in Phase B) meeting rescue and/or discontinuation criteria (refer to Sections 2.4.2.6 and 2.4.2.7). During Phase B, it is recommended that the investigator "treat-to-goal" if the patient's A1C is $\geq 7.0\%$ as described in Section 2.4.2.6.3.

Patients meeting progressively stricter glycemic rescue criteria will be eligible to initiate glycemic rescue therapy (Step 1 and Step 2). Please refer to [Table 1-1](#) and Section 2.4.2.6 for details.

Note: The patient and family will be instructed to monitor for ketonuria/ketonemia and check fingerstick blood sugars frequently and to contact the site if the patient experiences an acute intercurrent illness (e.g., fever $>101^{\circ}\text{F}$ [38.3°C] and/or gastrointestinal symptoms including vomiting and abdominal pain) at any time during the study. For patients not on baseline insulin therapy, insulin therapy may be initiated during a brief, 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 (i.e., <14 days) initiation 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 (i.e., no food, double-blind study medication, or drink except water and non-antihyperglycemic non-study medications as prescribed) for at least 10 hours prior to **Visits 1, 3, 8, 11, Rescue, and Discontinuation**. The investigator should manage insulin doses appropriately for patients on background 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 $\geq 80\%$ compliance with single-blind placebo medication if the interval between **Visit 2** and **Visit 3** is 7-14 days). 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**. Visits (with the exception of **Visits 1, 3, 8, 11, Step-1 rescue, Treat-to-target Step-1, or Discontinuation visits**) *may* be performed, if approved by the country and local IRB/EC, by a qualified health professional at the patient's home or location other than the site. These visits should be performed according to the guidelines that may exist at the participating institution, and should be consistent with the investigator's 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 the clinic **Visits 1, 3, 8, 11, Rescue, and Discontinuation**.
- The requirement not to take any blinded study medication the morning of the clinic visit for **Visits 8 and 11**.
Note: Non-study medications that are not antihyperglycemic medications should be taken as directed by the prescribing physician.
- The requirement to bring all study medication, blood glucose meter, hypoglycemia assessment tool(s), and any collected self-monitored blood glucose (SMBG) information to the clinic visit.
- Parent/legal guardian should not schedule the patient for an immunization 2-4 weeks prior to **Visits 3, 8, and 11**.

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, if available, (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:

- 1) not on an AHA (for ≥ 12 weeks prior to **Visit 1**) and have a **Visit 1** A1C of $\geq 6.5\%$ and $\leq 10.0\%$, OR
- 2) on a stable dose of insulin (see inclusion criterion #2), and have a Visit 1 A1C of $\geq 7.0\%$ and $\leq 10.0\%$,

and meet all other enrollment criteria will be eligible to enter the single-blind placebo run-in period. **Note:** The results of the antibody screen for anti-GAD or ICA-512 must be available and evaluated before the patient can be randomized at Visit 3.

The first dose of single-blind placebo should be taken as a witnessed dose in the clinic after completion of all Visit 2 study procedures. Patients will then take single-blind placebo as directed for one week prior to randomization (Table 1-1). It is essential that all procedures be performed *before* the patient takes the witnessed dose for this visit.

The hypoglycemia assessment tool(s) will be dispensed at **Visit 2**. Eligible patients will have 1) diet/exercise counseling; 2) training in performing SMBG 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

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 treatment with sitagliptin or placebo.

The first dose of double-blind study medications should be taken as a witnessed dose in the clinic *after* completion of all procedures for the study visit (Table 1-1). It is essential that all procedures be performed *before* the patient takes the witnessed dose for this visit.

2.4.2.5 Visit 3/Day 1 through Visit 11/Week 54: Double-Blind Treatment Period

Phase A: Double-Blind Study Medication: From Day 1 to Week 20 (Table 1-1)

Patients in the sitagliptin group will receive 1 tablet of sitagliptin prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals.

Patients in the placebo group will receive 1 tablet of sitagliptin-placebo prior to the morning meal and 2 tablets of metformin-placebo prior to both the morning and evening meals.

At **Visit 8**, it is essential that all procedures be performed *before* the patient takes the witnessed dose for this visit (except for patients undergoing MTT, see Appendix 6.7).

Refer to [Table 1-1](#) in Section 1.6 for treatment administration details and to Section 2.4.2.6 for glycemic rescue.

Note: Patients will always take 5 tablets per day (3 tablets prior to the morning meal and 2 tablets prior to the evening meal) from one single blister card.

Note: Visit 4 (Week 2) is a telephone call visit. The site should call the patient/parent to:

- monitor for AEs,
- review concomitant medications,
- review hypoglycemia assessment tool(s),
- review SMBG measurements, and rescue criteria,
- assess for compliance with diet and exercise and study medication,
- instruct on hypoglycemia symptoms and management.

Note: AEs and changes in concomitant medication should be documented in the appropriate electronic case report form (eCRF). Hypoglycemia should be documented in the hypoglycemia assessment (HA) eCRF (refer to Section 3.2.3.3).

Phase B: Double-Blind Medication: From Week 20 through Week 54 (Table 1-2)

Patients randomized to the sitagliptin group who have not initiated glycemic rescue therapy during Phase A will **continue** to receive sitagliptin and metformin-placebo.

Patients randomized to the placebo arm who have not initiated glycemic rescue therapy during Phase A, will continue to receive sitagliptin placebo and will initiate metformin (refer to [Table 1-2](#)).

At the start of Phase B, investigators should evaluate the patient's most recent renal function tests (including eGFR and creatinine values) and determine if the patient can safely initiate metformin in a blinded manner based on the local label for metformin.

At the start of Phase B, patients who are not undergoing a MTT must have the first dose of Phase B study medication dispensed at this visit as a witnessed dose in the clinic *after* completion of all procedures for the study visit. Patients who are undergoing a MTT will take the dose of ***double-blind study medication*** from the previous visit's blister-pack (Phase A) as a witnessed dose exactly 30 minutes prior to the start of the standard meal for the MTT (T= -30 minutes). For these patients, the first Phase B dose will be taken **AFTER** the study visit, as the evening dose (Tablets D and E). Please refer to Section 6.7 for dosing instructions. Refer to [Table 1-2](#) for treatment administration details and to Section 2.4.2.6 for glycemic rescue.

2.4.2.6 Glycemic Rescue

Mandatory glycemic rescue will be initiated in both Phase A and Phase B for patients meeting defined glycemic criteria ([Table 2-2](#)). The patient and parent/guardian will be (1) informed of the fasting fingerstick glucose values that meet the threshold corresponding to the patient's duration in the study (e.g., a patient has 3 consecutive fasting fingerstick values >225 mg/dL [12.5 mmol/L] between **Visits 5 and 6**) and (2) instructed to call the site if the patient has 3 consecutive days of fasting fingerstick glucose values that exceed the specified thresholds. Patients and parents should be counseled that if one fasting fingerstick glucose value is above the threshold for rescue, the fasting fingerstick glucose value has to be checked the following morning. If the fasting fingerstick glucose value is above the threshold for rescue on two consecutive days, the fasting fingerstick glucose has to be checked on the third day as well, and the site called if all three values are above the threshold 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 2-2](#)) at each visit. For reference, site personnel will record the threshold level in the fingerstick glucose log book provided to the patient as well.

When the patient calls the site with fasting fingerstick glucose values that exceed the thresholds for 3 consecutive days, the site should call the patient for an 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 at the local and central laboratory. The FPG value obtained at the local laboratory can be used to assess rescue criteria. The patient will be rescued if the FPG is greater than the threshold specified in [Table 2-2](#). Rescue Step 1 involves blinded rescue treatment (implemented through IVRS) and if that fails, the second step (Rescue Step 2) will involve open-label insulin.

Patients who, in the investigator's judgment, are not compliant with blinded study medication should be retrained by site personnel on compliance with treatment and diet/exercise. The patient should be contacted a week later to assess if fasting fingerstick glucose values still meet rescue criteria and follow rescue procedures.

At the rescue Step 1, or Treat to Goal Step 1 Visit, patients should return their current study medication kit to the clinic and stop taking study medication from that kit at that time. At this rescue Step 1/Treat to Goal Step 1 visit, a new kit will be dispensed. Each blister pack in the new kit will contain both the patient's study medication before rescue and the rescue medication. The patient will only take a total of 5 tablets from one blister pack per day.

For rescue Step 2 or Treat to Goal Step 2, there will be no changes to the blister packs, and the patient will continue to take the 5 tablets per day (study medication and rescue medication). Open-label insulin will be initiated at this point for patients who are not on insulin. Patients who are already on insulin therapy from the Screening Visit will have their insulin dose uptitrated.

Note: Investigators should evaluate the patient's most recent renal function tests (including eGFR and creatinine values) and determine if the patient can safely initiate Step 1 glycemic rescue therapy in a blinded manner based on the local label for metformin.

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

The initiation of insulin for patients not on insulin at screening, or an increase in insulin dose of $>15\%$ from baseline for patients on background insulin, will be considered Rescue Step 2, even if they have not undergone Rescue Step 1 and a rescue visit should occur. Procedures performed for this Rescue Visit (refer to Section 1.7) will depend on whether the patient has previously undergone Rescue Step 1 procedures or not:

- If the patient has previously undergone Rescue Step 1, then all Rescue Step 2 Visit procedures must be performed prior to initiation or uptitration of insulin.
- If the patient has not previously undergone Rescue Step 1, then all Rescue Step 1 Visit procedures must be performed prior to initiation or uptitration of insulin.

Note: For Step 2 open-label rescue (Section 2.4.2.6.2) and for Step 2 treat-to-goal (Section 2.4.2.6.3), if initiating insulin is unacceptable or considered inappropriate, an alternate antihyperglycemic (oral) medication may be used for patients ≥ 18 years of age at the discretion of the investigator (in either Phase A or Phase B). The use of DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, etc.), metformin, or GLP-1 receptor agonists is prohibited for purposes of alternate rescue medication.

Note: Patients < 18 years of age for whom initiating insulin or up-titration of insulin for Step 2 open-label rescue (Section 2.4.2.6.2) or for Step 2 Treat-to-Goal (Section 2.4.2.6.3) is considered clinically inappropriate will need to be discontinued from study medication.

Note: For patients who are undergoing a MTT see Appendix 6.7.

2.4.2.6.1 Rescue Step 1 (Blinded)

After randomization, all patients (including patients on insulin as background therapy) meeting protocol-specified glycemic criteria (Table 2-2) must initiate blinded glycemic rescue therapy (sitagliptin or metformin) as specified in Table 2-3, Table 1-1 and Table 1-2. For patients on background insulin therapy, the insulin dose should not be up-titrated for Step 1 rescue.

A patient must be rescued if:

- fasting fingerstick glucose measurements at home meet the rescue thresholds for three consecutive days and is confirmed by a FPG value obtained at an unscheduled visit from a local laboratory that meets rescue criteria (a split sample should be sent to the central lab); OR

- a single FPG value from the central laboratory at any visit meets rescue criteria even if the patient does not report fasting fingerstick glucose values above the threshold.

In Rescue Step 1, study medication and rescue medication (both included in the same blister card) will be administered in a double-blind, double-dummy manner.

Table 2-2

Glycemic Rescue Criteria

	FFSG Thresholds ¹	FPG Thresholds ²
After Week 2 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 14	>200 mg/dL (11.11 mmol/L)	>200 mg/dL (11.11 mmol/L)
After Week 14 through Week 54	>180 mg/dL (10.00 mmol/L)	>180 mg/dL (10.00 mmol/L)
FFSG= fasting fingerstick glucose; FPG= fasting plasma glucose.		
¹ The initial FFSG values that would trigger repeat FFSG measurements. An FPG measurement will be triggered if 3 consecutive FFSG values meet this criterion, and rescue will be initiated if the FPG is above threshold.		
² - After assessing for patient compliance with study medication, perform confirmatory FPG if first a.m. fasting fingerstick glucose value is greater than the defined threshold on 3 consecutive days.		

Table 2-3

Protocol-Specified Glycemic Rescue Medication

	Treatment Group	Rescue Step 1 (Blinded)	Rescue Step 2 (Open-label) ¹
Phase A	Sitagliptin	Metformin ²	Insulin
	Placebo	Metformin ²	Insulin
Phase B	Sitagliptin	Metformin ²	Insulin
	Metformin³	Sitagliptin	Insulin

AHA= antihyperglycemic agent; DPP-4=dipeptidyl peptidase IV; GLP-1= glucagon-like peptide 1.
¹If initiation of insulin is considered unacceptable for a given patient who is ≥ 18 years of age, an alternative oral AHA may be used at the discretion of the investigator. The use of open-label DPP-4 inhibitors, metformin, or GLP-1 receptor agonists, is prohibited for rescue. For patients on background insulin therapy if up-titration of insulin is unacceptable, no alternate oral AHA may be used and the patient will need to be discontinued from study medication (refer to Section 2.4.2.7). Patients < 18 years of age for whom initiating insulin or uptitration of insulin for is considered clinically inappropriate will need to be discontinued from study medication.
² Patients who are not able to tolerate a higher dose of metformin will have their dose reduced at an unscheduled visit and should continue on the maximal tolerated dose for the duration of the study.
³ Patients in the placebo/metformin arm who initiate metformin treatment in Phase B.

Note: Even if rescued, patients will always take 5 tablets per day from one single blister card.

Note: For patients who are undergoing a MTT see Appendix 6.7.

Patients who initiated Step 1 blinded glycemic rescue therapy during Phase A will continue on their blinded study medication and blinded rescue therapy (contained in the same blister pack) for the remainder of the trial and initiate or uptitrate their dose of open-label insulin (Step 2 rescue) if they become eligible.

2.4.2.6.2 Rescue Step 2 (Open-Label)

Six weeks after initiating Rescue Step 1, and after considering patient compliance with blinded study medication as stated in Section 2.4.2.6, if the patient's glucose levels continue to meet glycemic thresholds presented in Table 2-2 the patient *will continue* taking the combination of blinded study therapy and blinded rescue medication from Rescue Step 1 and, in addition, will initiate or uptitrate their dose of open-label insulin therapy (Table 2-3). The insulin regimen and dosing will be at the discretion of the investigator (based on accepted local, national or international guidelines for the indication and use of insulin).

For patients on background insulin therapy, insulin doses can be up-titrated for Rescue Step 2; the change in insulin dose would be at the discretion of the investigator. Any change in insulin dose $> 15\%$ of the screening dose for this purpose will be considered as "Rescue Step 2". Six weeks after initiating Rescue Step 2 or Treat to Goal Step 2, for patients who are receiving basal insulin, the investigator can choose to add prandial insulin if deemed appropriate.

Note: Patients requiring transient (i.e., < 14 days) initiation of insulin or an increase in their 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 Step 2.

If initiation of insulin use is considered unacceptable for a given patient ≥ 18 years of age, an alternative oral AHA may be used at the discretion of the investigator (refer to Section 2.4.2.6).

Note: For patients who are undergoing an MTT see Appendix 6.7.

2.4.2.6.3 Treat-to-Goal Phase B

During Phase B (i.e., from **Visit 8**) A1C values will be unmasked to the investigator by the central laboratory if $\geq 7.0\%$. Patients with fasting fingerstick glucose < 180 mg/dL during Phase B, may at the discretion of the investigator, be treated to achieve a glycemic goal of A1C $< 7.0\%$ (or as close to normal without significant hypoglycemia) if, in the investigator's judgment, the patient has been compliant with study medication. The procedures outlined in Sections 2.4.2.6.1 and 2.4.2.6.2 for initiating Step 1 rescue and Step 2 rescue respectively should also be used to implement Step 1 treat-to-goal (Table 2-4) and Step 2 treat-to-goal for an A1C $\geq 7.0\%$.

Treat-to-Goal Step 1

In order to achieve the glycemic goal of $< 7.0\%$ (or as close to normal without significant hypoglycemia) during Phase B, those patients who did not initiate blinded glycemic rescue Step 1 during Phase A will be eligible to initiate blinded treatment to achieve an A1C of $< 7.0\%$ (Treat-to-Goal- Step 1).

Note: For patients who are undergoing an MTT see Appendix 6.7.

Table 2-4

Blinded Treat-to-Goal- Step 1

Blinded Rescue Agent	Blinded Treatment Assignment	
	Sitagliptin	Metformin
	Metformin	Sitagliptin

Treat-to-Goal Step 2 (Open-Label)

At least six weeks after initiating Rescue Step 1 or Treat-to-Goal Step 1, if the patient's A1C is $\geq 7.0\%$, the patient *will continue* taking the combination of blinded study therapy and medication from Step 1 and, in addition, may initiate or up-titrate their dose of open-label insulin therapy.

The insulin regimen and dosing will be at the discretion of the investigator. The dose of insulin can be titrated to achieve the glycemic goal of A1C of $< 7.0\%$. Patients for whom such up-titration cannot be safely achieved will be discontinued from study medication.

Patients meeting glycemic rescue criteria for whom the addition or up-titration of open-label insulin (Treat-to-Goal Step 2) or alternate glycemic rescue medication is deemed clinically inappropriate by the investigator will be discontinued from study medication.

For patients on background insulin therapy, insulin doses can be up-titrated for Treat-to-Goal Step 2; the change in insulin dose would be at the discretion of the investigator. Any change in insulin dose >15% of the screening dose for this purpose will be considered as “Treat-to-Goal Step 2”.

Note: Six weeks after initiating Rescue Step 2 or Treat to Goal Step 2, for patients who are receiving basal insulin, the investigator can choose to add prandial insulin if deemed appropriate.

If initiation of insulin use is considered unacceptable for a given patient ≥ 18 years of age, an alternative oral AHA may be used at the discretion of the investigator (refer to Section 2.4.2.6).

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 (AE) or a laboratory safety test abnormality. All patients will be followed until resolution (i.e., return to normal or patient’s baseline, or diagnosis determined, or course of abnormalities established) for any laboratory safety test abnormality resulting in discontinuation.

The reason for protocol-specified discontinuation from the study is listed below.

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

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 3.2.3.19 for follow-up of these patients. Initiation of open-label AHA will not be considered as prohibited medication in these patients.

- b) **Hyperglycemia:** Patients ≥ 18 years of age meeting glycemic rescue criteria >6 weeks after initiating Rescue Step 1 or Step 1 Treat-to-Goal, for whom:

- 1- the addition of open-label insulin or the addition of an alternate glycemic rescue medication (Rescue Step 2 or Treat-to-goal Step 2) is deemed clinically inappropriate by the investigator,

OR

- 2- up-titration of open-label insulin (Rescue Step 2 or Treat-to-goal Step 2) for patients on background insulin or for those who have initiated insulin at rescue or up-titration of an alternate glycemic rescue medication is deemed clinically inappropriate by the investigator.

Patients <18 years of age for whom initiating insulin or up-titration of insulin for Step 2 open-label rescue (Section 2.4.2.6.2) or for Step 2 Treat-to-Goal (Section 2.4.2.6.3) is considered clinically inappropriate will need to be discontinued from study medication.

- c) **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).

Patients who are on open-label insulin (background or rescue therapy) or an alternate titratable oral agent for Rescue Step 2 or Treat to Goal Step 2 and meet these criteria can have their insulin/alternate agent dose reduced or interrupted at the investigator's discretion and may continue in the study.

Note: The investigator should make sure the patient's glucose meter and test strips are functioning accurately and that the test procedure is being correctly performed by the patient prior to discontinuation.

- d) Elevation in alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) ALT/AST ≥ 3 -times the ULN as specified in Appendix 6.5.

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 (see the guidance document entitled *Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials* in the Investigator Trial File Binder and refer to the ECI guidance in Section 3.4.6.2.).

- e) eGFR that is consistently <50 mL/min/1.73m².

Note: 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).

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

- g) Pregnancy

Note: A positive urine pregnancy test requires immediate interruption of study medication until serum β -hCG 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.

- h) Phase A: Patient develops any condition for which sitagliptin is contraindicated according to the approved labels in the country in which the study site is located.

Phase B: 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.

Note: Patients who have undergone Step-1 rescue in Phase A and all patients in Phase B should be discontinued if their serum creatinine or eGFR values contraindicate the use of metformin based on the local label.

- i) 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 3.2.3.22. Please refer to Section 3.2.3.19 on how to manage patients who discontinue study medication but who do not withdraw consent.

Note: For patients who are undergoing an MTT see Appendix 6.7.

2.4.2.8 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 the study) to query for serious adverse events. If any serious adverse event requires a supplemental procedure, this should be performed as medically necessary (Refer to section 3.2.3.19).

2.4.3 Beginning and End of Study Definition

The study begins when the first patient signs the ICF. End of Study will be declared when the last patient 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 patient 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 assessment of: A1C, FPG, lipid panel, and measures of beta cell function (change from baseline in HOMA- β , proinsulin/insulin ratio, and, in a subset of patients who agree to undergo a standard meal challenge, 2-hour PMG and indices of insulin secretion derived from C-peptide, insulin, and glucose profiles).

2.6 LIST OF SAFETY MEASUREMENTS

Safety assessments will include collection of adverse events, clinical evaluation (physical examination, vital signs, body weight), laboratory safety studies (blood chemistry, hematology, urine microalbumin/creatinine ratio, and urinalysis), visual oral examination, supplemental dental data, radiologic assessments (bone age), and growth assessments (measurement of height and calculation of BMI, growth velocity). In addition, biochemical markers of bone turnover, calcitonin, CD26, IGF-1 and IGF-BP3 levels will be assessed.

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.

Details of the statistical analysis plan for the supplemental dental data sub-study will be provided in a separate document.

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 2-5](#) below.

The primary efficacy hypothesis will be evaluated by comparing sitagliptin vs. placebo on change from baseline in A1C at Week 20. No multiplicity adjustment is planned as there is a single comparison of 2 treatments using 1 endpoint in the primary hypothesis. Other efficacy analyses will be considered supportive and/or explanatory.

Table 2-5

Summary of Analysis Strategy for Key Efficacy Endpoint

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary			
A1C – Change from baseline at Week 20	cLDA	FAS	Model-based
A1C= hemoglobin A1c; cLDA= constrained longitudinal data analysis; FAS= full analysis set.			

2.7.2 Safety Analyses

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. Adverse events of symptomatic hypoglycemia and selected Gastrointestinal adverse events (diarrhea, nausea, abdominal pain [including discomfort], and vomiting) are pre-specified Tier 1 safety parameters for which p-values and 95% confidence intervals for between-treatment differences in the percentage of patients with the adverse event of symptomatic hypoglycemia will be calculated using the Miettinen and Nurminen (M&N) method.

2.7.3 Power and Sample Size

This study will randomize at least 190 patients, but no more than 220 patients, including approximately 10 to 11 patients randomized to the metformin arm prior to its removal from the study design in amendment 5 to this protocol (P083-05). Power calculations are based on 90 patients in each of the sitagliptin and placebo treatment groups.

A sample size of 90 patients per arm will be equivalent to an effective sample size of 82 patients per arm 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 82 patients per arm will provide 82% power to detect a treatment difference of 0.5% at Week 24 ($\alpha=0.05$, two-sided test) assuming the conditional standard deviation is 1.1 %. The half-width of the 95% CI is expected to be 0.34%.

Table 2-6 shows the power based on two true differences using $\alpha=0.05$ (two-sided).

Table 2-6

Power for Superiority in Change from Baseline in A1C
82 Effective Patients per Group and $\alpha = 0.05$ (two-sided)

True Difference (%)	Standard Deviation (%)	Power (%)
0.6	1.1	93%
0.5	1.1	82%

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 [1-21]. 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; 9-11], 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 [30-32], 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 is associated with the development of microvascular complications, particularly nephropathy [36-39], as well as the presence of several cardiovascular risk factors that increase the likelihood of early macrovascular complications in this population [3; 39-42]. As in adults, blood glucose levels influence the development and progression of both the microvascular and likely macrovascular complications of T2DM [36; 43]. Therefore, given the substantial lifelong cumulative exposure to hyperglycemia for this population, the availability of effective therapies is necessary.

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 [45-47]. Although initially effective in lowering A1C, studies suggest that 35-50% of pediatric patients need an additional agent within a year of diagnosis [48]. Since the development and 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; 49-50], the development of safe and effective agents that target various aspects of these key defects is important [51].

Sitagliptin, an orally active, well-tolerated, potent and selective inhibitor of dipeptidyl peptidase IV (DPP-4), provides glycemic improvement by increasing the concentration of incretin hormones, including the key glucoregulatory hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which act to lower glucose through enhancement of insulin biosynthesis and release and suppression of glucagon secretion [52]. Based upon its mechanisms of action and the similar pathophysiology underlying T2DM in youths and adults, the favorable safety and efficacy profiles of sitagliptin are predicted to be similar for youths relative to adults.

3.1.2 Rationale for Efficacy Endpoints

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. Moreover, A1C is the key glycemic parameter which correlates with reduction of risk of diabetic complications; hence, demonstration that sitagliptin lowers A1C is important in establishing the value of this medication in the management of patients with T2DM. Fasting plasma glucose will also be followed at each visit to characterize the time course of glucose control.

In this study, a 9-point meal tolerance test (MTT) will be obtained to assess treatment effects on fasting glucose, post-meal glucose and insulin secretion. Samples for glucose, insulin, and C-peptide will be taken at each time point, and proinsulin at time 0. This test will use a standardized, predominantly solid meal. The response to a solid meal should better model the patient's usual day-to-day food intake, and hence better predict the post-meal glucose control that sitagliptin can provide.

3.1.3 Rationale for Selection of Patient Population

This is a study designed to assess the safety and efficacy of sitagliptin in the pediatric population; because the safety of a new agent is best assessed in a drug naïve patient population, this study will enroll patients with T2DM who have not been on an AHA for ≥ 12 weeks prior to **Visit 1** and have inadequate glycemic control (A1C 6.5%-10%). Since T2DM is not prevalent in children less than 10 years of age, this study will only include patients 10 to 17 years of age (inclusive) with T2DM.

A drug naïve population of pediatric patients 10 to 17 years of age with T2DM is an important population in which to assess the safety and efficacy profile of a new agent. However, a significant proportion of pediatric patients 10 to 17 years of age with T2DM are being treated with insulin alone, and despite being on insulin, have inadequate glycemic control [53-57]. Thus, the addition of sitagliptin to ongoing insulin therapy is a potential, and likely, treatment regimen in pediatric patients. The safety and efficacy of the addition of sitagliptin to patients with inadequate glycemic control on insulin has already been established in adults, and a similar profile is expected in pediatric patients 10 to 17 years of age. Therefore, including insulin-using patients in this clinical trial will broaden the representativeness of the clinical trial population, and will allow the results to be more generalizable to a wider range of patients who could benefit from therapy with sitagliptin.

3.1.4 Rationale for Dose Regimen

Sitagliptin

The sitagliptin dose for this study was based on data from Protocol 081 (A single-dose study to assess the pharmacokinetics, safety, and tolerability of sitagliptin in adolescents). This study evaluated single oral 50-, 100-, and 200-mg doses in adolescents with type 2 diabetes, and compared the pharmacokinetics of sitagliptin in this population with that in adult patients with diabetes (Protocol 005). All doses were generally well-tolerated, with the 100-mg dose

meeting the prespecified primary hypothesis for similarity of sitagliptin $AUC_{(0-\infty)}$ between adults and adolescents. Furthermore, an exploratory PK/PD analysis indicated that the relationship between plasma sitagliptin concentration and DPP-4 inhibition is similar in adolescents and adults.

Metformin

The titration and dosing of metformin follows the guidelines in the label as well as clinical practice guidelines. Metformin/metformin placebo will be started at 500 mg/day. The dose will be increased in 500 mg weekly increments up to a total daily dose of 1000 mg bid, if tolerated, by 3 weeks.

3.1.5 Rationale for Placebo Use

The placebo-control group is an essential arm in this trial, as it supports the evaluation of safety and efficacy of sitagliptin in youths 10 to 17 years of age (inclusive) with T2DM and inadequate glycemic control. 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 placebo treatment group glucose levels, would not accurately characterize the glucose-lowering efficacy of sitagliptin in this population. Non-placebo controlled, active-comparator studies provide important information, but the efficacy profile of an agent is best characterized by comparison to placebo, especially in the first such trial of the agent in the pediatric population. Furthermore, in this first study of sitagliptin in this population, the safety profile of sitagliptin is best compared to placebo.

Despite the importance of this placebo-controlled study in characterizing the safety and efficacy of sitagliptin in this population, the medical risk of inadequate glycemic control has been considered and efforts to limit this risk have been implemented in this protocol. Although long-term—that is, over years—inadequate glycemic control has been shown to increase the risk of diabetic complications, the risk of short-term inadequate control is likely to be much smaller. To ensure that patients will not be exposed to poorer control for an undue period of time, strict glycemic rescue and discontinuation criteria have been included in the study design. Progressively stricter glycemic rescue/discontinuation criteria will be implemented, so that patients with poorer glycemic control will be rescued early in the double-blind treatment period. In addition, the placebo-controlled phase of this study (Phase A) will only last for 20 weeks, at the end of which all patients in the placebo group who have not met rescue criteria will be switched to active therapy (with metformin) in a blinded fashion. Furthermore, all patients will receive initial counseling for diet and exercise and ongoing monitoring of diet and exercise and will be counseled to monitor fingerstick glucose concentrations so that they can be 'rescued' promptly, should they meet rescue thresholds; all of these measures are expected to reduce the duration of exposure to prolonged hyperglycemia.

3.1.6 Future Biomedical Research

Merck will conduct Future Biomedical Research 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 6.13: Collection and Management of Specimens for Future Biomedical Research.

3.1.7 Supplemental Dental Data Sub-Study

Note: Procedures for the Supplemental Dental Data Substudy do not apply to Brazil and Serbia.

The visual oral examination (VOE) is an agency-mandated binding element in MK-0431 P083 based on pre-clinical findings observed in rats summarized below.

- In the 14-week oral range-finding study in rats, sitagliptin doses of 500 mg/kg/day, 1000 mg/kg/day, 1500 mg/kg/day, and 2000 mg/kg/day provided exposures margins of approximately 58-, 132-, 181-, and 271 fold, respectively, over the therapeutic AUC in patients receiving 100 mg/day of 8.5 $\mu\text{M}\cdot\text{hr}$. Thickened upper incisors were seen in males and females at 1500 mg/kg/day and 2000 mg/kg/day beginning in Drug Week 10. This change was also associated with degeneration of the incisor ameloblasts and odontoblasts and gingivitis noted histologically. There were no changes noted in the molar or other, non-incisor, teeth. Missing and broken upper incisors were also noted in males at 1500 mg/kg/day and males and females at 2000 mg/kg/day beginning in Drug Week 11. The broken teeth were considered secondary to the histologic findings in the teeth and gums. The NOEL for this change in the continuously growing incisor teeth was 500 mg/kg/day (approximately 58 fold margin over the AUC at the clinical dose of 100 mg/day).
- In the 2-year carcinogenicity study in rats, sitagliptin doses of 50 mg/kg/day, 150 mg/kg/day, and 500 mg/kg/day providing exposure margins of approximately 6-, 19-, and 58-fold, respectively, over the therapeutic AUC in patients receiving 100 mg/day of 8.5 $\mu\text{M}\cdot\text{hr}$. There was a dose-dependent increase in treatment-related horizontal striped discoloration and lightened upper and/or lower incisors in both males and females at all doses. The discoloration was first noted in Drug Week 31 (discoloration) and Drug Week 53 (lightening) at 500 mg/kg/day with nearly all animals exhibiting both teeth signs by study termination. At 150 mg/kg/day the discoloration was first noted in Drug Week 33 (males) or Drug Week 41 (females). At 50 mg/kg/day, only a few animals were observed with horizontal striped discoloration and/or lightened incisors by study termination.

- These dental findings were limited to the continuously growing incisors of the rat. There were no changes observed in teeth of the mice in the 14-week range-finding study (doses up to 1000 mg/kg/day providing exposure of up to 2340 $\mu\text{M}\cdot\text{hr}$) or in the 2-year carcinogenicity study (doses up to 500 mg/kg/day providing exposure of 597 $\mu\text{M}\cdot\text{hr}$). There was no evidence of developmental changes involving the teeth in the rabbit developmental toxicity studies. The mouse and rabbit also have continuously growing incisors. Further, these changes were not observed in the chronic dog or 3 month monkey studies conducted. Based on these findings it is concluded that the findings related to the rat incisors noted in the 14-week oral range-finding and carcinogenicity studies were species-specific findings.

The purpose of this sub-study is to augment the VOE data currently being collected in the main study P083. In addition, it will allow the dental data to be assessed by an independent reviewer who is a trained pediatric dentist.

Patients participating in the main study, P083 (new, and ongoing patients on/off study medication), will be asked to participate in a Supplemental Dental Data Sub-Study. Patients who completed 54 weeks of the main study (on/off study medication), including patients participating in MK-0431 P351 (a non-interventional follow-up study to MK-0431 P083), are also eligible to participate. Patients who have withdrawn consent from P083 are not eligible.

Note: Patients currently enrolled in MK-0431 P351 are also eligible to be contacted to participate in this sub-study.

Details of this sub-study are presented in Appendix 6.14: Supplemental Dental Data Sub-Study.

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 dose of thyroid medication regimen for at least 6 weeks prior to **Visit 1** and/or a stable dose of lipid-lowering and antihypertensive medications for at least 4 weeks prior to **Visit 1**.

Note: Thyroid medications to treat hyperthyroidism are prohibited.

Antihyperglycemic Medications

Double-blind study medication, and open-label insulin (background or rescue therapy), and alternate agents (other than metformin, or a DPP-4 inhibitor, or a GLP 1 receptor agonist) are

the only AHAs permitted in the study. Patients who discontinue study medication may be treated with antihyperglycemic medication as considered clinically appropriate.

Rescue and treat-to-goal medications indicated as part of the study protocol are explained in Section 2.4.2.6.

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 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 (i.e., 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 youths 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

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. At a minimum, the patient and parent/guardian will be instructed to monitor fingerstick glucose concentrations (1) once daily (including at least 2 measurements a week before breakfast) and (2) whenever they have symptoms of hypoglycemia, and (3) during intercurrent illnesses. **For patients on insulin (at randomization as background therapy, or if initiated for Step 2 glycemic rescue or Step 2 Treat to Goal), the investigator will counsel the patient and parent/guardian on the required 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 fasting fingerstick glucose values that meet glycemic rescue criteria (refer to Section 2.4.2.6.1) after randomization.

3.2.3.2 Monitoring for Ketonuria/Ketonemia

At **Visit 2/Week -1**, patients will be supplied with screening strips to monitor 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 or blood for ketonemia 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. If urine ketones are "moderate" or "large," or if ketonemia is positive at any time during the study 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 (e.g., 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 provided 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 (i.e., 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: 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: The Hypoglycemia assessment tool 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 (i.e., 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 event of symptomatic hypoglycemia must be reported as an adverse event on the adverse event 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 counseled 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. Subsequently, if the patient meets criteria for glycemic rescue, rescue Step 1 should be initiated in a blinded fashion (refer to Section 2.4.2.6.1) instead of increasing the insulin dose to the baseline dose. After initiating Step 1 rescue, insulin dose should be adjusted based on the patients glycemic response; the dose of insulin can be increased for Step 2 rescue (refer to Section 2.4.2.6.2). 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 in 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 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 6.1.

3.2.3.6 Laboratory Monitoring

Patients should be fasting for at least 10 hours before **Visits 1, 3, 8, 11, Rescue, and Discontinuation**. Fasting is not required prior to other visits.

All laboratory tests outlined in the Study Flow Chart (e.g., FPG, A1C, CBC, chemistry panel, lipid panel, TSH, etc.) and the blood samples for glucose collected during the MTT will be performed by the central laboratory (with the exception of the site fingerstick A1C, site and patient fingerstick glucose determinations, site dipstick urinalysis, pregnancy test, CD26 assay and diabetes autoantibody panel).

Glycemic measurements will be masked during the double-blind treatment period for A1C, FPG, and MTT measurements. 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 (and/or A1C value in Phase B) meeting rescue and/or discontinuation criteria (refer to Sections 2.4.2.6 and 2.4.2.7). In addition, during Phase B, it is recommended that the investigator "treat-to-goal" if the patient's A1C is $\geq 7.0\%$ as described in Section 2.4.2.6.3.

Laboratory test results for chemistry (e.g., 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 Section 2.3 and 2.4.2.7 respectively).

At or after **Visit 3/Day 1**, ALT and AST elevations greater or equal than 3-times the upper limit of normal (ULN) will be flagged by the central laboratory and patients will be retested, according to Appendix 6.5.

Further, CD26, IGF-1, IGF-BP3, and biochemical markers of bone turnover will be obtained (see Appendix 6.4). Samples for the measurement of CD-26 expression may not be collected in all patients. Throughout the study, CD26 values will remain masked to the patient and investigator. Information regarding any special procedures for the processing of these laboratory samples will be communicated separately.

3.2.3.7 ECG Procedures

ECGs performed at baseline (performed at or after **Visit 2/Week -1** up to and including **Visit 3/Week 0**), **Visit 8/Week 20**, **Visit 11/Week 54**, **Discontinuation Visit** (if applicable), and **Rescue Step 1 or Treat-to-Goal Step 1 Visit** (if applicable) will be read locally, and will not be sent to a central ECG reading laboratory.

3.2.3.8 Meal Tolerance Test (MTT)

For parent/guardians and patients who agree to participate, an MTT will be performed at **Randomization Visit 3/Day 1**, at **Visit 8/Week 20**, and at **Visit 11/Week 54 (and/or at the Rescue [Step 1 or Treat-to-Goal Step 1] Visit or Discontinuation Visit)** after a standard meal. Patients who participate in the MTT at **Visit 8/Week 20** will be contacted by the site the day after the visit to collect the date and time that the first dose of Phase B study medication was taken. The standard meal will consist of 1 can of a nutrition drink and 1 nutrition bar supplied by the Sponsor (approximate total nutrient content: 460 kcal, 9 g fat, 75 g carbohydrate, 18 g protein). For a chart of procedural steps, blood samples and collection times for the MTT, refer to **Appendix 6.7**.

Note: At **Visit 8/Week 20**, **Visit 11/Week 54** or the **Discontinuation Visit**, an MTT should not be performed if the patient has been previously rescued. An MTT should not be performed if the patient has been off double-blind study medication for ≥ 5 days, if the study medication was discontinued due to an adverse event, or if the visit occurs prior to **Visit 5/Week 4**.

Note: Patients on background insulin therapy will not have the MTT performed.

3.2.3.9 Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) is a health-related quality of life measure consisting of a 23-item generic core scale plus disease-specific modules to be completed by the child and parent individually [58, 65]. The generic core scale and the 28-item diabetes module will be used in this study. The generic core scale includes questions on physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). The diabetes module includes questions on diabetes symptoms (11 items), treatment barriers (4 items), treatment adherence (7 items), worry (3 items), and communication (3 items).

Data from the PedsQL (Pediatric Quality of Life Inventory) provided at Screening will provide valuable quality of life epidemiologic data for this population, which may contribute to scientific literature.

The PedsQL will be administered at the baseline visit in countries where local validated translations are available.

Note: The PedsQL will not be administered to illiterate parents and their children.

3.2.3.10 Tanner Staging Procedures

Tanner Staging will be performed in order to assess the physical measurements of sexual development. Tanner Staging will be performed at **Visits 3, 8 and 11** or the **Discontinuation Visit** (if applicable), and **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** (if applicable). Refer to Appendix 6.8 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.

3.2.3.11 Visual Oral Examination Procedures

A visual oral examination (including inspection of the teeth) will be performed at **Visits 3, 8, and 11** or the **Discontinuation Visit** (if applicable), and **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** (if applicable). Refer to Appendix 6.10 for visual oral examination procedures and to Appendix 6.14 for supplemental dental data sub-study details.

3.2.3.12 Bone Age Assessment Procedures

An X-ray of the left hand and wrist [standard postero-anterior (PA) view] will be obtained at **Visits 3, 8, and 11** or the **Discontinuation Visit** (if applicable), and **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** (if applicable). The bone age will be estimated based on the standards of Gruelich and Pyle by a central vendor. Details of the bone age assessment are available in a separate Independent Review Charter for this purpose. Baseline (**Visit 3**) and **Visit 8** X-rays will be read upon receipt at the Central Vendor; if there is a status of "skeletal maturity" for either the **Visit 3** or **Visit 8** X-ray, then no further X-rays are required during the study. See below for detailed guidance for specific study timepoints.

If a patient is rescued in Phase A:

- If before **Week 14**, then no further X-ray is required for the rest of the study,
- If between **Week 14** and **Week 20**, an X-ray should be obtained at the **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** but none thereafter.

If a patient is rescued in Phase B:

- If before **Week 36**, then no further X-rays are required for the rest of the study,
- If at **Week 36** or after, an X-ray should be obtained at the **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** but none thereafter.

If a patient is discontinued in Phase A:

- If before **Week 14**, then no further X-ray is required,
- If between **Week 14** and **Week 20**, an X-ray should be obtained at the **Discontinuation Visit**, but none thereafter.

If a patient is discontinued in Phase B:

- If before **Week 36**, then no further X-ray is required,
- If at **Week 36** or after, an X-ray should be obtained at the **Discontinuation Visit**, but none thereafter.

3.2.3.13 Informed Consent

3.2.3.13.1 General Informed Consent

The investigator must obtain documented consent from the parent/guardian of each potential patient in biomedical research or when an investigational drug is administered to patients in this clinical study prior to any procedure. In addition, documented assent forms must be obtained from the patients in this clinical study.

Consent must be documented by the dated signature of the parent/guardian of the patient 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. Assent must be documented by the dated signature of the patient along with the dated signature of the person conducting the assent discussion. A copy of the signed and dated consent and assent forms should be given to the patient and/or the parent/guardian before participation in the trial.

When the study population includes non-English speaking people, the information in the consent and assent forms should be translated and communicated to the patient in language understandable to the patient and parent/guardian. Either the investigator or Sponsor may take the responsibility for the translation; however, documentation must exist to demonstrate who performed the translation and that the translation was verified by an individual other than the person who performed the translation. Accurately translated consent and assent forms should be provided with a written statement by the translator (whether the translator is the investigator or a professional translator), indicating that the consent and assent forms are an accurate translation of the accompanying English version.

The initial informed consent and assent forms, any subsequent revised written informed consent and assent forms, and any written information provided to the patient and/or parent/guardian must receive the IRB/IEC's approval/favorable opinion in advance of use. The patient and parent/guardian should be informed in a timely manner if new information becomes available that may be relevant to the patient's and/or parent's/guardian's willingness to continue participation in the trial. The communication of this information will be provided and documented via revised consent and assent forms or addendum to the original consent and assent forms.

3.2.3.13.2 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.

3.2.3.13.3 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.

3.2.3.13.4 Consent for the Supplemental Dental Data Sub-Study

The investigator or qualified designee will explain the Supplemental Dental Data Sub-Study to the parent/legal guardian and patient, answer all of his/her questions, and obtain written informed consent from the parent/legal guardian and written informed assent from the patient (if patient can legally consent, only his/her consent will be obtained), before performing any procedure or obtaining any data related to the Supplemental Dental Data Sub-Study. A copy of the informed consent and assent will be given to the parent/legal guardian and patient. Refer to Appendix 6.14 for supplemental dental data sub-study details.

3.2.3.14 Future Biomedical Research Collection of Specimens

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

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

3.2.3.15 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.

3.2.3.16 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.

3.2.3.17 Stratification

Randomization at Visit 3 will be stratified by the patient's insulin use at Visit 1 into the following two strata: (1) insulin user; (2) non-insulin user.

3.2.3.18 Randomization/Allocation

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

3.2.3.19 Post-Study Follow-Up

- *Post-study 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 serious adverse events that occurred after the administration of the last dose of study medication. The date of the telephone contact should be recorded and any serious adverse events that have occurred should be recorded in the Adverse Event eCRF.

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

For patients who have completed the study prior to approval of amendment 12 (on/off study medication), including patients participating in P351, refer to Appendix 6.14 for supplemental dental data sub-study details.

- *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 serious adverse events that occurred after the administration of the last dose of study medication.

After the 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), collection of adverse events, VOE, and dental photos (for patients who consent, see Section 6.14). 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 (i.e., not at **Week 20** or **Week 54**), up until the patient has reached the Week 54 visit (i.e., the visit that is approximately 54 weeks from randomization **Visit 3/Day 1**). The purpose of these telephone contacts will be to assess for serious adverse events 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.

- ***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.

3.2.3.20 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 drug, but should continue to be monitored in the study.

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

3.2.3.21 Interruption/Discontinuation/Withdrawal from Study Medication

If a patient who has initiated Step-1 rescue therapy in Phase A, or is in Phase B of the study 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 metformin label) because the patient may be on metformin (i.e., either on blinded metformin or matching metformin placebo). 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 (e.g., 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 he/she 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.

3.2.3.21.1 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 (e.g., 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.

3.2.3.22 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 11/ Week 54**, and at the **Rescue [Step 1 or Treat-to-Goal Step 1] Visit**. Refer to the Study Flow Chart, Section 1.7, for details.

In the subset of patients who have undergone an MTT at baseline, an MTT will be performed at the **Discontinuation Visit**. However, an MTT should not be performed if the patient has been rescued. Also, at the **Discontinuation Visit**, an MTT should not be performed if the patient has been off double-blind study medication for ≥ 5 days, if the study medication was discontinued due to an adverse event, or if the visit occurs prior to **Visit 5/Week 4**.

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 3.2.3.19).

3.2.3.23 Collect Substance Use Information

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

3.2.3.24 Supplemental Dental Data Sub-Study

All sub-study procedures are outlined in Appendix 6.14.

3.3 EFFICACY MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Efficacy

Efficacy measurements include laboratory assessment of: A1C, FPG, fasting insulin and proinsulin, lipid panel. In a subset of patients who agree to undergo the 9-point MTT, samples of C-peptide, insulin, and glucose will be collected at all time-points: proinsulin will only be collected at time 0.

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, 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 hypoglycemia assessment tool(s) will be provided to the patient to collect hypoglycemia information.
- Laboratory safety studies will include blood chemistry (including ALT, AST, creatine phosphokinase [CPK], total bilirubin, and alkaline phosphatase), calcitonin, CD26 assay, 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 6.4.

- Visual oral examination, radiologic assessments (bone age), and growth assessments (measurement of height, calculation of growth velocity, TS, and serum IGF-1 and IGF-BP3).
- Biochemical markers of bone turnover: urine (second AM void) N-terminal cross-linking telopeptide of bone collagen (NTX) and creatinine; and serum bone-specific alkaline phosphatase (Ostase assay).

3.4.2 Data Monitoring

3.4.2.1 Executive Oversight Committee

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

3.4.2.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external DMC will monitor the interim data (including data from the Dental Sub-study) from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators)

and must have no competing interests that could affect their roles with respect to the trial. The DMC 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 DMC will make recommendations to the EOC regarding steps to ensure both patient safety and the continued ethical integrity of the trial. The DMC can recommend stopping the trial for either an unacceptable safety signal in one of the arms of the study or if in its opinion continuing double blind treatment is unethical.

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 DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC 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 patient 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:

- Administration of 2 or more tablets per day (≥ 200 mg) of sitagliptin/matching placebo for more than 1 day.
- Administration of more than 2 tablets per day (> 200 mg) of sitagliptin/matching placebo.

For recommended management of acute overdose, 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.

Investigators/site personnel are to consult the local, approved metformin product label for guidance on the definition of an overdose of metformin.

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 another 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 Non-serious 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 (e.g., 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/patient, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one’s ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [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/patient taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject/patient 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. 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/patient 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? 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? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study.) 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/PATIENT, 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. 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 Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.) 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/patient 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, but prior to unblinding, along with an explanation as to when and 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. Details of the analysis of data from the supplemental dental sub-study will be provided in a separate document.

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 (both the Phase A and Phase B periods) will be conducted as a double-blind study under in-house blinding procedures. At the end of the Phase A period, a copy of the database will be frozen after medical/scientific review has been completed, and Phase A data have been declared final and complete. Members of the study team will be unblinded in order to review and perform an analysis of all available data at the time of the database lock as well as author a CSR. This analysis addresses the primary hypothesis and, hence, is not an interim analysis. This first CSR will include the analysis of all Phase A (Week 0 to Week 20) data and all available data for Phase A+B (Week 0 to Week 54) at the time of this first database lock.

A separate, blinded (ie, blinded to participant-level treatment assignment) SPONSOR study team that has been identified will continue monitoring the conduct of the remaining Phase B study period. All personnel who are unblinded following the first database lock will be excluded from any future data review at the individual participant level. At the end of the 54-week study, the second database lock will occur after medical/scientific review has been performed, and data have been declared final and complete. A separate CSR will be prepared after the second database lock. This second CSR will include the analysis of all Phase A+B (Week 0 to Week 54) data.

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 are listed below. The baseline value will be defined as the **Visit 3/Week 0/Day 1** (randomization) measurement. If this measurement is not available, the last available pretreatment 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.

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. In addition, change from baseline in A1C will be analyzed at Week 14. Week 20 is the primary time point for efficacy analysis.

Table 3-2

Efficacy Endpoints

Endpoint Assessing Primary Hypothesis
Change from baseline in A1C at Week 20
Secondary Endpoints
Change from baseline in A1C at Week 54
Proportion of patients with A1C at goal (<7.0%, <6.5%) at Week 20 and Week 54
Change from baseline in fasting endpoints at Week 20 and Week 54:
<ul style="list-style-type: none"> • FPG • Insulin • Proinsulin • Proinsulin / Insulin Ratio • Homeostatic Model Assessment of β-cell function • Homeostatic Model Assessment of insulin resistance
Change from baseline in 2-Hour PMG
Change from baseline in AUC endpoints (Total AUC and Excursion AUC) at Week 20 and Week 54:
<ul style="list-style-type: none"> • Glucose • Insulin • C-peptide • Insulin AUC / Glucose AUC
Proportion of patients initiating glycemc rescue therapy by Week 20 and Week 54
Additional Endpoints
Change from baseline in A1C at Week 14
Time to initiation of glycemc rescue therapy at Week 20 and Week 54
Change from baseline in endpoints using the C-peptide minimal model at Week 20 and Week 54
Change from baseline in endpoints derived from 9-point MTT at Week 20 and Week 54
Percent change from baseline in lipid panel at Week 20 and Week 54:
<ul style="list-style-type: none"> • Triglycerides • LDL-C • HDL-C • Non-HDL-C • Total cholesterol
A1C= hemoglobin A1c; AUC=Area under the curve; FPG= fasting plasma glucose; HDL-C= high density lipoprotein cholesterol; LDL-C= low density lipoprotein cholesterol; PMG= post meal glucose.

If FPG is missing at visits where meal tolerance test (MTT) data are collected, FPG will be the average of the -10 minute and 0 minute measurements from the MTT.

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. Tier 1 safety endpoints are listed in the [Table 3-4](#).

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 6.6. These criteria are based upon elevations considered to be clinically meaningful relative to the laboratory normal ranges.

3.5.3.3 Derivation of Efficacy Endpoints

Computational details for efficacy endpoints listed in [Table 3-2](#) are provided below:

- $HOMA-\beta = 20 \times \text{fasting insulin (in mIU/mL)} \div \{[\text{FPG (in mg/dL)}] / 18\} - 3.5\}$
- $HOMA-IR = \text{fasting insulin (in mIU/mL)} \times \text{FPG (in mg/dL)} / (22.5 \times 18)$
- AUC endpoints will be derived via the trapezoidal rule using 9-point MTT measurements.
- Excursion AUC = incremental AUC above the level at the start of the meal. AUC below the level at the start of the meal will not contribute to the Excursion AUC.
- 2-Hour incremental PMG = Glucose at 120 minutes – glucose at 0 minutes
- Endpoints derived from 9-point MTT using the C-peptide minimal model
 - Static sensitivity to glucose (Φ_s): the effect of glucose concentration on beta-cell secretion
 - Dynamic sensitivity to glucose (Φ_d): the effect of the rate of change of glucose on insulin secretion when glucose concentration is increasing and above basal level
 - Overall sensitivity index (Φ): average insulin secretion rate \div average glucose simulation, calculated as a function of Φ_s , Φ_d , and Φ_b
 - Composite index of insulin sensitivity (ISI): $10,000 / \text{sqrt} [(\text{FPG} \times \text{FPI}) \times (\text{mean glucose concentration during the meal} \times \text{mean of insulin concentration during the meal})]$
 - Disposition indices: beta-cell function accounting for insulin sensitivity
 - Static (DI_s) = $\Phi_s \times \text{ISI}$
 - Dynamic (DI_d) = $\Phi_d \times \text{ISI}$
 - Overall (DI) = $\Phi \times \text{ISI}$

- Insulinogenic index = $[\text{insulin (in mcIU/mL) at 30 min.} - \text{insulin (in mcIU/mL) at 0 min.}] / [\text{glucose (in mg/dL) at 30 min.} - \text{glucose (in mg/dL) at 0 min.}]$
- For analyzing the ratio of proinsulin to insulin, insulin data in mcIU/mL will be converted to mmol/L by multiplying by 6.945.

3.5.3.4 Derivation of Safety Endpoints

- Bone age: The average of 2 readings at each time point will be used, unless the bone age is adjudicated. In situations where adjudication is required, the bone age specified by the adjudicator will be used (see details in the Independent Review Charter).
- Growth Velocity for chronologic age = $\text{Change from Baseline in Height} / \text{Change from Baseline in Chronologic Age}$
- Growth Velocity for bone age = $\text{Change from Baseline in Height} / \text{Change from Baseline in Bone Age}$
- BMI percentile: The percentile of BMI derived from the BMI-for-age percentile charts defined in Appendix 6.9.
- Skeletal maturation = $\text{Change from Baseline Bone Age} / \text{Change from Chronologic Age}$.
- The derivation of dental safety endpoints will be provided in the P083 Dental Analysis Plan.

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data. The FAS population will include all randomized patients who took at least one dose of study medication (except as noted in Appendix 6.12 for a patient who was randomized twice).

For analyses using the longitudinal data analysis (LDA) model, patients must also 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, patients must also have a baseline measurement.

All patients randomized within the incorrect stratum for insulin use will be classified according to the stratum they should have been randomized to in all analyses that include the stratification factor of insulin use. The intended stratum will be derived based on insulin use at Visit 1/Screening. An accounting of incorrectly stratified patients will be provided in the CSR.

For analyses of endpoints unique to the 9-point MTT, the analysis population will include only those patients who participated in the 9-point MTT.

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.

3.5.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized patients who took at least one dose of study treatment (except as noted in Appendix 6.12 for a patient who was randomized twice). Patients will be included in the treatment group corresponding to the study treatment they actually took for the analysis of safety data using the APaT population. This will be 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 Section 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 the $\alpha=0.05$ (2-sided) level.

Analyses will be performed for Phase A (Week 0 to Week 20) and Phase A+B (Week 0 to Week 54). In addition, change from baseline in A1C will be analyzed at Week 14. Between-group comparisons (sitagliptin vs. placebo) for all efficacy and safety endpoints will be performed for Phase A analyses only. The Week in the analysis is derived by mapping the relative day ranges listed in Appendix 6.11.

Data from patients already randomized to the metformin arm in P083 under previous amendments (from P083-01 to P083-04) will be summarized separately from the summaries and analyses addressing the objectives of the current protocol amendment. Data from patients who were randomized to placebo in Phase A followed by the sequence of either sitagliptin or metformin (for either rescue in Phase A, or the switch in Phase B, whichever is earlier) before amendment P083-05 implementation will be combined and included in the Phase A analysis as the Placebo Group. The data for patients who were randomized in Phase A to the sequence of placebo followed by sitagliptin and who initiated sitagliptin in Phase B before amendment P083-05 was initiated will be summarized separately in the Phase A+B analyses.

3.5.5.1 Statistical Methods for Efficacy Analyses

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 (sitagliptin versus placebo)

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 (sitagliptin versus placebo)

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.

Phase A (Week 0 to Week 20)

The primary efficacy analyses will compare sitagliptin to placebo in change from baseline in A1C at Week 20.

Primary Endpoint: TE Estimand

To address the primary hypothesis using the TE estimand, the mean change from baseline in A1C at Week 20 in the sitagliptin group will be compared to that in the placebo group using the estimated treatment difference via a constrained longitudinal data analysis (cLDA) model, proposed by Liang and Zeger [59]. This cLDA model assumes a common baseline

mean across treatment groups within each stratum (insulin use at screening) and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline values and the values observed at each post-baseline time point. The cLDA model will include terms for treatment, time, baseline BMI percentile, insulin use at screening (yes/no), and the interaction of time by treatment, unless the model fails to converge. To ensure model convergence, the stratification factor, insulin use, will be removed from the model if necessary. Time will be 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.

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 stratum. 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.

Change from baseline in A1C at Week 14 will also be assessed from the same cLDA model used for the analysis at Week 20.

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, 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: 14 to <20 weeks; C: 8 to <14 weeks; D: 0 to <8 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, each reference group (combination of deviation pattern and treatment group) that has one or more patients with missing data must contain at least one RD patient.

In these studies, patients were not required to return for clinic visits when discontinued from study medication until the implementation in September 2015 of amendment P083-09. Thus, the RD analysis may not be feasible due to insufficient observed Week 20 data post-discontinuation of study medication. In this 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 patient's baseline value plus a shift and standard deviation computed based on the root mean squared error from the ANCOVA model described above. For patients 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.

Two sensitivity analyses of TP estimand for change from baseline in A1C will be performed to assess the impact of missing data imputation. Both analyses will include measurements collected after discontinuation of study medication or initiation of rescue. One approach will use a jump to reference (J2R) pattern mixture model and the other approach will use a pattern mixture model in conjunction with the tipping point approach.

In the J2R analysis, the missing data due to dropout will be handled using J2R imputation, which falls under the category of pattern mixture models known as reference-based imputation. In J2R, missing data in the control group are imputed under the MAR assumption, while missing data in the treatment groups are imputed under a MNAR assumption using the control group profile for time points after withdrawal.

Standard multiple imputation techniques are overly conservative as they tend to overestimate parameter variances. Therefore, a more appropriate variance for the J2R based on pattern mixture model approximation will be used [66]. Specifically, based on its definition, the overall mean treatment difference (estimand) for J2R can be written as

$$\theta^{J2R} = (\pi_t \mu_t^d + (1 - \pi_t) \mu_t^p) - \mu_t^p = \pi_t (\mu_t^d - \mu_t^p)$$

Where π_t is the proportion of completers in the sitagliptin group, t is the last time point (i.e., Week 20), and μ_t^d and μ_t^p are the hypothetical means at last time point for the two groups under MAR. These means will be estimated based on Restricted Residual Maximum Likelihood (REML) from the primary cLDA model and will be used to compute

$\hat{\theta}^{J2R} = \hat{\pi}_t (\hat{\mu}_t^d - \hat{\mu}_t^p)$. The variance for J2R estimate of the treatment difference can be approximated by,

$$\text{var}(\hat{\theta}^{J2R}) = \hat{\pi}_t^2 \text{var}(\hat{\mu}_t^d - \hat{\mu}_t^p) + (\hat{\mu}_t^d - \hat{\mu}_t^p)^2 \hat{\pi}_t (1 - \hat{\pi}_t) / n$$

where n is sample size in the sitagliptin group. The first term $\text{var}(\hat{\mu}_t^d - \hat{\mu}_t^p)$ can be computed based on the REML from the cLDA model.

In the pattern mixture model in conjunction with the tipping point approach, the missing values will be imputed based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values from the primary cLDA model. For each imputed value, a positive adjustment Δ will be added for the sitagliptin group (to the detriment of sitagliptin). The inference will be carried out for a range of values of Δ . The smallest value of Δ that renders the significant result into non-significant is the tipping point value, which provides a measure of robustness of the primary result.

All p-values are based upon a 't-distribution' with Kenward-Rogers degrees of freedom adjustments derived from the primary cLDA model.

Secondary Endpoints

All other continuous efficacy endpoints except triglycerides will be analyzed using the cLDA model described above for A1C. For analyses of lipid endpoints, the response vector will consist 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.

Summary statistics will be provided using observed data for change from baseline in 2-hour PMG, AUC endpoints, and endpoints derived from 9-point MTT at Week 20.

Triglycerides will be analyzed using a nonparametric method: an ANCOVA based upon Tukey's normalized ranks on the percent change from baseline [60]. 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 [61] 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 75th and 25th 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 M&N method [62], an unconditional, asymptotic method, stratified by baseline BMI percentile (\geq or < median), insulin use at screening (yes/no), and baseline A1C ($>$ or \leq median). If necessary due to sparse cells, stratification factors will be removed. 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 0431083. 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. The estimated response rates and adjusted effective sample sizes 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 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 $\geq 7.0\%$.

A time-to-event analysis will be performed for the initiation of glycemic rescue therapy up to Week 20. Patients will be considered as rescued if they initiated protocol prespecified rescue therapy. Patients with no events will be censored at the completion of Phase A or discontinuation from the study during Phase A. The protocol prespecified rescue therapy will pertain to Step 1 rescue (see Section 2.4.2.6 of protocol). The proportion of patients initiating glycemic rescue therapy by Week 20 in each treatment group will be summarized. A plot of the Kaplan-Meier estimate of the distribution of the time-to-initiation of glycemic rescue therapy during Week 0 to Week 20 will be provided for each treatment arm and a log-rank test, comparing the time-to-initiation distribution of sitagliptin versus placebo will be conducted. [Table 3-3](#) summarizes the analysis strategy for efficacy endpoints at Week 20.

Table 3-3

Analysis Strategy for Efficacy Variables at Week 20

Endpoint/Variable	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Change from baseline in A1C	P (TE)	cLDA	FAS	Model-based
	P (TP)	ANCOVA	FAS	RD/RTB [†]
	Sen (TP)	cLDA	FAS	J2R
	Sen (TP)	cLDA	FAS	Tipping Point
Secondary Endpoints				
Change from baseline in FPG	P (TE)	cLDA	FAS	Model-based
Proportion of patients with A1C at Goal (<7.0%, <6.5%) at Week 20	P	M&N	FAS	Multiple Imputation "not at goal"
	S	CMH	FAS	
	S	M&N	FAS/Subgroup [‡]	Multiple Imputation
Other Endpoints				
Percent change from baseline in lipid parameters (other than triglycerides)	P	cLDA	FAS	Model-based
Percent change from baseline in triglycerides	P	Non-parametric method	FAS	LOCF
Change from baseline in Insulin, Proinsulin, 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 Week 0 to Week 20	P	Kaplan-Meier	FAS	DAO
Proportion initiating glycemic rescue therapy during Week 0 to Week 20	P	Summary statistics	FAS	DAO
ANCOVA= analysis of covariance; cLDA= constrained longitudinal data analysis; DAO=data as observed; FAS= full analysis set; J2R=Jump-to-reference; P=Primary approach; RD= Retrieved-Dropout; RTB=Return-to-Baseline; S=Secondary approach; Sen=Sensitivity approach; TE=Treatment effect; TP=Treatment policy. [†] If RD is not feasible due to insufficient data post discontinuation from study medication, RTB imputation will serve as the primary approach for TP. If RD is feasible, RTB will be performed as a secondary approach. [‡] Subgroup=patients with baseline A1C ≥7.0% (applicable to A1C goal <7.0% analysis).				

Week 0 to Week 54 Analyses

The statistical analyses at Week 54 will be analogous to those at Week 20 except that no between-group comparisons will be provided for Week 54. The efficacy endpoints will be summarized for within-group mean change from baseline with estimates and 95% confidence intervals calculated from the analysis model.

Additionally, 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 75th and 25th percentiles, respectively. Missing values will be imputed from the last observed post-baseline measurement.

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), PDLCs, laboratory tests, vital signs, waist circumference, BMI, growth velocity, Tanner Staging data, urine microalbumin/creatinine ratio, and CD26. All safety endpoints will be analyzed using summary statistics. For the Week 20 analysis, the following analysis approaches will be used:

- For all safety endpoints except hypoglycemia, data will be summarized including data following the initiation of rescue or intensification therapy (IR).
- Hypoglycemia endpoints will be summarized excluding data measured following the initiation of rescue therapy or intensification therapy (ER).

The Treatment Period will include all data from randomization up to 14 days after the last dose of study medication. 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 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.

For the **Week 54** analysis, the same approaches from **Week 20** will be applied except that the primary approach for SAEs at Week 54 will include all post-randomization follow-up, without an upper day limit.

Listings of all AEs (regardless of seriousness) reported more than 14 days after the end of the Treatment Period and of PDLCs occurring beyond the Treatment Period will be provided.

The analysis of safety results will follow a tiered approach (Table 3-4). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (summary measures, specific terms, system organ class terms) and predefined limits of change in laboratory and vital signs parameters 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 predefined limits of change will belong to Tier 3.

The threshold of at least 4 patients with events has been chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size have less than 4 patients with 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 as a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

The continuous endpoints waist circumference and BMI will be considered Tier 2 safety parameters. The endpoints IGF-1, IGF-BP3, Bone Age (as Δ Bone Age/ Δ Chronologic Age), Growth Velocity Percentile (for both bone age and chronologic age), biochemical markers of bone turnover [Urine NTx/Creatinine ratio; Bone specific Alkaline Phosphatase] and calcitonin, urine albumin/creatinine ratio, percentage change from baseline in CD26 and endpoints in accessing Tanner staging will be considered Tier 3 safety parameters. Changes from baseline in laboratory parameters, vital signs and urine parameters that are not pre-specified as Tier 1 or Tier 2 endpoints will also be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change (or percentage change) from baseline values will be provided in table format at Week 20 and 54. Mean change from baseline over time will be plotted with the corresponding standard errors for both Week 20 and 54.

The data from the oral examination case report forms will be summarized.

Adverse events of symptomatic hypoglycemia and selected gastrointestinal (GI) adverse events (i.e., nausea, vomiting, abdominal pain or discomfort, diarrhea) are Tier 1 endpoints. p-values (Tier 1 only) and 95% confidence intervals for between-treatment differences in the percentages of patients with events will be calculated using the M&N method [62], an unconditional, asymptotic method. For continuous Tier 2 safety parameters, change from baseline or percent change from baseline will be analyzed using the same cLDA model described in Section 3.5.5.1. Only 95% confidence interval will be provided. For Tier 2 AEs, 95% confidence intervals for between-treatment differences will be provided using the M&N method.

[Table 3-4](#) summarizes the analysis strategy for safety endpoints for the Phase A and Phase A+B analysis. The strategy to address multiplicity issues with regard to multiple endpoints is described in Section 3.5.6, Multiplicity.

Table 3-4

Analysis Strategy for Safety Parameters in Phase A and A+B

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics	
Tier 1	Any AE of symptomatic hypoglycemia	X	X	X	
	Selected gastrointestinal events (Diarrhea, Nausea, Abdominal Pain [†] , 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		X	X	
	Any Requiring medical assistance Not requiring medical assistance				
	Change from baseline in BMI, BMI percentile and waist circumference		X	X	
Tier 3	Specific AEs, SOCs or PDLCs (incidence < 4 patients in all of the treatment groups)			X	
	Change from Baseline Results (Labs and Vital signs)				
	Percent change from baseline in IGF-1 and IGF-BP3				
	Bone Age (as Δ Bone Age/ Δ Chronologic Age)				
	Growth Velocity Percentile (for both bone age and chronologic age)				
	Change from baseline in markers of bone turnover [Urine NTx/Creatinine ratio, Bone specific Alkaline Phosphatase] and Calcitonin				X
	Change from baseline Urine albumin/creatinine ratio				
Change from baseline in endpoints for accessing Tanner Stage					
	Percentage change from baseline in CD26				

AE= adverse event; BMI= body mass index; PDLc= predefined limits of change; SOC= system organ class.
[†] Includes abdominal pain lower, abdominal pain upper, abdominal pain, abdominal discomfort and epigastric discomfort.
[‡] 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 background insulin and for patients not on background insulin at screening.

The Tier 1 analysis for hypoglycemia will include the numbers and percentages of patients experiencing one or more adverse events of symptomatic hypoglycemia, regardless of 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 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 (i.e., 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 (i.e., 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 (i.e., 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, Demographics, and Other Analyses

Demographic and Baseline Characteristics

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), time since diagnosis of T2DM (days), 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, American Indian or Alaska Native or Other), ethnicity (Hispanic/Latino or not) and Baseline BMI percentile ($<95\%$ and $\geq 95\%$).
- Baseline A1C, and distribution of A1C at baseline (\geq or $<$ median A1C).
- Baseline FPG
- Time since diagnosis of T2DM ($>$ or \leq median)
- Insulin use at Visit 1(yes/no)
- Baseline substance use (tobacco/alcohol)
- Baseline skeletal maturation status (skeletally mature: yes/no)
- PedsQL at screening

3.5.6 Multiplicity

As there is only one hypothesis in the study, no multiplicity control is needed for the study hypotheses. Comparisons involving other efficacy endpoints and time points are considered supportive and will be made at the $\alpha=0.05$ nominal level (two-sided). No multiplicity adjustment will be performed on these other comparisons.

From a safety standpoint, application of a multiplicity adjustment could potentially mask a safety concern. Thus, no control of Type I error rate beyond the per-comparison $\alpha=0.05$ nominal level will be applied to the safety analyses, with the realization that spurious statistical significance may be observed for some endpoints.

3.5.7 Sample Size and Power Calculations

This study will randomize approximately 190 patients, but no more than 220 patients, including approximately 10 to 11 patients randomized to the metformin arm prior to its removal from the study design in amendment 5 to this protocol (P083-05). Therefore, there will be approximately 180 to 210 patients randomized to the sitagliptin and placebo/metformin (Phase A/Phase B) treatment groups in a 1:1 ratio. Power calculations are based on 90 patients in each of the sitagliptin and placebo treatment groups.

A sample size of 90 per treatment group will be equivalent to an effective sample size of approximately 82 per treatment group 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 82 per treatment will provide 82% 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 0.34%.

These calculations were based upon the following assumptions:

- Cumulative attrition rates at Weeks 8, 14, and 20 are 0.07, 0.10, and 0.15, respectively
- A conditional correlation matrix at Weeks 8, 14, 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 PN036.

Table 3-5 shows the power using $\alpha=0.05$ (two-sided). The observed between-group difference (sitagliptin minus placebo) in change from baseline in A1C in adult ranges from -0.50% to -1.03% after 18 to 24 weeks of treatment. The observed standard deviation in adults with the similar A1C entry criteria ranges from 0.65% to 1.09%. Unpublished internal analyses of analyses of previous sitagliptin studies 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 3-5

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

Difference (%)	Standard Deviation (%)	Power (%)
0.6	1.1	93%
0.5	1.1	82%

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 with a minimum of 8 patients per treatment group in each subgroup:

- Baseline A1C: \geq or $<$ median
- Gender
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age: ≤ 14 or > 14
- Baseline BMI percentile $>$ or \leq Median
- Time since diagnosis of diabetes at baseline: $>$ or ≤ 1 year
- Background insulin (yes/no)

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

The consistency of the treatment effect will be assessed in the context 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 A1C, treatment, baseline BMI, subgroup, insulin use at screening (yes/no), and treatment-by-subgroup interaction. If necessary due to sparse cells, the stratification factor will be removed from the 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.

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% confidence intervals 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.

Data will be analyzed and a study report generated when the last patient completes Phase A (ie, after all randomized patients complete Visit 8/Week 20 or have discontinued from Phase A of the study). Investigators and patients will remain blinded to study drug treatment assignment until all patients have completed the trial (ie, all randomized patients complete Visit 11/Week 54 or have discontinued from the study) and the second database is locked. The first unblinding and analysis is not an interim analysis because it includes the complete data for analysis of the primary efficacy endpoint.

3.5.10 Medication Adherence

The computation of medication adherence will be based on the study medication case report form. A day within the Double-blind Treatment Period will be considered an adherent day if the patient reports one tablet from each column (labeled as A, B, C, D, E) in the prescribed blister card (a total of 5 tablets in a day).

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

For each patient, two rates will be calculated. The adherence rate summarizes adherence to assigned study medication over the patient's duration of study participation. The compliance rate summarizes the adherence with study medication during the Treatment Period only.

$$\text{Adherence Rate (\%)} = \frac{\text{Number of Adherent Days}}{\text{Number of Days in the Study}} \times 100\%$$

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

The "Number of Days in the Study" is the total number of days from Day 1 (or the randomization day for non-treated patients) to the day of study completion or study discontinuation excluding the 14 days of post-study follow-up.

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.

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

3.5.11 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics and frequencies for the "Number of Days on Therapy" by treatment group.

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

3.6.1 Product Descriptions

Investigational materials will be provided by the Sponsor as summarized in [Table 3-6](#). Blister card configuration is summarized in [Table 3-7](#).

Table 3-6

Product Descriptions

Product Name & Potency	Dosage Form
Sitagliptin 100 mg (as sitagliptin phosphate)	Tablet
Placebo to match sitagliptin 100 mg (as sitagliptin phosphate)	Tablet
Metformin hydrochloride 500 mg	Tablet
Placebo to match metformin hydrochloride 500 mg	Tablet

Table 3-7

Blister Card Configuration

Blister Card Column Label	Product Name & Potency	Dosage Form	Dose Regimen
A	Sitagliptin 100 mg (as Sitagliptin Phosphate) or Placebo	Tablet	One tablet daily prior to morning meal
B	Metformin Hydrochloride 500 mg, or Placebo	Tablet	One tablet daily prior to morning meal
C	Metformin Hydrochloride 500 mg, or Placebo	Tablet	One tablet daily prior to morning meal
D	Metformin Hydrochloride 500 mg, or Placebo	Tablet	One tablet daily prior to evening meal
E	Metformin Hydrochloride 500 mg, or Placebo	Tablet	One tablet daily prior to evening meal

All placebos were created by the Sponsor in the image of the active product.

Insulin will be supplied by the investigator site as needed. The investigator or designee will record the lot number, expiration date, and drug dispensed.

3.6.2 Packaging Information

Patients will receive blinded blister packs for both Run-in and Blinded Treatment. Run-in blister packs will be received in a weekly kit containing 2 blister cards. Blinded Treatment will be received in monthly kits containing 5 blister cards.

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

3.6.3 Clinical Supplies Disclosure

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

Treatment 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.

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

3.6.4 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 as specified on the label or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

3.6.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the patients and the amount remaining at the conclusion of the trial.

For all trial sites, the country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

3.6.6 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 information:

“You have participated in a study conducted by the Sponsor. This is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug Metformin Hydrochloride as much as possible. You may also have received the active drug Metformin Hydrochloride as manufactured by Aurobindo.”

3.6.7 Distributing to Sites and Dispensing to Patients

Study personnel will have access to IVRS to allocate patients, to assign drug to patients and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

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 Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., 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 (e.g., thorough understanding of clinical trial methods, appropriate enrollment of patient cohort, timely achievement of study milestones, and 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.

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6. APPENDICES

6.1 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, 1-2 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 will be measured after voiding (to the nearest 0.2 kg). 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 certified weight to study sites that do not have them. **The scale must be calibrated according to the manufacturer's instructions at set-up and when it is transferred or moved. Additional calibration 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 (e.g., 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 upon mounting the stadiometer to the wall, and according to the manufacturer's instructions thereafter.

Waist Circumference

Instructions for using tension-controlled measuring tapes:

The tape measure used should be a 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.

6.2 BLOOD PRESSURE TABLE FOR GENDER/AGE/HEIGHT FOR BOYS AGE 10 TO17

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 if available – otherwise, these guidelines should be used.

Ref [63]

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

Years of Age	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 if available – otherwise, these guidelines should be used.

Ref [63]

6.4 LABORATORY EVALUATIONS

Fasting plasma glucose (FPG) test (Visits 1, 3, 8, 11, Rescue, and Discontinuation)

Whole blood hemoglobin A_{1c} (A1C) test (Visits 1, 3, 6, 7, 8, 9, 10, 11, Rescue, and Discontinuation)

Note: Do not collect A1C at **Rescue** or **Discontinuation Visits** if the occurs before **Visit 6/Week 8**.

Fasting Serum C-Peptide Test (Visit 1)

Diabetes Autoantibody Panel (Visit 1)

Glutamic acid decarboxylase 65- kDa autoantibody (GAD65-Ab)

Insulinoma-associated protein-2 autoantibody (IA2 Ab)

Fasting Serum Insulin and Proinsulin Tests (Visits 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1], and Discontinuation)

If a patient is undergoing the MTT, then do not obtain fasting insulin and proinsulin.

Do not perform fasting serum insulin and proinsulin tests on patients on background insulin therapy.

9-Point MTT in a subset of patients (Visits 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

Glucose

Insulin

C-peptide

Proinsulin (only at time zero)

Note: An MTT should not be performed at the **Visit 8/Week 20**, **Visit 11/Week 54** or the **Discontinuation Visit** if the patient has been rescued. Also, an MTT should not be performed at the **Discontinuation Visit** if the patient has been off double-blind study medication ≥ 5 days, if the study medication was discontinued due to an adverse event, or if the visit occurs prior to **Visit 5/Week 4**.

The MTT will not be performed for patients on background insulin therapy.

Lipid Analyses (Visits 1, 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

Total cholesterol

Triglycerides (TG)

HDL cholesterol

LDL cholesterol-calculated

Non-HDL cholesterol – calculated

Hematology (Visits 1, 3, 5, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] 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, 8, 9, 10, 11, Rescue [Step 1 or Treat-to-Goal Step 1], 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, 5, 6, 7, 8, 9, 10, 11, Rescue and Discontinuation) for all females performed 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, 2, 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1], 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 should not be performed if patient is menstruating.

Urine microalbumin/creatinine ratio (Visits 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

The urine sample for microalbumin/creatinine ratio 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

CD26 Assay (Visit 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

CD26

CD3

CD8

If the **Rescue [Step 1 or Treat-to-Goal Step 1] Visit** occurs prior to **Visit 8**, a sample for the CD26 assay should be obtained at that time instead of at **Visit 8/Week 20**. For patients who have not received rescue therapy in Phase B, if a sample for CD26 was not obtained or analyzed at **Visit 8**, it can still be obtained at or prior to **Visit 9**.

IGF-1 and IGF-BP3 (Visit 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

Biochemical Markers of Bone Turnover and Calcitonin (Visit 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation)

Urine (second AM void) N-terminal cross-linking telopeptide of bone collagen (NTX) and creatinine

Serum calcitonin

Serum bone-specific alkaline phosphatase (Ostase assay)

Future Biomedical Research Samples

Serum (SST) and Plasma (EDTA) Samples (**Visits 3, 8, 11, Rescue [Step 1 or Treat-to-Goal Step 1] and Discontinuation**)

Blood (DNA) for FBR (**Visit 5**).

6.5 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 (i.e., ALT or AST ≥ 3 -times the upper limit of normal [ULN]). Under these circumstances, the Central Laboratories will alert the Investigators/ Coordinators. In addition, when ALT and/or AST levels are elevated beyond the clinical significant margin above, the Investigators/Coordinators must recall the patient, attempt to identify the cause of the elevation, and repeat the blood test(s). Detailed instructions are provided below.

For patients who have ALT or AST increases (either ALT or AST ≥ 3 -times the ULN) with a total bilirubin lab value ≥ 2 -times ULN and, at the same time, the alkaline phosphatase lab value is < 2 -times ULN (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 (Section 3.4.6.2). Alkaline phosphatase reference ranges for age and sex are listed in the table below.

Alkaline Phosphatase Reference Ranges by Age and Sex¹

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		

For patients with ALT or AST increases (either ALT or AST ≥ 3 -times the ULN) but who *do not* also meet the above criteria for both total bilirubin and alkaline phosphatase, the process below should be followed. These events do not qualify as ECIs per protocol (see Section 3.4.6.2).

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

1. Obtain further information.
2. Careful questioning of recent alcohol consumption, including a recent change in pattern of alcohol use.
3. Search for drug-related causes of hepatitis and liver injuries (acetaminophen; amiodarone; aspirin; chlorpromazine; dantrolene; erythromycin; halothane; isoniazid; methyl dopa; nitrofurantoin; oxyphenisatin; perhexiline maleate; phenytoin; propylthiouracil; rifampin; sulfonamides; tetracyclines) or other new medications.

4. Search for alternative medical causes such as cholelithiasis, recent alcohol consumption, history of intercurrent illness (e.g., viral syndrome), hepatitis, or potential exposure to viral hepatitis (transfusion).
5. Repeat determination of ALT, AST, total bilirubin, and alkaline phosphatase (within 3 days of initial report of abnormal level).
6. Perform serologic tests including: (a) Hepatitis A (IgM); (b) Hepatitis B (surface antigen and core IgM); and (c) Hepatitis C (antibody).

B. Actions

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

1. If ALT or AST levels are ≥ 3 -times ULN, but ≤ 5 -times ULN, consideration can be given to keeping patient on 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.

6.6 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 \geq 1.5 g/dL	N	Y
WBC Count (10^3 /microL)	1. Decrease \geq 50% and value < LLN	Y	Y
	2. Increase \geq 20% and value > ULN	Y	Y
Neutrophil Count (10^3 /microL)	1. Decrease \geq 20% and value < LLN	Y	Y
	2. Increase \geq 20% and value > ULN	Y	Y
Lymphocyte Count (10^3 /microL)	1. Decrease \geq 20% and value < LLN	Y	Y
	2. Increase \geq 20% and value > ULN	Y	Y
Platelet Count (10^3 /microL)	1. Decrease \geq 25% and value < LLN	Y	Y
	2. Increase \geq 100% and value > ULN	Y	Y
Laboratory – Chemistry			
BUN (mg/dL)	1. Increase \geq 50% and value > ULN	N	Y
Serum Creatinine (mg/dL)	1. Increase \geq 0.3 mg/dL	N	Y
Total Bilirubin (mg/dL)	1. Value \geq 2 \times ULN	Y	Y
Direct Bilirubin (mg/dL)	1. Increase \geq 50% and value > ULN	Not applicable for this study	Not applicable for this study
AST (IU/L)	1. Value \geq 3 \times ULN	Y	Y
	2. Value >5 \times ULN	Y	Y
	3. Value >10 \times ULN	Y	Y
	4. Value >20 \times ULN	Y	Y
ALT (IU/L)	1. Value \geq 3 \times ULN	Y	Y
	2. Value >5 \times ULN	Y	Y
	3. Value >10 \times ULN	Y	Y
	4. Value >20 \times ULN	Y	Y
AST (IU/L) or ALT (IU/L)	1. Value \geq 3 \times ULN	Y	Y
	2. Value >5 \times ULN	Y	Y
	3. Value >10 \times ULN	Y	Y
	4. Value >20 \times ULN	Y	Y
AST (IU/L) or ALT (IU/L)+ Total Bilirubin (mg/dL)	1. ALT \geq 3 \times ULN or AST \geq 3 \times ULN with Bilirubin \geq 2 \times ULN	Y	Y
Alkaline Phosphatase (IU/L)	1. Value >1.5 \times ULN	Y	Y
Serum Uric Acid (mg/dL)	1. Increase \geq 50% and value > ULN	Y	Y
Serum Sodium (mEq/L)	1. Decrease \geq 10 mEq/L and value < LLN	N	Y
	2. Increase \geq 10 mEq/L and value > ULN	N	Y
Serum Potassium (mEq/L)	1. Decrease \geq 1.0 mEq/L and value < LLN	N	Y
	2. Increase \geq 1.0 mEq/L and value > ULN	N	Y
Serum Calcium (mg/dL)	1. Increase \geq 1.0 mg/dL and value > ULN	N	Y
	2. Decrease \geq 1.0 mg/dL and value < LLN	N	Y
[†] Increases and decreases are relative to baseline. LLN = Lower limit of normal; ULN = upper limit of normal; WBC = white blood cell; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase.			

6.7 MEAL TOLERANCE TEST (MTT) BLOOD SAMPLES, COLLECTION TIMES AND PROCEDURE

Blood Samples and Collection Time (Minutes From Start of Meal)									
	-10	0	10	20	30	60	90	120	180
9-point MTT									
Glucose	X	X	X	X	X	X	X	X	X
Insulin	X	X	X	X	X	X	X	X	X
C-Peptide	X	X	X	X	X	X	X	X	X
Proinsulin		X							

Note: The MTT will not be performed on patients on background insulin therapy.

9-point MTT

Samples will be collected 10 minutes before ingesting the meal (T = -10 min), immediately *prior* to start of ingesting the meal (T=0 min), at 10 minutes (T=10 minutes) after the start of the meal, at 20 minutes (T=20 minutes) after the start of the meal, at 30 minutes (T=30 minutes) after the start of the meal, at 60 minutes after the start of the meal (T=60 min), at 90 minutes (T=90 minutes) after the start of the meal, at 120 minutes after the start of the meal (T=120 min), and at 180 minutes at the start of the meal (T=180 minutes).

Note: At **Visit 8**, patients will take the dose of double-blind study medication from the previous visit's blister-pack (Phase A) as a witnessed dose 30 minutes prior to the start of the standard meal for the MTT (T= -30 minutes).

Samples for glucose, insulin, and C-peptide will be collected at *all* time points. Proinsulin will be collected only at time zero (T=0 min).

Note: All blood samples for the 9-point MTT should be carefully timed, and the label with the appropriate time point should be placed on the blood sample tubes.

An MTT should not be performed at **Visit 8/Week 20**, **Visit 11/Week 54**, or the **Discontinuation Visit** if the patient has been rescued. Also, an MTT should not be performed at the **Discontinuation Visit** if the patient has been off double-blind study medication ≥ 5 days, if the study medication was discontinued due to an adverse event, or if the visit occurs prior to **Visit 5/Week 4**.

Meal Tolerance Test Procedures

The following procedures should be performed in the order specified:

- 1) An indwelling catheter to obtain samples is preferred (using either a heparin lock or an infusion IV with saline to keep the vein open and catheter used only for blood sampling).
- 2) Fasting blood samples obtained (See Study Flow Chart [Section 1.7] for specific samples to obtain).

3) Dosing of Study Medication:

Visit 3/Day 1: First dose of double-blind study medication should be taken *after* all blood samples for the MTT are obtained (i.e., after the 180 minute sample is drawn).

Visit 8/Week 20 and Visit 11/Week 54 (or at Discontinuation Visit/Rescue [Step 1 or Treat-to-Goal Step 1] Visit): Patients will take the dose of *double-blind study medication* from the previous visit's blister-pack as a witnessed dose exactly **30 minutes prior to ingesting the standard meal for the MTT (T=-30 minutes)**. Patients who participate in the MTT at **Visit 8/Week 20** will be contacted by the site the day after the visit to collect the date and time that study medication was taken.

- 4) Meal administered immediately after time "0" blood samples for glucose, insulin, and proinsulin are obtained.
- 5) Carefully draw timed blood samples for glucose, insulin, C-peptide and proinsulin (time zero only) relative to the start of the meal: -10, 0 (immediately prior to eating), 10, 20, 30, 60, 90, 120, and 180 minutes. The "0" time should be considered from when the patient starts eating. *Blood samples should be carefully timed and the label with the appropriate time point should be placed on the blood tubes.*

The patient should remain sitting or supine during the period of the test, with the exception of going to the restroom. The patient should be encouraged to eat the standard meal (see below for description of standard meal), over a period of up to 15 minutes. At the **Visit 3/Day 1 MTT**, if the patient is unable to finish the meal in 15 minutes, the period may be extended to 20 minutes. If the entire meal (bar and drink) is not eaten in 20 minutes, the amount of the bar and drink ingested should be documented, and a *similar* amount of the bar and drink should be provided at **Visit 8/ Week 20 and Visit 11/Week 54 (or at Discontinuation Visit/Rescue [Step 1 or Treat-to-Goal Step 1] visit) MTTs** and should be consumed in a similar period of time.

If the patient is unable or unwilling to ingest the meal or finishes only a minimal amount (e.g., <50%), the MTT should be stopped without further sample collection. If the patient was unable or unwilling to complete the MTT at **Visit 3/ Day 1**, the patient should not have a MTT performed at **Visit 8/Week 20 or Visit 11/Week 54 (or at Discontinuation Visit/Rescue [Step 1 or Treat-to-Goal Step 1] visit)**. Patients with hypersensitivity or dietary restrictions to the contents of the nutrition drink or bars will omit the protocol-specified MTT.

6.8 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

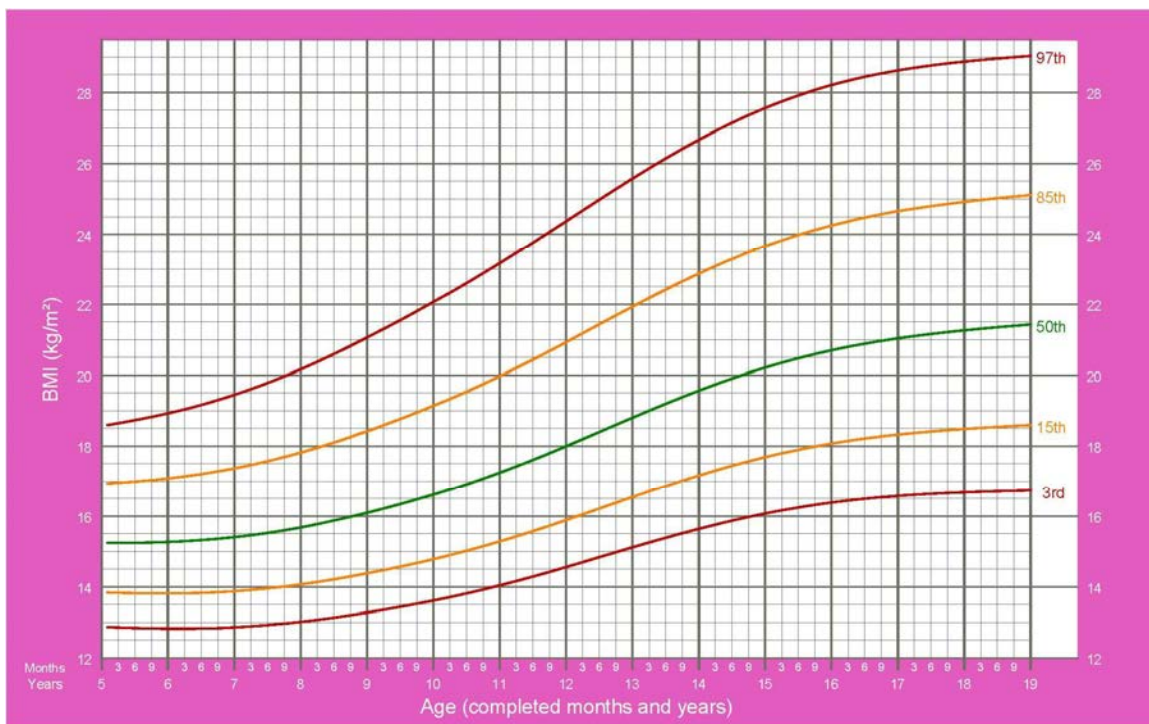
6.9 BMI-FOR-AGE CHARTS

Sites should follow their approved country specific BMI-for-age percentile charts, if available (e.g., sites within the United States will refer to the Centers for Disease Control charts). If an approved country-specific BMI-for-age percentile chart is not available, refer to the World Health Organization charts shown in the figures 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 (to determine BMI, please refer to Appendix 6.1).
- The body mass index-for-age percentile will be at the intersection of the child’s age and BMI measurement.

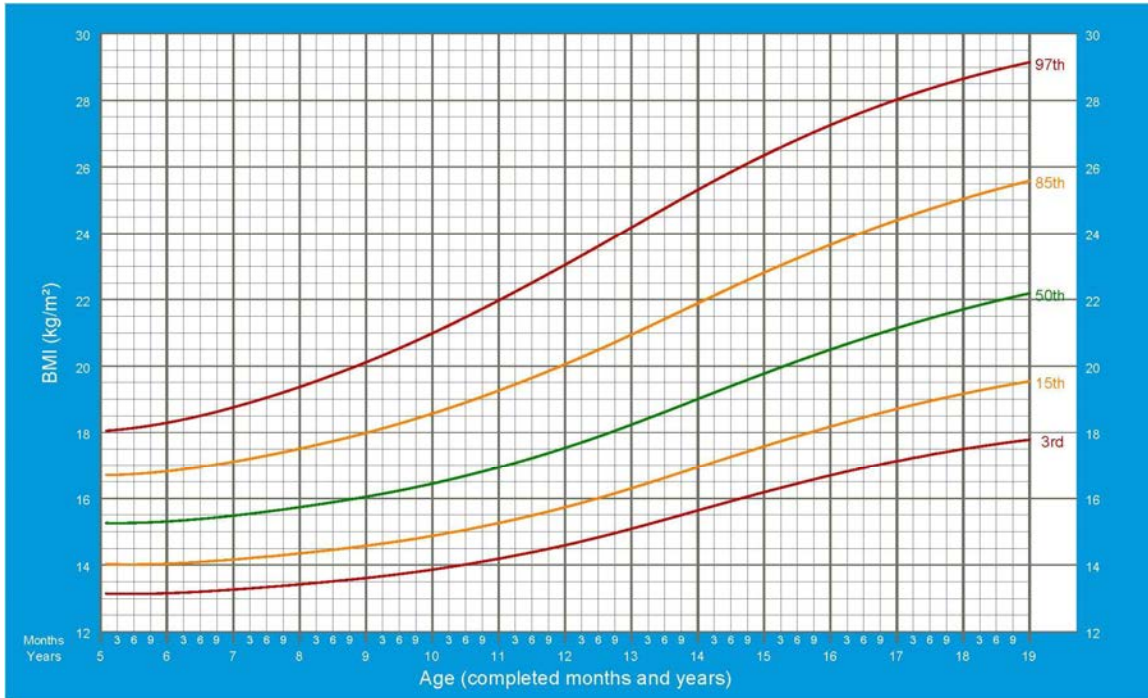
BMI-for-Age—Girls, 5 to 19 Years (Percentiles)



2007 WHO Reference [64]



BMI-for-Age—BOYS, 5 to 19 years (percentiles)



2007 WHO Reference [64]

6.10 VISUAL ORAL EXAMINATION PROCEDURES

The investigator will perform a visual oral examination * by completing the following steps. The evaluation will be recorded on the eCRFs.

1. Patient brushes their teeth without toothpaste. The investigator observes whether the gums bleed.
2. The investigator wipes teeth with gauze.
3. The investigator uses a flashlight and mirror to visually evaluate the gums (start top right to left then bottom left to right) and each tooth (same sequence).

*: Investigators have been trained to perform the VOE through materials specifically designed for this purpose. This training will be repeated periodically.

6.11 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 (e.g., AEs and PDLCS), all results will be included without mapping to individual time points.

Required Phase	Relative Day Range prior amendment 05	Relative Day Range amendment 05 and beyond	Week
	<i>Day Relative to Start of Trial[†]</i>	<i>Day Relative to Start of Trial[†]</i>	
Any	Day ≤1	Day ≤1	0
A	43 ≤ Day ≤70	43 ≤ Day ≤70	8
A	71 ≤ Day ≤105	71 ≤ Day ≤119	14
A	Day ≥106	Day ≥120	20
	<i>Day Relative to Start of Phase B[‡]</i>	<i>Day Relative to Start of Phase B[‡]</i>	
B	1 < Day ≤112	1 < Day ≤112	30
B	113 ≤ Day ≤196	113 ≤ Day ≤196	42
B	Day ≥197	Day ≥197	54

[†]Start of Phase A is defined as first dose of Phase A study medication for all treated patients and the randomization 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 8 day for patients who entered Phase B off study medication.

In addition, the following will be used to map the relative day ranges to weeks for other endpoints. The following 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, insulin related parameters, physical exams, and CD26.

Required Phase	Relative Day Range	Week
	<i>Day Relative to Start of Trial[†]</i>	
Any	Day ≤1	0
A	Day ≥70	20
	<i>Day Relative to Start of Phase B[‡]</i>	
B	Day ≥119	54

[†]Start of Phase A is defined as first dose of Phase A study medication for all treated patients and the randomization 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 8 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**.

6.12 PATIENT RANDOMIZED TWICE

One patient is known to have been randomized twice. This patient consented to amendment 083-05 but was given a randomization number belonging to amendment 083-01 because the site had not activated amendment 083-05 in IVRS prior to this randomization. This patient received study medication under the first randomization number for 6 days prior to being discontinued from the study. The patient was randomized a second time under amendment 083-05, 3 days after the discontinuation from the study and was given a second randomization number. The patient received study medication and continued participation in the study under the second randomization number.

In the clinical study report, both randomization numbers will be presented in tabulations of study disposition. Data associated with the second randomization number will be included in demographic, safety, and efficacy tables. No adverse events were reported and no post-randomization efficacy and safety data were collected under the first randomization number.

6.13 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

6.13.1 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.

6.13.2 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.

6.13.3 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.

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 (i.e., 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 (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

6.13.4 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 (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

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

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

6.13.6 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 (e.g., 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.

6.13.7 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.

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

6.13.9 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 (e.g., Disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

6.13.9.1 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.

6.13.10 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 (i.e., 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.

6.13.11 Self-Reported Ethnicity

Parents/guardians of patients who participate in future biomedical research will be asked to provide ethnicity of the patient. Patients who do not wish to provide this data may still participate in future biomedical research.

Questions

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

6.14 SUPPLEMENTAL DENTAL DATA SUB-STUDY

Note: *Procedures for the Supplemental Dental Data Substudy do not apply to Brazil and Serbia.*

6.14.1 Sub-Study Objective

The purpose of this sub-study is to enhance the dental data collected from the visual oral examination to support secondary objectives to summarize data on the change from baseline in measures of dentition at Week 20 and Week 54 (Section 2.1.2).

6.14.2 Sub-Study Design and Procedures

New and ongoing patients (on or off study medication) participating in the main study, P083, will be asked to participate in this sub-study to collect supplemental dental data. Patients who previously completed 54 weeks of the main study (on or off study medication) are also eligible to participate. Patients who have withdrawn consent from P083 are not eligible.

Note: Patients currently enrolled in MK-0431 P351 are also eligible to be contacted to participate in this sub-study.

For all patients participating in the sub-study, supplemental dental data will consist of:

1. The patient's dental records for dental exams performed prior to the study (closest available record prior to randomization), during the study, at completion of the study, and after completion of the study (for patients who have completed the study prior to the approval of the dental sub-study amendment).
2. Dental photographs taken at the time points indicated in the sub-study flow charts (Table 6-1, Table 6-2, and Table 6-3).

Details regarding procedures for dental records and photographs can be found in the separate instruction document provided to the investigator.

Note: These dental assessments as part of the dental data sub-study are in addition to the VOE procedures listed in the main protocol conducted by the investigator.

For patients who have completed 54 weeks of the main study prior to entering the sub-study, supplemental dental data will also include:

1. A visual oral examination (including inspection of teeth) performed by the investigator as described in Appendix 6.10.
2. Collection of events and medications of particular dental interest starting at Week 54 of the main study until the post main study Dental Visit (Table 6-3). Serious AEs are to be recorded as described in Section 3.4.6.1. Procedure-related adverse events occurring on the day of the post-study dental exam will be recorded on the Adverse Events eCRF. Non-serious dental events occurring after completion of the main study through the Dental Visit will be recorded on the Medical History – New Conditions eCRF.

Independent Reviewer Assessment

A Dental Charter will define how the independent reviewer will evaluate all relevant, available data for each patient (including but not limited to VOE, dental records and dental photographs) and determine if there has been an overall change in the patient's dental status.

All personnel involved in the review process will remain blinded to treatment allocation throughout the trial.

6.14.3 Sub-Study Sample Size

There is no predetermined sample size for this sub-study. All eligible patients randomized into the main study and who consent to participate will be included in this sub-study.

6.14.4 Sub-Study Inclusion Criteria

1. Patient was randomized into P083 and has taken at least one dose of study medication, including new and ongoing patients (on or off study medication), and patients who previously completed 54 weeks of the main study (on or off study medication).

Note: Patients currently enrolled in MK-0431 P351 are also eligible to be contacted to participate in this sub-study.

2. a) Patient who can legally consent, understands the sub-study procedures, and voluntarily agrees to participation by giving informed written consent; or b) Patient who cannot legally consent, has an age-appropriate understanding of the study procedures, and gives informed written assent and their parent/guardian agrees to participation by giving informed written consent. If the parent/guardian is illiterate, see Section 3.2.3.13.1 for details.

6.14.5 Sub-Study Patient Definition

New Patients – Patients who have been randomized after the approval of amendment 12.

Ongoing Patients – Patients who were randomized prior to approval of amendment 12 AND:

- are continuing on study medication, or
- have discontinued study medication and are within 54 weeks of randomization

Completed Patients - Patients who completed 54 weeks from date of randomization to P083 (includes patients on or off study medication and patients participating in P351).

6.14.6 Sub-Study Flow Charts

Sub-study flow charts for new patients, ongoing patients, and patients who previously completed 54 weeks of the main study are outlined in [Table 6-1](#), [Table 6-2](#), and [Table 6-3](#).

Note: For all new and ongoing patients, sub-study visits will be combined with the pre-existing visits for the main study. **No new or additional visits are required.**

Table 6-1

Sub-Study Flow Chart for New Patients

	Screening	Week 0/ Day 1	Week 20	Week 54	Rescue Step 1 or Treat to Goal Step 1 or Discontinuation
Obtain informed consent and assent ¹	X				
Evaluate inclusion criteria	X				
Dental photographs		X	X	X	X
Collection of dental records	X ²	X ³	X ³	X ³	X ³
<ol style="list-style-type: none"> 1. Consent/assent forms must be signed prior to any sub-study specific procedures. 2. The patient’s parent/guardian and/or the patient will be asked if the patient has had any dental exams prior to screening. If so, the closest available record before randomization will be obtained from the patient’s personal dentist (if consent/assent provided). 3. The patient’s parent/guardian and/or the patient will be asked if the patient has had any dental exams since the last study visit. If so, these records will be obtained from the patient’s personal dentist (if consent/assent provided). 					

Table 6-2

Sub-Study Flow Chart for Ongoing Patients

	First Clinic Visit Following Dental Sub-Study Amendment Approval ¹	Week 20	Week 54	Rescue Step 1 or Treat to Goal Step 1 or Discontinuation
Obtain informed consent and assent ²	X			
Evaluate inclusion criteria	X			
Dental photographs	X	X	X	X
Collection of dental records	X ³	X ⁴	X ⁴	X ⁴
<ol style="list-style-type: none"> 1. Ongoing patients will be able to participate in this sub-study starting at their first clinic visit (per the main protocol) following dental sub-study amendment approval at the site. For patients who have discontinued study medication, this First Clinic Visit would be either Week 20 or Week 54. 2. Consent/assent forms must be signed prior to any sub-study specific procedures. 3. The patient’s parent/guardian and/or the patient will be asked if the patient has had any dental exams prior to the first clinic visit after this sub-study approval at the site. If so, the closest available record before randomization and all available records since randomization will be obtained from the patient’s personal dentist (if consent/assent provided). 4. The patient’s parent/guardian and/or the patient will be asked if the patient has had any dental exams since the last study visit. If so, these records will be obtained from the patient’s personal dentist (if consent/assent provided). 				

Table 6-3

Sub-Study Flow Chart for Patients who Completed 54 weeks of the Main Study

	Dental Visit (Post Main Study)
Obtain informed consent and assent ¹	X
Evaluate inclusion criteria	X
Collect post treatment dental events and medications ²	X
Monitor for adverse events ³	X
Visual oral examination (including inspection of teeth) ⁴	X
Dental photographs	X
Collection of dental records ^{5,6}	X
<ol style="list-style-type: none"> 1. Consent/assent forms must be signed prior to any sub-study specific procedures. 2. Collect events and medications of particular dental interest. 3. The AE reported should occur in conjunction with the dental sub-study visit. 4. Patients returning after completing P083 will have a visual oral examination (see Appendix 6.10). 5. The patient's parent/guardian and/or the patient will be asked if the patient has had any dental exams prior to randomization to P083. If yes, the closest available dental record prior to randomization will be collected from the patient's personal dentist (if consent/assent provided). 6. The patient's parent/guardian and/or the patient will be asked if the patient has had any dental exams during his/her participation in P083 and after completion of 54 weeks of this main study. If so, these records will be collected from the patient's personal dentist (if consent/ assent provided). 	

6.15 LIST OF PRIOR AMENDMENTS

Amendment 01 dated 14-Jan-2013, Global.

Amendment 02 dated 30-Apr-2013, Country-specific, Germany.

Amendment 03 dated 30-Mar-2013, Country-specific, Mexico.

Amendment 04 dated 29-Apr-2013, Country-specific, Brazil.

Amendment 05 dated 19-Feb-2014, Global.

Amendment 06 dated 06-Mar-2014, Country-specific, Germany.

Amendment 07 dated 01-Dec-2014, Global.

Amendment 08 dated 07-Jan-2015, Country-specific, Germany.

Amendment 09 dated 27-Aug-2015, Global

Amendment 10 dated 16-Oct-2015, Country-specific, Germany

Amendment 11 not released.

Amendment 12 dated 27-Jan-2017, Global.

Amendment 13 dated 20-Feb-2017, Country-specific, Germany.

Amendment 14 not released.

Amendment 15 not implemented.

7. ATTACHMENTS

Merck & Co., Inc. 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.

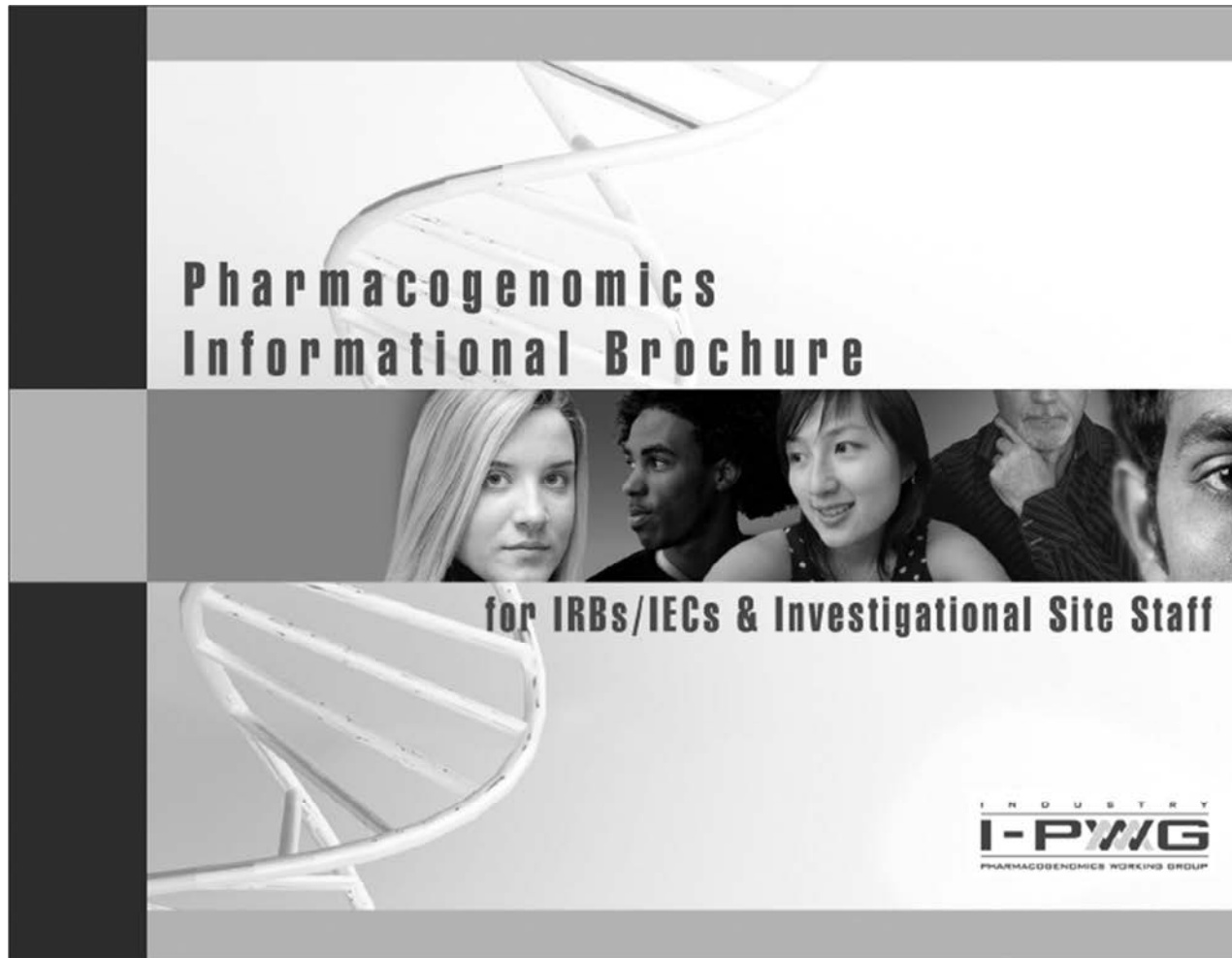
C. Funding for Travel and Other Requests

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."



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.

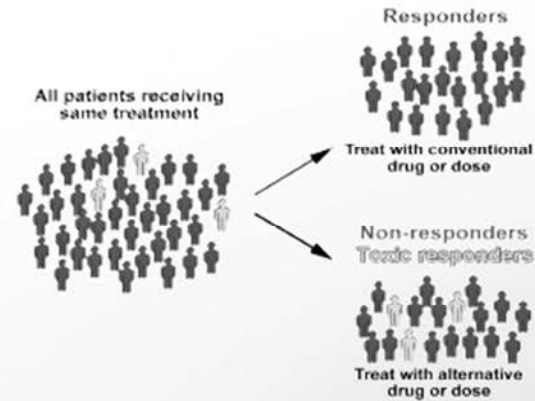
Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

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 RNA¹, 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.



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

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



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 studies². These elements build upon existing basic elements of informed consent for clinical research on human subjects³.

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. 2006⁴.

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 E15¹. 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.



Table adapted from ICH Guidance E15

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

ii) Separation of Data and Restricted Access

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

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data

usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form².

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)^{3, 4} 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),

EMA (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 submissions¹⁹.

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>.



Glossary

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

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

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

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

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

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

6

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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
