Protocol H9X-IN-GBGR

A 24-week Multicenter, Open-label, Single-arm Study to Evaluate Safety in Patients With Type 2 Diabetes Mellitus in India Treated With Dulaglutide

NCT05659537

Approval Date: 19-Jun-2023

Title Page

Protocol Title:

A 24-week multicenter, open-label, single-arm study to evaluate safety in patients with type 2 diabetes mellitus in India treated with dulaglutide.

Protocol Number: H9X-IN-GBGR

Amendment Number: H9X-IN-GBGR (b)

Compound: Dulaglutide (LY2189265)

Brief Title:

A study to investigate adverse and serious adverse events with dulaglutide in participants with type 2 diabetes mellitus in India.

Study Phase: 4

Sponsor Name: Eli Lilly and Company

Legal Registered Address:

Plot No. 92, Institutional Area, Sector 32, Gurugram, Haryana 122001, India

Regulatory Agency Identifier Number: Not applicable

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-117803

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Initial Protocol	02-Jun-2022

Amendment (b)

The amendment is considered to be non-substantial because it is not likely to have a significant impact on the

- safety or the rights of the study participants
- reliability and robustness of the data generated in the clinical study, and
- the quality or safety of any investigational medicinal product used in the study.

Overall rationale for the amendment

Protocol H9X-IN-GBGR titled "A 24-week multicenter, open-label, single-arm study to evaluate safety in patients with type 2 diabetes mellitus in India treated with dulaglutide" has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Marked X for AEs in Screening column	Corrected the error.
	Added "temperature" in Vital signs	Corrected the error.
	Removed "insulin dose (if the patient is taking insulin)" in Diary compliance check	Patient Diary does not have a provision of capturing Insulin Dose. Insulin dose can be captured in source document (eCRF)
Section 2.1 Study Rationale	Deleted "combination therapy" for 0.75mg in Study Rationale.	0.75 mg is not recommended as a combination therapy in the label - it is only approved as a monotherapy- since 0.75 mg dose is approved, one can maintain the patient on this if the patient is not able to tolerate 1.5 mg for some reason or as is common practice, one can start on 0.75 mg and build up the dose to 1.5 mg.

Section Number and Name	Description of Change	Brief Rationale
Figure 6.1	For GI Side effects, - Yes, superscript "a" was added to clarify.	Corrected the error.
Section 6.5 Dose modification	Updated language by adding "permitted only once".	There could be a titration in the initial part of the study as explained in the dispensing scenarios which usually covers the first 4-6 weeks in the study. Thereafter and once this happens, this titration is not allowed beyond that period.
Section 6.8 Concomitant therapy	Replaced the hypoglycemia word to "hyperglycemia"	The chances of developing hypoglycemia with dulaglutide per se is less. However, if there is an occasional hypoglycemia in a patient following dulaglutide start, the concomitant dose of SU and or insulin should be modified as per the PI discretion.
Section 7.1.3 Temporary Discontinuation	Updated the language to "allowed once" and added that "Study drug discontinuation decision will be taken post the titration in the initial 4-6 weeks of the study"	Corrected the error. Study drug discontinuation decision will be taken post the titration in the initial 4-6 weeks of the study.
Section 8.2.5. Hepatic Monitoring	For additional hepatic data collection, "hepatic safety CRF" and "collection in the hepatic safety in" was deleted.	There is no eCRF page for hepatic safety. All central lab data are received through medical listing and not being captured in eCRF.
Section 8.3.1 Timing and Mechanism for Collecting Events	SAE CRF was corrected to SAE paper form in the table	Corrected the error.
Section 9.3 Analyses Sets	For enrolled participant analysis set, Description was updated to include "screen positive"	To be consistent with SAP.
Section 10.3.4 Recording and Follow-Up of AE and/or SAE and Product Complaints	"Facsimile transmission of SAE paper form" was updated to "E-mail transmission of SAE paper form". "SAE CRF pages" was corrected to "SAE paper form"	Corrected the error.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A 24-week multicenter, open-label, single-arm study to evaluate safety in patients with type 2 diabetes mellitus in India treated with dulaglutide.

Brief Title:

A study to investigate adverse and serious adverse events with dulaglutide in participants with type 2 diabetes mellitus in India.

Regulatory Agency Identifier Number: Not applicable

Rationale:

Once weekly dulaglutide was approved on 23 December 2014 by CDSCO. As per the approved label in India, once-weekly 1.5 mg dulaglutide is recommended as a combination therapy in patients with T2DM in addition to the ongoing OHAs and/or insulin. In select cases, for example, in patients with metformin intolerance, 0.75 mg dulaglutide is recommended as monotherapy. The CDSCO had stipulated a Phase 4 study to document the experience of the local population with T2DM from India as a clause toward marketing authorization for dulaglutide in India. A Phase 4 observational study to assess the safety including AEs and SAEs with dulaglutide in patients with T2DM India is currently ongoing. This Phase 4 clinical study, over and above the observational study, is being proposed to fulfill this marketing authorization clause.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Assess the safety profile of 1.5 and 0.75 mg dulaglutide in patients with T2DM in India	Incidence of AEs (deaths, SAEs, TEAEs, and hypoglycemia, including severe hypoglycemia) Proportion of patients reporting AEs and SAEs between baseline and Week 24 Incidence of GI AEs
Secondary	
Change in HbA1c for pooled doses of dulaglutide	Mean change in HbA1c from baseline to Week 24
Exploratory	
Change in body weight	Mean change in body weight from baseline to Week 24
Change in FBG	Mean change in FBG from baseline to Week 24
Change in vital signs	Change in systolic blood pressure, diastolic blood pressure, and pulse rate from baseline to Week 24

Overall Design

This is a Phase 4, single-arm study to study the safety of dulaglutide in patients with T2DM in India who are on stable doses of oral antihyperglycemic medications with or without stable doses

of basal or premix insulin for the last 3 months prior to screening. The efficacy profile of dulaglutide will be measured as a secondary endpoint.

Brief Summary:

The purpose of this study is to assess the safety profile of 1.5 and 0.75 mg dulaglutide in patients with T2DM in India.

The study includes a

- Screening Visit
- 2-week lead-in period
- 24-week treatment period, and
- follow-up period 4 weeks after the last treatment.

Study Population:

In general, participants may take part in the study if they

- are 18 years of age or older, at the time of signing the informed consent
- reside in India
- have a diagnosis of T2DM of at least 1-year duration currently treated with stable doses of oral antihyperglycemic medications with or without stable doses of basal or premix insulin for the last 3 months prior to screening. Premix insulin is allowed up to twice daily in the screening period to be taken up further. Doses of other OHAs will be optimized as per investigator's discretion. Patients on thrice-daily premix insulin or full basal bolus insulin (insulin regimen 3-4 times daily) therapy are excluded from the study
- have HbA1c ≥7.5% and ≤11.5%, both inclusive, at screening, and
- have BMI ≥23 kg/m^2.

In general, participants may not take part in the study if they have

- a diagnosis of T1DM or latent autoimmune diabetes, or specific type of diabetes other than T2DM
- been treated with antihyperglycemic medication like GLP-1 RA or have a prior history of any contraindication to GLP-1 RA therapy within 3 months prior to screening, or
- eGFR <15 ml/min/1.73m^2.

Number of Participants:

An estimated 250 participants will be screened, and assuming a 20% screen failure rate, an estimated 200 participants will be initiated on IP. Assuming a 20% dropout rate by the end of the study period, approximately 160 patients at the end of the study would allow for an adequate description of AEs and other safety outcomes. This is required to fulfill the market authorization clause.

Intervention Groups and Duration:

This table lists the intervention used in this clinical study.

Intervention Name	Dulaglutide
Dosage Levels	0.75 or 1.5 mg
Route of Administration	Subcutaneous injection
Frequency of Administration	Once weekly

The following circumstances are permitted:

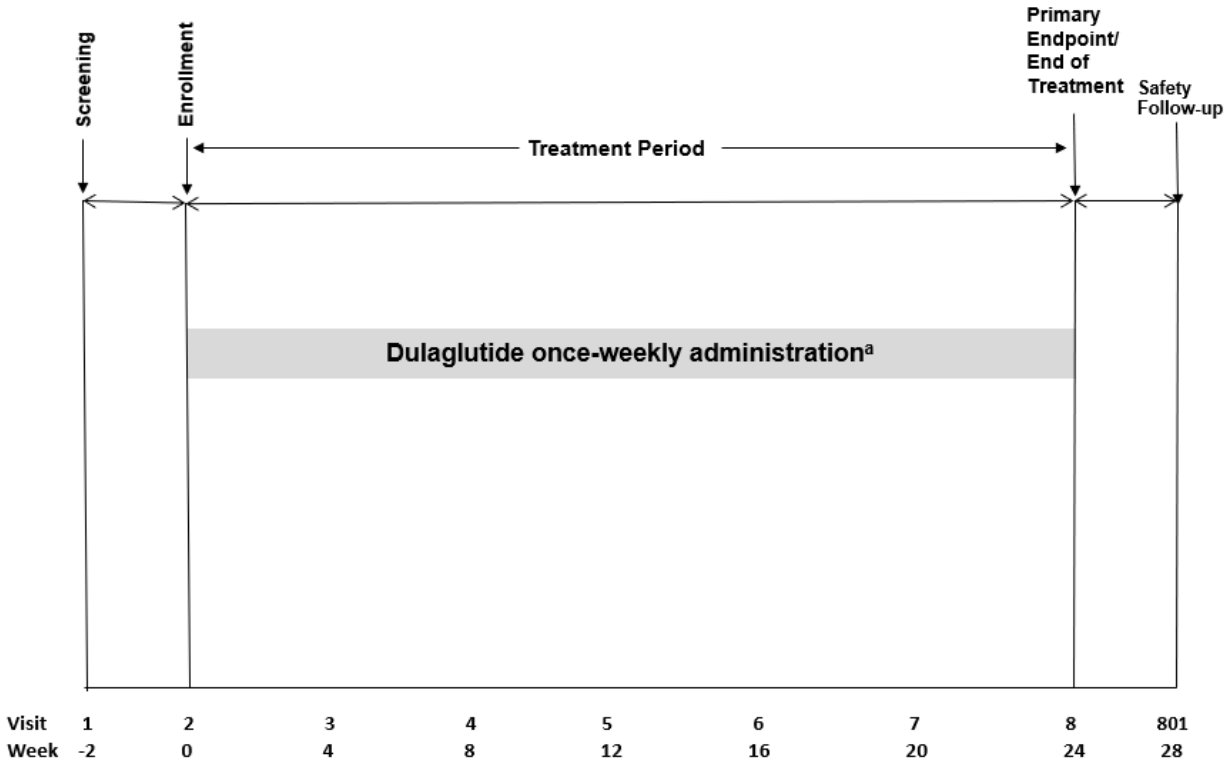
1. Treatment will be started with dulaglutide 1.5 mg as combination therapy or dulaglutide 0.75 mg as combination therapy or monotherapy. For patients who report GI AEs after starting treatment with 1.5 mg dulaglutide, the investigator may reduce the dose to 0.75 mg based on symptoms reported by patients. Treatment will be continued with 0.75 mg for 2 to 3 weeks. Thereafter, the 1.5-mg dose will be reintroduced.
2. As per common practice in India, treatment may be started with 0.75 mg dulaglutide as a combination therapy in select cases (Wasir et al. 2018). The dose may be up titrated to 1.5 mg after a period of 2 to 4 weeks in consultation with the medical monitor.

Ethical Considerations of Benefit/Risk:

Considering the clinical data to date and measures taken to minimize risk for the participants in this study, the potential risks identified in association with dulaglutide are justified by the anticipated benefits that may be afforded to persons with T2DM.

Data Monitoring Committee: No

1.2. Schema



[a]The following circumstances are permitted: 1. Treatment will be started with dulaglutide 1.5 mg as combination therapy or dulaglutide 0.75 mg as combination therapy or monotherapy. For patients who report GI adverse events after starting treatment with 1.5 mg of dulaglutide, the investigator may reduce the dose to 0.75 mg based on symptoms reported by patients. Treatment will be continued with 0.75 mg for 2-3 weeks. Thereafter, 1.5 mg dose will be reintroduced. 2. As per common practice in India, treatment may be started with 0.75 mg of dulaglutide as a combination therapy in select cases. The dose may be up titrated to 1.5 mg after a period of 2 to 4 weeks in consultation with the medical monitor.

1.3. Schedule of Activities (SoA)

	Screening	Treatment Period							Follow-Up	Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**801**	
Weeks from Start of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Visit Interval Tolerance (days)	**±3**	**—**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Visit Detail	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**	**T**	**T=telehealth visit F=fasting visit**
Informed consent	X									The ICF must be signed by patients or their caregivers before any -protocol specific tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion or exclusion criteria, review, and confirm	X	X								The Investigator will confirm inclusion and exclusion criteria prior to enrollment and administration of first dose of study intervention.
Demographics	X									Includes ethnicity (where permissible), year of birth, gender, and race
Preexisting conditions and medical history, including relevant surgical history	X									Collect all ongoing conditions and relevant past surgical and medical history
Prespecified medical history (indication and history of interest)	X									
Prior treatments for indication	X									

Concomitant medications	X	X	X	X	X	X	X	X		
AEs	X	X	X	X	X	X	X	X	X	AEs are any events that occur after signing the informed consent. These will also include any AE reported after the first dose of dulaglutide.
Hypoglycemia events	X	X	X	X	X	X	X	X	X	Clinical assessment based on participant history and diary entries
Physical Evaluation										
Height	X									Participant should remove shoes.
Weight	X	X			X			X		
Vital signs	X	X			X			X		Includes temperature, blood pressure, and pulse rate. Measure 3 times, using the same arm, after participant has been sitting at least 5 min and before ECG tracing and collection of blood samples for laboratory testing. Of the 3 measurements, the blood pressure and pulse rate values observed during the third and final measurements will be entered in the eCRF. Additional vital signs may be measured as necessary at investigator's discretion.
Physical examination	X									This includes examination for any sensory loss, motor neuropathy, and retinopathy. Additional physical

										examinations may be completed as necessary at investigator's discretion.
12-lead ECG (local)	X									Participants should be supine for approximately 5-10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.
Diabetes counseling, training, and education		X			X			X		Includes SMBG and hypoglycemia (see Section 5.3). After Visit 2, conduct as needed.
Provide training on paper diary and glucometer		X			X					After Visit 2, conduct as needed. Refer to Section 4.1.
Participant Diary and Blood Glucose Meter										
Dispense paper diary and glucometer		X			X					Dispense supplies as needed. Re-dispense paper diary at Visit 5.
Diary compliance check		X	X	X	X	X	X	X		Review entries of BG and dulaglutide. If participant is not compliant, study personnel will re-educate the participant on study requirements for continued study participation.
Collect information from study diary		X	X	X	X	X	X	X		Includes SMBG results, hypoglycemic events, , date, and exact time of every study drug injection.

Laboratory Tests and Sample Collections										
Hematology	X	X			X			X		
HbA1c	X	X			X			X		
Clinical chemistry	X	X			X			X		
FBG		X			X			X		
Lipid panel		X						X		
Urinalysis	X									
Serum pregnancy test	X	X								For only WOCBP
Urine pregnancy (local)		X								The test will be done only for WOCBP. The result must be available prior to first dose of intervention. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.
Follicle-stimulating hormone	X									Perform as needed to confirm postmenopausal status in women. Definition in Section 10.4.
eGFR (CKD-EPI)	X	X						X		
Urinary albumin/creatinine ratio		X						X		
Dosing-Related Activities										
Dosing and injection training		X			X					After Visit 2, conduct as needed.
Distribute study drug		X			X					
IMP administration		Once weekly								The first dose will be administered under medical

				supervision by the investigator or designee at the clinical site. Subsequent doses will be self-administered by participants at home.

Abbreviations: BG = blood glucose; CKD-EPI = chronic kidney disease-epidemiology; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ICF = informed consent form; IMP = investigational medicinal product; SMBG = self-monitored blood glucose; WOCBP = women of childbearing potential.

2. Introduction

Dulaglutide (LY2189265; Eli Lilly and Company [Lilly], Indianapolis, IN, USA) is a long-acting GLP-1 RA that was approved on 23 December 2014 by CDSCO for the treatment of adults with T2DM.

2.1. Study Rationale

Once-weekly dulaglutide was approved on 23 December 2014 by CDSCO. As per the approved label in India, once-weekly 1.5 mg dulaglutide is recommended as a combination therapy in patients with T2DM in addition to the ongoing OHAs and/or insulin. In select cases, for example, in patients with metformin intolerance, 0.75 mg dulaglutide is recommended as monotherapy. The CDSCO had stipulated a Phase 4 study to document the experience of the local population with T2DM from India as a clause toward marketing authorization for dulaglutide in India. A Phase 4 observational study to assess the safety including AEs and SAEs with dulaglutide in patients with T2DM India is currently ongoing. This Phase 4 clinical study, over and above the observational study, is being proposed to fulfill this marketing authorization clause.

2.2. Background

Of the current population burdened with T2DM, 60% are Asians (Hu 2011). As of 2021, India has an estimated 74 million people with diabetes, the second largest number for any individual country in the world. The projected growth of patients with diabetes between 2021 and 2045 in India is one of the highest in the world. By 2045, approximately 125 million people in India are projected to be suffering from diabetes (IDF Diabetes Atlas [https://diabetesatlas.org/]). T2D is the most common type of diabetes, accounting for over 90% of all diabetes cases. There is a paucity of data on the current state of T2DM glycemic control in India. The recently concluded India Diabetes Study has highlighted the need for optimum cardiovascular risk control in recently diagnosed T2DM in India, along with the need for optimum glycemic control. GLP-1 RA along with sodium-glucose co-transporter-2 inhibitors are being increasingly used in patients with T2DM in India for optimal glycemic control along with additional benefits of weight loss and cardiovascular event prevention. Dulaglutide, which is a once-weekly GLP-1 RA, is available in India since the last 5 years and is being used as combination therapy in patients with T2DM and in select cases (for example, metformin-intolerant patients) as monotherapy as well. The efficacy and safety of dulaglutide have been well established in the AWARD program, which has shown powerful and sustained HbA1c reduction for up to 2 years, and in the cardiovascular outcome study, which has shown reduction in outcomes in patients with T2D both with cardiovascular disease and those with risk factors. Dulaglutide is well tolerated with predominant side effects being GI in nature and dominated by nausea, vomiting, and diarrhea. Some patients have also complained of abdominal pain, loss of appetite, dyspepsia, and constipation.

A detailed description of the chemistry, pharmacology, efficacy, and safety of dulaglutide is provided in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dulaglutide may be found in the IB and patient information leaflet.

2.3.1. Risk Assessment

The AE profile with dulaglutide has been mainly GI in nature, with nausea, diarrhea, and vomiting being the most common AEs.

The measures taken in the present proposed study are sufficient to ensure the safety of the participants in this study, and the risks due to AEs are outweighed by the potential benefits seen with the molecule.

2.3.2. Benefit Assessment

The AWARD program, which included 10 completed placebo- and/or active-controlled Phase 3 studies of more than 5800 patients with T2DM, has shown powerful and sustained HbA1c reduction in patients with T2DM with additional benefits of weight loss. The REWIND study showed that dulaglutide improves cardiovascular outcomes in patients with T2DM with established cardiovascular disease or with risk factors, and no new safety concerns were reported (Gerstein et al. 2019). Additionally, real-world studies in India of more than 700 patients in patients with T2D showed that dulaglutide reduced HbA1c and reduced weight as a secondary benefit. Mild-to-moderate GI AEs were reported, which is at par with what is seen with GLP-1 RAs (Ghosal and Sinha 2018; Robinson et al. 2020; Srivastava et al. 2018).

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with dulaglutide are justified by the anticipated benefits that may be afforded to participants with T2DM.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Assess the safety profile of 1.5 and 0.75 mg dulaglutide in patients with T2DM in India	Incidence of AEs (deaths, SAEs, TEAEs, and hypoglycemia, including severe hypoglycemia) Proportion of patients reporting AEs and SAEs between baseline and Week 24 Incidence of GI AEs
Secondary	
Change in HbA1c for pooled doses of dulaglutide	Mean change in HbA1c from baseline to Week 24
Exploratory	
Change in body weight	Mean change in body weight from baseline to Week 24
Change in FBG	Mean change in FBG from baseline to Week 24
Change in vital signs	Change in systolic blood pressure, diastolic blood pressure, and pulse rate from baseline to Week 24

4. Study Design

4.1. Overall Design

This is a Phase 4, single-arm study to study the safety of dulaglutide in patients with T2DM in India who are on stable doses of oral antihyperglycemic medications with or without stable doses of basal or premix insulin for the last 3 months prior to screening. The efficacy profile of dulaglutide will be measured as a secondary endpoint.

The study consists of a

screening visit
2-week lead-in period
24-week treatment period, and
safety follow-up visit.

Screening and lead-in

Visit 1: Screening

Interested participants will sign the appropriate informed consent document(s) prior to initiating any procedures.

The investigator will review medical history, symptoms, risk factors, and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, the site will perform the diagnostic procedures to confirm eligibility.

Treatment period

Visit 2

Participants will receive their glucometer and first paper diary .

Participants will receive training on

- diabetes self-monitoring and management
- study glucometer
- paper diaries, and
- study requirements.

All participants will be treated with once weekly dulaglutide throughout the treatment period, as described in Section 6.1.

Visit 3 through Visit 8 and safety follow-up Visit 801

Study personnel will collect the first paper diary and dispense a second paper diary at Visit 5.

Study personnel and participants will complete all visit procedures described in the SoA.

4.2. Scientific Rationale for Study Design

Primary endpoint

The primary measurement is the incidence of AEs, a widely used measure to study safety profiles.

Overall design

Dulaglutide is approved in India for the treatment of T2DM. Dulaglutide, like other GLP-1 RAs that are available in India, is an established mode of therapy for T2DM. The aim of this study is to investigate the AEs and SAEs that may occur when patients with T2DM take dulaglutide. Hence, a comparator group has not been considered for this study.

The most common side effects with dulaglutide are GI in nature and mainly comprise of nausea, vomiting, and/or diarrhea. These usually occur early during therapy, are mostly mild to moderate in nature, and are self-limiting over the next 2 to 4 weeks after therapy initiation. A Phase 1 study with dulaglutide in elderly patients with T2DM from has shown reduction of FBG and postprandial glucose with the first dose of dulaglutide. Statistically significant HbA1c reduction and weight loss as a secondary benefit have been seen with dulaglutide compared to placebo within 12 weeks of start of therapy in the AWARD studies and various published real-world experiences. Hence, the proposed treatment duration of 24 weeks in this study is a reasonable timeframe to observe the effects of dulaglutide both from an AE and efficacy perspective. The follow-up visit after the last dose is designed to capture any safety data that may occur after the drug is stopped.

4.3. Justification for Dose

Dulaglutide will be recommended as per the approved label in India. Once-weekly 1.5 mg dulaglutide is recommended as a combination therapy with ongoing OHAs and/or insulin. In select cases, for example, in patients with metformin intolerance, 0.75 mg dulaglutide is recommended as monotherapy or combination therapy, and this will be at the investigator's discretion.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The intended study population is adult patients who have been diagnosed with T2DM for at least 1 year.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Participants are 18 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants have a diagnosis of T2DM for at least 1 year, currently treated with stable doses of oral antihyperglycemic medications with or without stable doses of basal or premix insulin for the last 3 months prior to screening. Premix insulin is allowed up to twice daily in the screening period to be taken up further. Doses of other OHAs will be optimized as per investigator's discretion. Patients on thrice-daily premix insulin or full basal bolus insulin (insulin regimen, 3 to 4 times daily) therapy are excluded from the study.
3. Participants have HbA1c ≥7.5% and ≤11.5%, both inclusive, at screening.

Weight/BMI

4. Participants have BMI ≥23 kg/m^2.

Sex and Contraceptive/Barrier Requirements

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

5. Male study participants: No male contraception is required except in compliance with specific local government study requirements. Female study participants: For the contraception requirements of this protocol, see Section 10.4.

Informed Consent

6. Participants are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other Inclusions

7. Residents of India

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

8. Participants have a diagnosis of T1DM or latent autoimmune diabetes, or specific type of diabetes other than T2DM (for example, monogenic diabetes, diseases of the exocrine pancreas, or drug-induced or chemical-induced diabetes).
9. Participants have eGFR <15 mL/min/1.73 m^2.
10. Participants have a prior history of intolerance to GLP-1 RA or ultrasonographical or radiological (CT/MRI) evidence or a history of acute or chronic pancreatitis.
11. Participants have a prior history of decompensated liver disease with or without evidence of ascites. SGPT/SGOT/amylase ≥3 × ULN at baseline.
12. Participants have a history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 in the patient or in the family.
13. Participants have an active or untreated malignancy, except for successfully treated basal or squamous cell carcinoma.

Prior/Concomitant Therapy

14. Participants have been treated with antihyperglycemic medication like GLP-1 RA alone or in combination or have a prior history of any contraindication to GLP-1 RA therapy within 3 months prior to screening.
15. Participants have been treated with dipeptidyl peptidase-4 inhibitors within 4 weeks prior to screening.

Other Exclusions

16. Participants have known hypersensitivity or allergy to dulaglutide or its excipients.
17. Participants are on systemic steroids for any period of more than 14 days.
18. Participants have severe GI disease, including severe gastroparesis.
19. Participants have T2DM along with morbid obesity and being considered for bariatric surgery
20. Participants are persons of childbearing potential who

    - are pregnant or intend to become pregnant
    - are lactating/breastfeeding (including the use of a breast pump)
    - are unwilling to remain abstinent or use birth control, or
    - test positive for pregnancy at the time of screening.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Diabetes management counseling

Qualified study personnel will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia, should it occur. Diabetes self-management counseling should be reviewed throughout the study, as needed.

Dietary and exercise considerations

Study participants should generally follow a healthy meal plan and continue their usual exercise habits throughout the course of the study.

Dietary and exercise restrictions

Study participants should not initiate an intensive diet or exercise program with the intent of reducing body weight at any time during the study, other than the lifestyle and dietary measures for diabetes treatment.

Blood donation

Study participants should not donate blood or blood products during the study or for 4 weeks following their last study visit.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to dulaglutide. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes

- demography
- screen failure details
- eligibility criteria, and
- any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after 4 weeks from the date of screen failure after discussion with the medical monitor from the Lilly team. Rescreened participants should be assigned a new participant number for every screening or rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study. All entry criteria must be met within the specified intervals in the SoA.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

This table lists the intervention used in this clinical study.

Intervention Name	Dulaglutide
Dosage Levels	0.75 or 1.5 mg
Route of Administration	Subcutaneous injection
Frequency of Administration	Once weekly

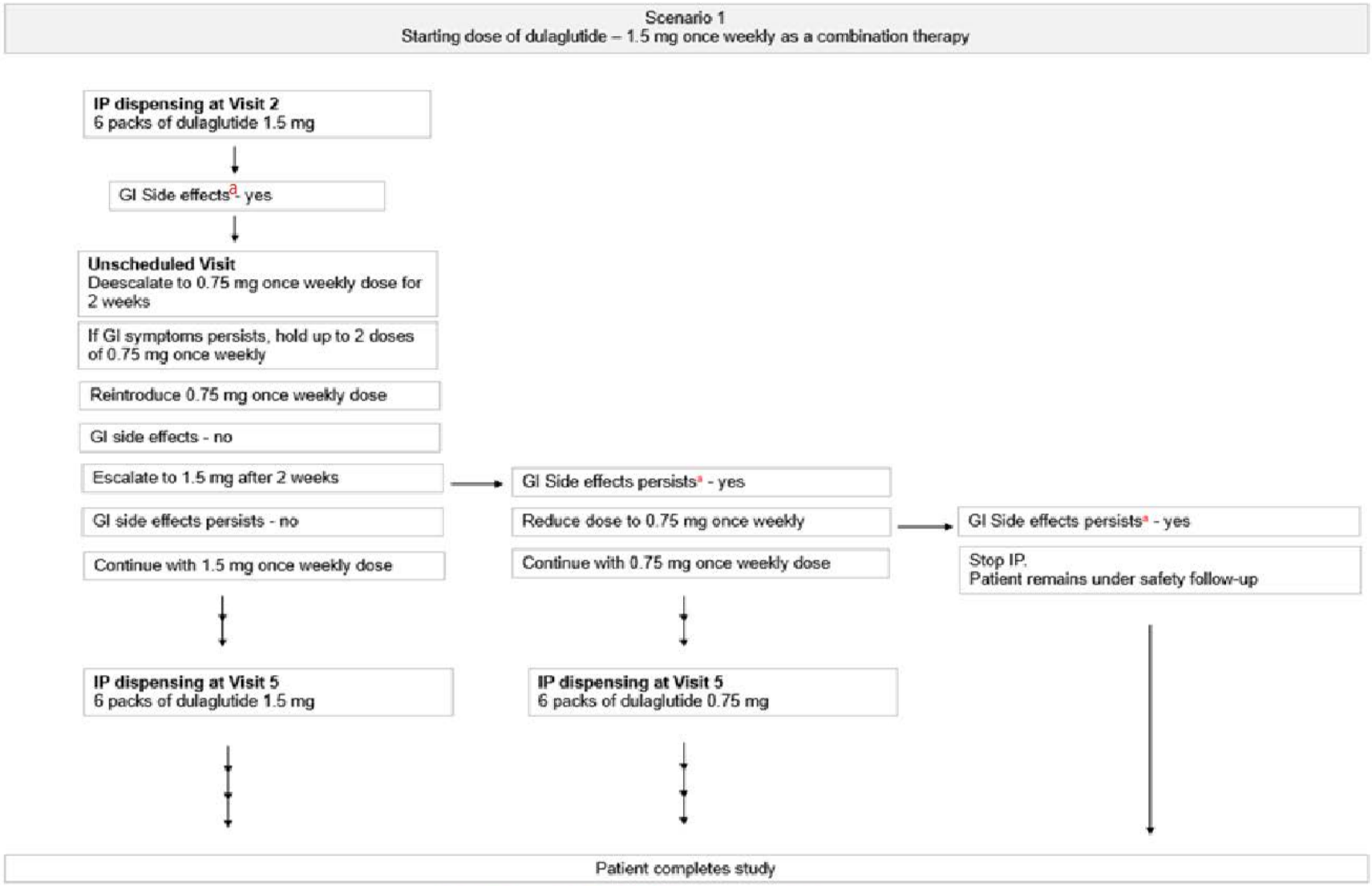
The following circumstances are permitted:

1. Treatment will be started with dulaglutide 1.5 mg as combination therapy or dulaglutide 0.75 mg as combination therapy or monotherapy. For patients who report GI AEs after starting treatment with 1.5 mg dulaglutide, the investigator may reduce the dose to 0.75 mg based on symptoms reported by patients. Treatment will be continued with 0.75 mg for 2 to 3 weeks. Thereafter, the 1.5-mg dose will be reintroduced.
2. As per common practice in India, treatment may be started with 0.75 mg dulaglutide as combination therapy in select cases. The dose may be up titrated to 1.5 mg after a period of 2 to 4 weeks in consultation with the medical monitor.

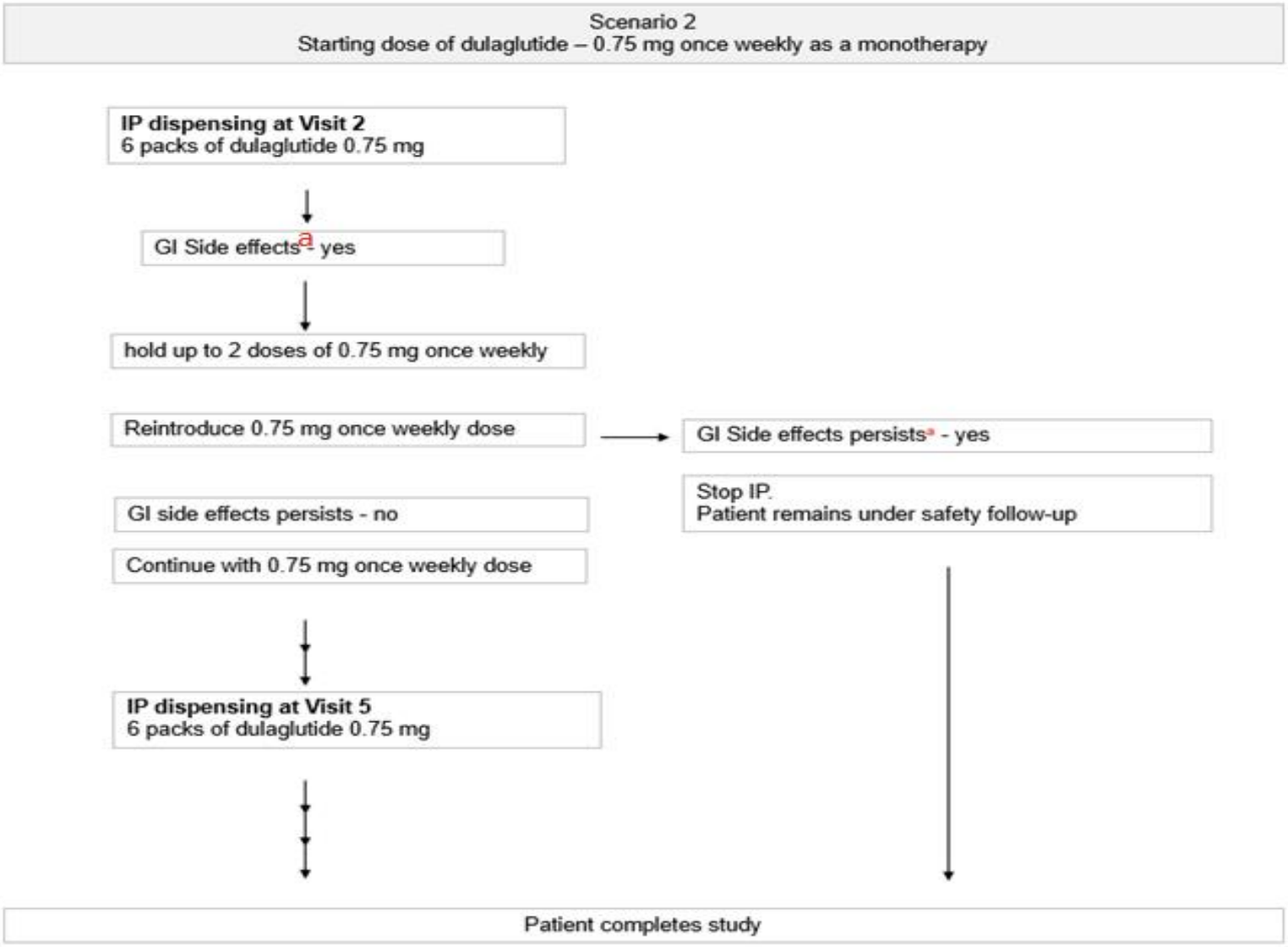
IP dispensing scenarios

IP dispensing will be done at Visit 2 for first 3 months of therapy and again at Visit 5 for next 3 months of therapy.

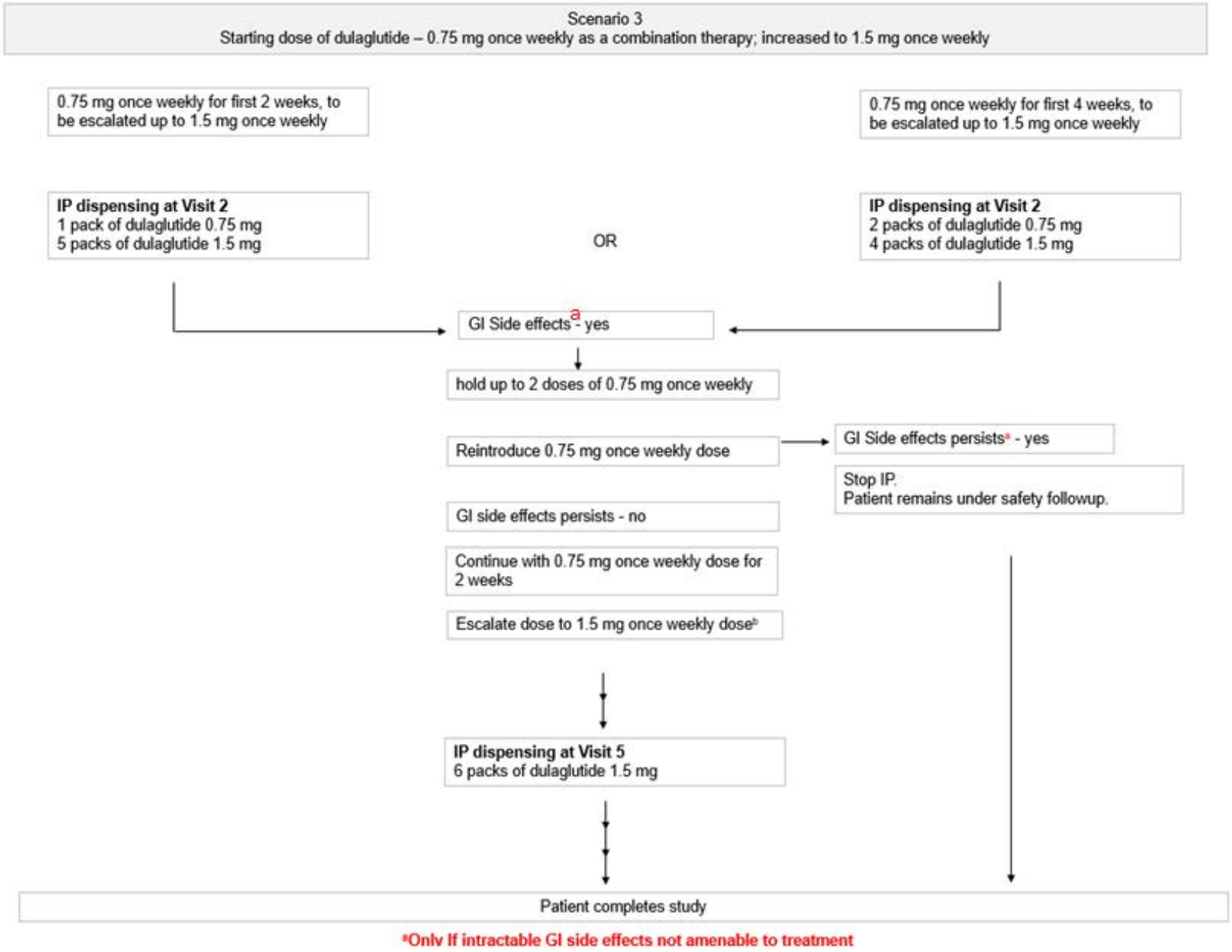
The various IP dispensing scenarios are shown in Figure 6.1.



[a]Only If intractable GI side effects not amenable to treatment



[a]Only If intractable GI side effects not amenable to treatment


Scenario 3
Starting dose of dulaglutide – 0.75 mg once weekly as a combination therapy; increased to 1.5 mg once weekly
0.75 mg once weekly for first 2 weeks, to be escalated up to 1.5 mg once weekly
0.75 mg once weekly for first 4 weeks, to be escalated up to 1.5 mg once weekly
IP dispensing at Visit 2
1 pack of dulaglutide 0.75 mg
5 packs of dulaglutide 1.5 mg
OR
IP dispensing at Visit 2
2 packs of dulaglutide 0.75 mg
4 packs of dulaglutide 1.5 mg
GI Side effects[a] - yes
hold up to 2 doses of 0.75 mg once weekly
Reintroduce 0.75 mg once weekly dose
GI Side effects persists[a] - yes
Stop IP.
Patient remains under safety followup.
GI side effects persists - no
Continue with 0.75 mg once weekly dose for 2 weeks
Escalate dose to 1.5 mg once weekly dose[b]
IP dispensing at Visit 5
6 packs of dulaglutide 1.5 mg
Patient completes study
[a]Only if intractable GI side effects not amenable to treatment

Abbreviations: F2F = face to face; GI = gastrointestinal; IP = investigational product; QW = once weekly; T = telephonic.

[b] Refer to the process in Panel 1 for scenario. Note:

1 pack of dulaglutide contains 2 pens.

Note: Patient followed up every 4 weeks on a remote basis till V4/ V8 (F2F) or V801 which is end of study visit (T).

Note: All efforts must be taken by the investigator to ensure that patients comply to therapy.

Note: All pens that are not used must be returned to the site at Visit 5 when the patient comes back for repeat F2F visit.

Note: Dulaglutide is provided as a combination with either other antihyperglycemic medications or in combination with insulin (basal, basal plus or premixes up to twice daily insulin regimen)

Figure 6.1. IP dispensing scenarios – Scenario 1 (top panel), Scenario 2 (middle panel), and Scenario 3 (bottom panel).

Packaging and labeling

Study interventions will be supplied by Lilly in accordance with current good manufacturing practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Rescue Medicine

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least the 4 weeks following the first administration of study intervention. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded.

6.1.2. Background Therapy or Standard of Care

For most patients with T2DM, standard of care stipulates treatment with OHAs and/or insulin. In this study, participants will be treated once weekly with dulaglutide 1.5 mg as combination therapy or dulaglutide 0.75 mg if used as monotherapy. Dulaglutide 0.75 mg can also be considered as a combination therapy dosage in very frail patients as per investigator discretion after discussion with the study monitor.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate storage conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized study personnel until these are provided to the participants to take home.
3. The investigator or authorized study personnel is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Intervention Compliance

The first dose will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the Sponsor as requested.

Subsequent doses will be self-administered by participants at home. Compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and documented in the source documents and CRF.

6.5. Dose Modification

Dose modifications are permitted only once in the following circumstances. The dose modification will be permitted only once within a maximum of 4 to 6 weeks after starting treatment with dulaglutide.

- As per common practice in India, treatment may be started with 0.75 mg of dulaglutide as combination therapy. The dose may be up titrated to 1.5 mg after a period of 2 to 4 weeks in consultation with the medical monitor. For patients who report GI AEs after starting treatment with 1.5 mg dulaglutide, the investigator may reduce the dose to 0.75 mg based on symptoms reported by patients. Treatment will be continued with 0.75 mg for 2 to 3 weeks. Thereafter, the 1.5-mg dose will be reintroduced.

6.6. Continued Access to Study Intervention After the End of the Study

The Sponsor will not provide participants with any ongoing supplies of study intervention after they have completed the study treatment period or permanently discontinued the study intervention.

6.7. Treatment of Overdose

For this study, any dose of dulaglutide greater than 1.5 mg within a 72-hour period will be considered an overdose.

Lilly does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration, including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Centrally acting pre-emetic medications are permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor. In cases of hyperglycemia, treatment with insulin or OHAs is permitted as per investigator discretion.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

Participants who stop dulaglutide permanently may receive another glucose-lowering medication at the investigator discretion. The new glucose-lowering medication will be recorded on the appropriate CRF.

A participant should be permanently discontinued from study intervention if the participant

- becomes pregnant during the study
- requests to discontinue dulaglutide
- did not take dulaglutide for more than 4 consecutive weeks or missed more than 4 consecutive doses of dulaglutide at any time during the study
- is inadvertently enrolled (this would be decided in consultation with the Sponsor's medical officer), or
- should permanently discontinue the study intervention for safety reasons, in the opinion of the investigator.

7.1.1. Liver Chemistry Stopping Criteria

Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver tests

In study participants with normal or near-normal baseline liver tests (ALT, AST, and ALP <1.5× ULN based on the normal limits determined by the testing laboratory), the study drug should be **interrupted** and close hepatic monitoring should be done if 1 or more of these conditions occur.

Elevation	Exception
ALT or AST >8× ULN	
ALT or AST >5× ULN for >2 weeks	
ALT or AST >3× ULN and either TBL >2× ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.
ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3× ULN, when the source of increased ALP is the liver	

Elevation	Exception
ALP >2.5× ULN and TBL >2× ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.
ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal (as determined by the testing laboratory).

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, and ALP ≥1.5× ULN), the study drug should be **interrupted** if 1 or more of these conditions occur.

Elevation	Exception
ALT or AST >4× baseline	
ALT or AST >3× baseline for more than 2 weeks	
ALT or AST >2× baseline and either TBL >2× ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.
ALT or AST >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5× baseline, when the source of increased ALP is the liver	
ALP >2× baseline and TBL > 2× ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2× ULN.
ALP >2× baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal (as determined by the testing laboratory).

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued.

7.1.2. Hypersensitivity Reactions

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be **permanently discontinued** from the study intervention, and the Sponsor's designated medical monitor should be notified.

If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the designated medical monitor from the study sponsor team.

7.1.3. Temporary Discontinuation

Criteria for temporary discontinuation of dulaglutide

The investigator may temporarily interrupt study treatment due to an AE, clinically significant variation in laboratory value, COVID-19 infection, hospital visits, travel, emergency surgery, hospitalization, or shortage of study treatment supply. Interruption in study treatment for 4 weeks or more will lead to permanent discontinuation of study treatment.

This will be allowed once at any time during the study. This information should be documented by the investigator. The study drug discontinuation decision will be taken post the titration in the initial 4-6 weeks of the study.

Guidance for temporary discontinuation of dulaglutide

Every effort should be made by the investigator to maintain participants in the study and to restart dulaglutide promptly, as soon as it is safe to do so.

Participants will continue their study visits and follow-up according to the SoA.

Participants should resume the dose prescribed before the temporary dosing interruption or as advised by the investigator.

Recording temporary discontinuation of dulaglutide

The dates of dulaglutide interruption and restart must be documented in source documents and entered in the CRF.

Participant noncompliance should not be recorded as interruption of dulaglutide in the CRF.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent, and
- if a study participant is diagnosed with any type of diabetes mellitus other than T2D.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and posttreatment follow-up, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. For participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site, the site personnel or designee is expected to make diligent attempts to contact till 4 weeks from the scheduled visit.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all randomly assigned participants, including those who did not get IP. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Efficacy will be measured by HbA1c and fasting glucose. See Section 3 for specific efficacy endpoints.

Glucose monitoring

Participants will receive a sponsor-approved glucometer and related testing supplies for use during the study.

Site personnel will train the participant on correct use of the glucometer for self-monitoring BG and reporting of hypoglycemia data in the paper diary.

As directed by the investigator, they may use the glucometer

- whenever hypoglycemia is experienced or suspected
- when there is awareness of increased risk related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing
- when patients take concomitant insulin therapy or sulfonylureas.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

Physical examination at screening

The complete physical examination will include, at a minimum, assessments of these systems:

- cardiovascular
- respiratory
- GI, and
- neurological.

Height and weight will be measured and recorded.

Additional assessments include

- clinical signs and symptoms related to T2D
- T2D-related illnesses, and
- injection-site reactions.

8.2.2. Vital Signs

Blood pressure and pulse rate will be measured as specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

8.2.3. Electrocardiograms

Local and single 12-lead ECG will be obtained as outlined in the SoA.

ECGs will initially be interpreted by the investigator or qualified designee at the site as soon as possible after ECG collection, and ideally, while the participant is still present, to determine whether the participant meets entry criteria and for immediate participant management, should any clinically relevant findings be identified.

The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document their review of the ECG printed at the time of evaluation.

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered to be clinically significantly abnormal during participation in the study or within 2 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal or baseline within a period judged reasonable by the investigator, the etiology should be identified, and the Sponsor should be notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then report the information as an AE.

8.2.5. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests (Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur.

If a participant with baseline results of	**develops the following elevations:**
ALT or AST <1.5× ULN	ALT or AST ≥3× ULN
ALP <1.5× ULN	ALP ≥2× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for the possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

- symptoms
- recent illnesses, for example,
    - heart failure
    - systemic infection
    - hypotension, or
    - seizures
- recent travel
- history of concomitant medications, including over-the-counter, herbal, and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of	**develops the following elevations:**
ALT or AST <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs or symptoms[a], or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs or symptoms[a], or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥2× baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

What a comprehensive evaluation should include

At a minimum, this evaluation should include physical examination and a thorough medical history, as well as

- tests for PT-INR
- tests for viral hepatitis A, B, C, or E
- tests for autoimmune hepatitis, and
- an abdominal imaging study (for example, ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for

- a hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography

- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or
- a liver biopsy.

Additional hepatic data collection in study participants who have abnormal liver tests during the study

Collect additional hepatic safety data in CRFs if a participant

- develops a hepatic event considered to be an SAE
- discontinues study intervention due to a hepatic event, or
- has changes in laboratory results described in this table

If a participant with baseline results of	develops the following elevations,	then
Elevated serum ALT		Collect additional hepatic safety data in the hepatic safety CRF.
ALT <1.5× ULN	ALT to ≥5× ULN on 2 or more consecutive blood tests	
ALT ≥1.5× ULN	ALT ≥3× baseline on 2 or more consecutive blood tests	
Elevated TBL		
TBL <1.5× ULN	TBL ≥2× ULN, except for participants with Gilbert's syndrome	
TBL ≥1.5× ULN	TBL ≥2× baseline	
Elevated ALP		
ALP <1.5× ULN	ALP ≥2× ULN on 2 or more consecutive blood tests	
ALP ≥1.5× ULN	ALP ≥2× baseline on 2 or more consecutive blood tests	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; CRF = case report form; TBL = total bilirubin; ULN = upper limit of normal.
Note: The interval between the 2 consecutive blood tests should be at least 2 days.
See Section 10.5 for hepatic laboratory tests.

8.2.6. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3, Appendix 3:

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, are considered related to the study intervention or study procedures, or caused the participant to discontinue the study intervention or study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the ICF	The last safety follow-up visit	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	The last safety follow-up visit	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the investigator	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

[a] SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive dulaglutide.

After learning of pregnancy in the female partner of a study participant, the investigator will

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent, record pregnancy information on the appropriate form and submit it to the Sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of

- gestational age
- fetal status (presence or absence of anomalies), or
- indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor, as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue dulaglutide. The participant will follow the standard discontinuation process and continue directly to the follow-up phase. The follow up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Systemic Hypersensitivity Reactions

Many drugs, including biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the Sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. Participants who experience a systemic hypersensitivity reaction are recommended to be treated per national and international guidelines.

8.3.4. Injection-Site Reactions

Symptoms and signs of a local injection-site reaction may include

- erythema
- induration
- pain
- pruritus
- lipodystrophy, and
- edema.

If an injection-site reaction is reported by participant or study personnel, additional information about this reaction will be collected in the CRF.

8.3.5. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat it. Hypoglycemia events entered into the participant paper diary will be reviewed by investigators at site visits or over telephone.

Hypoglycemia classification and definitions

Level 1

Glucose <70 mg/dL and ≥54 mg/dL

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2

Glucose <54 mg/dL

Level 2 hypoglycemia is also referred to as documented or BG confirmed hypoglycemia. The glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3

Severe hypoglycemia

A severe hypoglycemic event is characterized by altered mental or physical status requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for its treatment.

The determination of an episode of severe hypoglycemia is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

Examples of severe hypoglycemia in adults are

- altered mental status and the inability to assist in their own care
- semiconscious or unconscious, or
- coma with or without seizures.

Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

Nocturnal hypoglycemia

Nocturnal hypoglycemia is a hypoglycemia event, including severe hypoglycemia, that **occurs at night** and presumably during sleep between midnight and 0600 (6:00 am).

Reporting of severe hypoglycemic events

If a hypoglycemic event meets the criterion of severe, the investigator must record the event as serious on the SAE paper form and report it to Lilly as an SAE.

The investigator should also determine if repeated or prolonged episodes of hypoglycemia occurred prior to the severe event.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest include

- amylase and lipase ≥3× ULN
- pancreatitis
- medullary thyroid cancer or any other solid organ cancer

- medullary thyroid C-cell hyperplasia/neoplasm, and
- GI events including nausea and vomiting.

If either of these are reported, sites will be prompted to collect additional details. For each event, assessment of severity, duration, and investigator's opinion of relatedness to study drug and protocol procedure will be captured.

8.4. Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.6. Genetics

Genetics will not be evaluated in this study.

8.7. Biomarkers

Biomarkers will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters will not be evaluated in this study

9. Statistical Considerations

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary, key secondary, and exploratory endpoints.

9.1. Statistical Hypotheses

Not applicable

9.2. Statistical Methodology

Descriptive summary statistics will be presented for patient demographics, and AE frequency and percentage will be summarized.

Details are provided in Section 9.4.

9.3. Analyses Sets

For purposes of analysis, the following populations are defined:

Participant Analysis Set	Description
Enrolled	• All participants who sign informed consent form and are screen positive
FAS	• All patients who received at least 1 dose of study treatment and have at least 1 measurement of HbA1c after study treatment
Per-protocol set	All patients in the FAS who meet the following criteria • have no important protocol deviations that could impact the assessment of the primary objective (see SAP) • are at least 80% compliant with the study drug in terms of dose taken • have no instance of deviation from persistence with study drug in terms of no more than the 15 days gap between 2 consecutive doses • complete the treatment phase (24 weeks) for the primary endpoint
Safety analysis set	• All patients who received at least 1 dose of study treatment

Abbreviations: FAS = full analysis set; HbA1c = hemoglobin A1c; SAP = statistical analysis plan.

The FAS is used to analyze endpoints related to the efficacy objectives, and the safety analysis set is used to analyze the endpoints and assessments related to safety.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All data will be entered, verified, and archived by a CRO external to Lilly and/or at Lilly. Data listings, summaries, and analyses will be performed by a CRO under the guidance and approval of statisticians at Lilly.

Summary statistics will be provided for the observed value, and change from baseline will be summarized.

Unless otherwise specified, listings will include all enrolled patients. Efficacy analyses will be conducted using the FAS.

Similarly, the exploratory measures (change in body weight from baseline and change in FBG from baseline) will be evaluated in the FAS population.

Also, safety analyses will be conducted on the safety population. The exploratory measures of vital signs (change in SBP, DBP, and pulse rate from baseline) will be analyzed using the safety population).

Unless otherwise specified, testing effect of dulaglutide on change from baseline will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided.

For continuous measures, summary statistics will include number of patients, mean, SD, median, minimum, maximum, and interquartile ranges for both the actual and the change from baseline measurements. Number of missing values will be specified along with this information.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Number of missing values will be specified along with this information.

No multiplicity adjustment will be done in this study.

Change from baseline will only be calculated for patients with both baseline and post baseline values as:

Change from baseline = postbaseline value – baseline value.

The analysis for other continuous exploratory efficacy and safety measurements and continuous laboratory measures at 24 weeks will use the MMRM. It will be used to model change from baseline in FBG and any other safety or efficacy endpoints. Missing data will be assumed missing at random and will be accommodated by the MMRM.

The MMRM using restricted maximum likelihood will be done for analyses of change in FBG from baseline (note: statistical comparison will not be conducted) during the entire study period.

The MMRM could be repeated for other safety and efficacy endpoints.

For FBG, summary statistics will be provided for the observed value and change from baseline value based on the MMRM.

An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If this analysis fails to converge, the following covariance structures will be tested in order.

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by visit
3. Compound symmetry with heterogeneous variances, by visit
4. Toeplitz

5. Autoregressive
6. Compound symmetry without heterogeneous variances, by visit

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

If none of the models converge then an analysis of covariance using LOCF imputation with similar terms as in the MMRM (except no terms that include visit) will be used in its place.

The MMRM for each of the endpoints will include the respective baseline score and any covariate.

Baseline insulin use will be included as covariate in the model if convergence is met. Dose will be included as a covariate in the models, if appropriate. Details will be included in the SAP. Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.4.2. Primary Endpoints Analysis

AEs (deaths, SAEs, TEAEs, and hypoglycemia, including severe hypoglycemia)

Frequency and percentage of AE occurrence (including deaths, SAEs, TEAEs, hypoglycemia, including severe hypoglycemia and GI disorders) will be presented for the study duration using safety population.

The proportion of patients with AEs and SAEs occurring within the duration of the study (24 weeks) after being administered dulaglutide 1.5 or 0.75 mg will be presented.

The proportion of patients with AEs, TEAEs, and SAEs occurring within the duration of the study (24 weeks) after being administered dulaglutide 1.5 or 0.75 mg and 95% CIs will be estimated based on normal approximation.

The incidence of AE (death, SAE, and TEAE) will be summarized. The rate per year will be assessed using a negative binomial model with the log of the study treatment exposure time as an offset variable.

The incidence of hypoglycemic AEs will be summarized. The number of hypoglycemic events per subject over the study period will be analyzed as continuous variables and will be summarized (mean, median, SD, SE, minimum, and maximum).

The rate per year of hypoglycemic events, that is, the number of hypoglycemic events per patient-year (365.25 days) will be assessed using a negative binomial model, with baseline HbA1c and baseline insulin usage as covariates and the log of the study treatment exposure time as an offset variable.

The incidence of AEs will be calculated based on the number of new AEs out of the total eligible population using the following formula:

Number of new AEs post intervention/Total eligible population *100.

Exposure-adjusted AE incidence will be presented by the severity and preferred term for the primary analysis.

It is defined as

$$\frac{\text{Number of patients with new or worsened AEs during treatment period}}{\text{Patient-year exposure}/365.25}$$

Patient-year exposure is counted in days up to the AE (or end of time at risk for subjects without AE).

Incidence of gastrointestinal AEs

The incidence of GI AEs per week will be plotted over time from baseline up to 24 weeks. The proportion of subjects with at least 1 GI AE will be plotted from baseline up to Week 24. A plot of prevalence by severity (mild, moderate, or severe) for nausea, vomiting, and diarrhea over the 24-week period will be provided for the rate of GI AEs.

Three Cox proportional hazard models, each with covariates for baseline HbA1c and baseline insulin use, will be used to model the time to the first onset of nausea, vomiting, or diarrhea TEAE, respectively.

9.4.3. Secondary Endpoints Analysis

Change in HbA1c from baseline to 24 weeks of therapy with dulaglutide 1.5 or 0.75 mg

The change in HbA1c level from baseline to Weeks 12 and 24 for all available data including post-rescue medication values will be analyzed using descriptive statistics (mean, median, SD, SE, minimum, maximum, and number with missing values). In addition, for the actual value and change from baseline, a descriptive analysis using LOCF will be performed, using the baseline or 12-week value, if the 24-week value is missing or occurred after use of rescue medication.

For subjects requiring rescue medication (see Section 6.1.1), HbA1c values recorded after the first administration of rescue medication will not be considered for analysis, and these values will be considered as missing. The MMRM, as described in Section 9.4.1 will be used for analysis of the change in HbA1c level from baseline to Weeks 12 and 24.

If convergence is not met in the MMRM, the change in HbA1c level from baseline to Week 24 will be analyzed using the general linear model for the FAS population. The general linear model will evaluate the change from baseline in HbA1c level as the dependent variable and the baseline value of HbA1c as covariate. The LOCF method of missing value imputation will be used.

FAS population will be used for analysis as per planned treatment.

The analyses will be repeated for the per-protocol population.

9.4.4. Exploratory Endpoints Analysis

The actual values and change from baseline will be summarized by descriptive statistics (mean, median, SD, SE, minimum, and maximum) by visit for the FAS population and for the per-protocol population for the following parameters:

- body weight
- FBG

- SBP
- DBP, and
- pulse rate.

Details of exploratory analyses will be documented in SAP.

9.4.5. Other Safety Analyses

Laboratory measurements

Continuous chemistry and hematology measures will be summarized by descriptive statistics at baseline and at different visits (Section 1.3) for the safety population.

Continuous chemistry and hematology measures will be summarized as change from baseline to Week 24 using the general linear model, with the baseline value of the response variable as covariate.

All laboratory measurement analyses will be repeated for the Per Protocol population.

AEs analyses

AEs will be listed by

- subject
- SOC
- Medical Dictionary for Regulatory Activities® PT
- severity, and
- relationship to the study disease, drug, or procedure for all subjects.

AEs (including injection-site reactions and neoplasms) will be summarized as TEAEs for the safety population. TEAEs are defined as events that are newly reported after the first study drug treatment or are reported to have worsened in severity after the first study drug treatment. The proportion of subjects experiencing each TEAE will be presented by PT, SOC, and treatment group. The proportion of subjects experiencing each TEAE that is assessed as possibly related to the study disease, drug, or procedures will also be summarized. TEAEs will be summarized by PT within SOC and by PT by decreasing frequency.

All SAEs will be listed by subject and summarized by treatment as counts and percentages. Similar analyses will be performed for discontinuations due to AEs.

All AEs analyses will be repeated for the PPS population.

9.4.6. Other Analyses

A detailed description of subject disposition will be provided at the end of the study.

Concomitant medications, including previous therapy for diabetes, will be summarized by different categories and concomitant medication treatment group using the safety population. All concomitant therapies that were originally mapped using the WHO Drug Dictionary in the ClinTrial database will be further classified using Anatomical Therapeutic Chemical codes for reporting purposes.

Subject compliance with study medication will be assessed at each visit of the treatment period and overall.

Subgroup analysis will be done on the primary, secondary, and exploratory data based on the stratification of age (<65 and ≥65), HbA1c (<8.5 and ≥8.5), sex, and BMI category (<27 and ≥27) if needed. Details will be provided in SAP.

9.5. Interim Analysis

No interim analyses and/or sample size re-estimation are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly Medical Director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

9.6. Sample Size Determination

An estimated 250 participants will be screened, and assuming a 20% screen failure rate, an estimated 200 participants will be initiated on IP. Assuming a 20% dropout rate by the end of the study period, approximately 160 patients at the end of the study would allow for an adequate description of AEs and other safety outcomes. This is required to fulfill the market authorization clause.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - applicable ICH GCP guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
  - reporting to the Sponsor or designee significant issues related to participant safety, participant rights, or data integrity.
- Investigator sites are compensated for participation in the study as detailed in the CTA.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, as requested, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records and datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- The Sponsor has processes in place to ensure data protection, information security' and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

Reports

The Sponsor will disclose a summary of study information, including tabular study results, as per local law or guidelines.

Data

The Sponsor provides access to all individual participant data collected during the trial, after anonymization.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (for example, laboratory data). The

investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs, and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (for example, CROs).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; the safety and rights of participants are being protected; and the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- In addition, the Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

An EDC will be used in this study for the collection of data. The site will maintain a separate source for the data entered by the site into the Sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered as source data and for confirming that data reported are accurate and complete by signing the CRF.

Any data, for which paper documentation provided by the subject will serve as the source document, will be identified and documented by each site in that site's study file. Paper

documentation provided by the subject may include subject diary. Data from these paper documentations will be transcribed to eCRFs at the sites.

eCRF data will be encoded and stored in a clinical trial database. Data managed by a central vendor will be stored electronically in the central vendor's database system. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

Data from complaint forms submitted to the Sponsor will be encoded and stored in the global product complaint management system.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data that are reported or entered in the CRF and are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

The Sponsor or Sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to

For study termination:

- discontinuation of further study intervention development

For site termination:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
- total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the Sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.10. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the Sponsor, will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table here will be performed by the Lilly-designated laboratory or by the local laboratory, as specified in the table.

Local laboratory results are only required if the central laboratory results are not available in time for study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

In circumstances where the Sponsor approves local laboratory testing in lieu of central laboratory testing (in the table), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Percent and absolute count of	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	

Clinical Laboratory Tests	Comments
Gamma-glutamyl transferase	
Blood urea nitrogen	
Creatinine	
Uric acid	
Total protein	
Albumin	
Glucose	Fasting at baseline and Week 24
Cholesterol	
Triglycerides	
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein	
Low-density lipoprotein (LDL-C)	This value will be calculated. If triglycerides >400 mg/dL, the direct LDL will be assayed
Very-low-density lipoprotein (VLDL-C)	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Evaluated locally
Follicle-stimulating hormone	Assayed by Lilly-designated laboratory. Performed as needed to confirm participant's postmenopausal status
Urine Chemistry	Assayed by Lilly-designated laboratory
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory
Estimated glomerular filtration rate (chronic kidney disease-epidemiology)	
Urinary albumin/creatinine ratio	
Additional Testing	Assayed by Lilly-designated laboratory
Hemoglobin A1c	

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the study intervention. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. See definitions in Section 10.7. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to the hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.
f. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint
A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: deficiencies in labeling information, and use errors for device or drug-device combination products due to ergonomic design elements of the product. PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and facilitate process and product improvements. Investigators will instruct participants to contact the site as soon as possible if they have a PC or problem with the study intervention so that the situation can be assessed. An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and PC information is reported on the PC form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and an AE/SAE.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC form for PCs.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the IB for dulaglutide and Product Information for insulin glargine and insulin lispro in their assessment. • For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always assesses the causality for every event before the initial transmission of the SAE data to the Sponsor or designee. • The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include
  o additional laboratory tests or investigations
  o histopathological examinations, or
  o consultation with other healthcare professionals.
• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on an SAE paper form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting can be found in site training documents.

SAE Reporting via Paper Form
E-mail transmission of the SAE paper form is the preferred method to transmit this information to the Sponsor. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper form within the designated reporting time frames. Contacts for SAE reporting can be found in site training documents.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Females of childbearing potential

Adult females are considered WOCBP unless they are WNOCBP.

Females not of childbearing potential

Females are not considered WOCBP if they

- do not have a uterus, including having a congenital condition such as Mullerian agenesis
- are infertile due to surgical sterilization, or
- are postmenopausal.

Examples of surgical sterilization include

- total hysterectomy
- bilateral salpingo-oophorectomy
- bilateral salpingectomy, or
- bilateral oophorectomy.

Postmenopausal state

The postmenopausal state should be defined as a woman

- at any age, at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
- at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with follicle-stimulating hormone levels >40 mIU/mL
- 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, **or**
- at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[a]Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Guidance for women of childbearing potential

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods calendar ovulation symptothermal, or post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine and serum result at enrollment. See the protocol Schedule of Activities for subsequent pregnancy testing requirements.
Contraception	Agree to use 1 highly effective method (less than 1% failure rate) of contraception or a combination of 2 effective methods of contraception These forms of contraception must be used for the duration of the study.

Guidance for all men

No male contraception is required except in compliance with specific local government study requirements.

Examples of different forms of contraception

Methods	Examples
Highly effective contraception (<1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women weighing <198 pounds or <90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• barrier method with use of a spermicide
	  o male condom with spermicide
	  o diaphragm with spermicide or cervical sponge, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective.

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic evaluation testing

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	Clinical Chemistry
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase
Differential:	Aspartate aminotransferase
Neutrophils, segmented	Gamma-glutamyl transferase
Lymphocytes	Creatine kinase
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol
Prothrombin time, INR	Haptoglobin
Serology	Immunoglobulin A (quantitative)
Hepatitis A virus testing:	Immunoglobulin G (quantitative)
HAV total antibody	Immunoglobulin M (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus testing:	**Urine Chemistry**
Hepatitis B surface antigen	Drug screen
Hepatitis B surface antibody	Ethyl glucuronide
Hepatitis B core total antibody	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody
Hepatitis B core IgG antibody	Anti-smooth muscle antibody [a]
HBV DNA[b]	Anti-actin antibody[c]

Hematology

Hepatis C virus testing:

- HCV antibody
- HCV RNA[b]

Hepatitis D virus testing:

- HDV antibody

Hepatitis E virus testing:

- HEV IgG antibody
- HEV IgM antibody
- HEV RNA[b]

Microbiology[d]

Culture:

- Blood
- Urine

Clinical Chemistry

Epstein-Barr virus testing:

- EBV antibody
- EBV DNA[b]

Cytomegalovirus testing:

- CMV antibody
- CMV DNA[b]

Herpes simplex virus testing:

- HSV (Type 1 and 2) antibody
- HSV (Type 1 and 2) DNA[b]

Liver kidney microsomal type 1 antibody

[a] Not required if anti-actin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend onsite visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the Sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ERBs, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the Sponsor grants written approval for changes in study conduct, the Sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations:

Remote visits

Types of remote visits

Telemedicine: Telephone- and/or technology-assisted virtual visits are acceptable to complete appropriate assessments according to the SoA, if written approval is provided by the Sponsor.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the Sponsor.

Other alternative locations: Laboratory draws may be done at an alternate location in exceptional circumstances, if written approval is provided by the Sponsor.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

Return to onsite visits

Every effort should be made to enable participants to return to onsite visits as soon as reasonably possible, while ensuring the safety of both participants and site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing, except for HbA1c and serum glucose testing. Lilly-designated laboratory testing must be retained for HbA1c and serum glucose.

The local laboratory must be qualified in accordance with applicable local regulations.

Obtain local labs for safety hematology, chemistry, hormone panel, and urinalysis, when applicable, per the SoA. Safety labs should be obtained as specified in the SoA.

All labs will be reviewed by the investigators. Sign and date review of local labs per normal process and follow-up with the participant as needed. Results will not be recorded in the CRF.

Lilly Medical should be informed of any labs that meet criteria for temporary or permanent study intervention discontinuation.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal onsite visits, the site should work with the Sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and

- arranging delivery of study supplies.

These requirements must be met before action is taken.

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site, for example, participant's home, the investigator and/or the Sponsor should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained and intact packaging upon receipt.
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening or the lead-in visits are considered valid for a maximum of 24 days. The following rules will be applied for active, non-enrolled participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 24 days from the signing of the ICF to the start of treatment, the participant will proceed to the next study visit per the usual SoA, provided that the treatment is started within 30 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 24 days from signing of the ICF to the start of treatment, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by the randomization visit.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as onsite visits, the windows for visits may be adjusted, upon further guidance from the Sponsor. This minimizes missing data and preserves the intended conduct of the study.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing or shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AWARD	Assessment of Weekly AdministRation of LY2189265 in Diabetes
BG	blood glucose
BMI	body mass index
CDSCO	Central Drugs Standard Control Organisation
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	chronic kidney disease-epidemiology
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	coronavirus disease 2019
CRF	case report form A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor for each trial participant.
CRO	contract research organization
CTA	clinical trial agreement
Data monitoring committee	A data monitoring committee, or data monitoring board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
FBG	fasting blood glucose
GCP	good clinical practice
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

IP	investigational product A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also “IMP.”
IRB	institutional review board
LOCF	last observation carried forward
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, the right route, and at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a PC • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, summary of product characteristics, IB, local label, and protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed model for repeated measures
OHAs	oral hypoglycemic agents
participant	Equivalent to the CDISC term “subject”: an individual who participates in a clinical trial, either as a recipient of an IMP or as a control
PC	product complaint
PPS	per-protocol set The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PT	preferred term
PT-INR	prothrombin time-international normalized ratio
QTL	quality tolerance limit

SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2D	type 2 diabetes
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WOCBP	women of childbearing potential

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