Protocol I4L-IN-ABEX(b)

A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India

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A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India

Basal Insulin Glargine (LY2963016; Basaglar)

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1. Synopsis

Title of Study:
A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India

Rationale:
Basaglar® (LY2963016; Eli Lilly and Company [Lilly], Indianapolis, IN, USA, and Boehringer Ingelheim, Ingelheim Rheim, Germany) is an insulin glargine product which received marketing approval in India in 2017 as a biosimilar of LANTUS® (Sanofi Aventis, Paris, France) insulin glargine. It is approved for the treatment of patients with type 1 and type 2 diabetes mellitus (T2DM) above 2 years of age. As a clause towards marketing approval, the Drug Controller General of India, in accordance to the biosimilar guidelines for India, recommended that Basaglar be studied in a minimum of 200 additional local subjects without specific guidance towards objective of the study from an efficacy or safety perspective.

Patients with T2DM who are unable to meet glycemic targets in spite of being on oral antihyperglycemic medications and/or glucagon-like peptide-1 receptor agonist and need to initiate basal insulin, are usually preferred for treatment with Basaglar. Hence, it was decided to conduct the study in these patients. The efficacy of the drug is well established based on results from 3 randomized controlled trials in patients with type 1 diabetes and T2DM. In this study, we would seek to understand the safety of this drug in the local Indian population in accordance with the biosimilar guidelines of India.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To assess risk of hypoglycemia in adult subjects with T2DM in India who will be administered Basaglar	• Incidence of total (symptomatic or asymptomatic, with FBG level ≤54 mg/dL [3.0 mmol/L]) hypoglycemic events at Week 24
Secondary	
• To assess adverse events and other safety parameters in adult subjects with T2DM in India	• SAEs and TEAEs • Rates per 30 days and per subject year of total (symptomatic or asymptomatic) hypoglycemic events • Incidence and rates per 30 days and per subject-year of nocturnal, severe, documented symptomatic and asymptomatic hypoglycemic events • Basal insulin dose (U/day and U/kg/day) • Change in weight and BMI at Week 24 from baseline
• To assess efficacy of Basaglar in adult subjects with T2DM in India	• Change in HbA1c at Week 12 and Week 24 from baseline • Percentage of subjects reaching HbA1c targets ≤6.5% or <7% • Change in FBG levels at Weeks 4, 8, and 12 from baseline • Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24 • Change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline • Intrasubject variability, as measured by SD of 7-point SMBG levels
• To assess outcomes reported by adult subjects with T2DM in India	• Change in Insulin Treatment Satisfaction Questionnaire score at Week 24 from Week 4

Abbreviations: BMI = body mass index; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; SAE = serious adverse event; SD = standard deviation; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event; SMBG = self-monitored blood glucose.

Summary of Study Design:

Study I4L-IN-ABEX is a multicenter, open-label, single-arm study, that will enroll insulin-naïve subjects with T2DM. The study period consists of a screening period (Week -2 to Week 0), a treatment period (Week 0 to Week 24), and a safety follow-up visit at Week 28.

Treatment Arms:

This is a single-arm study. Enrolled subjects will be treated with Basaglar using a self-titration scheme as outlined below.

Fasting Blood Glucose (mg/dL)	Fasting Blood Glucose (mmol/L)	Dose Adjustments (Units)
<80	<4.4	-2
80-100	4.4-5.6	0
101-130	5.6-7.2	+2
131-160	7.3-8.9	+4
161-190	8.9-10.6	+6
>190	>10.6	+8

Number of Subjects:

Indian regulatory authorities have recommended the study to be done in a minimum of 200 local subjects. Assuming a 15% screen failure rate, approximately 295 subjects will be screened, so that 250 subjects can be enrolled. Assuming a drop-out rate of 20%, the target is to have a minimum of 200 subjects completing the present study.

In the India subpopulation of ELEMENT 5 study, 5 of the 46 insulin-naïve subjects experienced at least 1 hypoglycemic event (total hypoglycemia incidence with glucose levels ≤54 mg/dL [3.0 mmol/L]) during the overall study period. When considering the total ELEMENT 5 population, 146 out of 489 subjects (30%) experienced at least 1 hypoglycemic event during the overall study period. Based on these estimates, the precision with 250 and 200 subjects would be as follows (95% confidence interval for proportion shown based on normality assumption):

Sample Size	Estimated Proportion	Standard Error	Width of Proportion to 95% Confidence Limit	Width of Interval (2 Sides)	95% Lower Confidence Limit	95% Upper Confidence Limit
250	11%	2.0%	3.9%	7.80%	7.1%	14.9%
250	30%	2.9%	5.7%	11.40%	24.3%	35.7%
200	11%	2.2%	4.3%	8.60%	6.7%	15.3%
200	30%	3.2%	6.4%	12.80%	23.6%	36.4%

Statistical Analysis:

No randomization will be performed as this is a single-arm study. The sample size was calculated assuming a 15% screen failure rate, with a target to have a minimum of 200 subjects completing the study. No interim analyses and/or sample size re-estimation are planned to be performed.

Statistical Methodology:

Primary endpoint: Incidence of the total (symptomatic and asymptomatic) hypoglycemic events at Week 24 will be assessed as number and percentage of subjects experiencing at least 1 event over the study period.

Secondary outcomes: Actual values and change in glycated hemoglobin (HbA1c) level from baseline to Week 12 and Week 24 will be analyzed in a descriptive manner on non-missing values and last observation carried forward-imputed values. Additionally, a general linear model will be performed on the full analysis set (FAS), with change from baseline in HbA1c level as the dependent variable and the baseline value of HbA1c as a covariate.

The number of hypoglycemic events per subject, the rate of hypoglycemic events per 30 days, and the rate per year, that is, the number of hypoglycemic events per subject year (365.25 days) will be assessed using a negative binomial model, with baseline HbA1c as a covariate and the log of the study treatment exposure time as an offset variable.

The analysis for other continuous secondary efficacy and safety measurements and continuous laboratory measures will use the general linear model for the FAS population with the baseline value of the response variable as a covariate.

2. Schedule of Activities

Table ABEX.1. Schedule of Activities

Procedure	Screening	Treatment Period							Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8**	**9/ET**	
Week of Study	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Allowable Deviation +/- (days)		**3**	**7**	**7**	**7**	**7**	**7**	**7**		
Informed consent	X									
Subject number assigned	X									
Inclusion and exclusion criteria	X									
Clinical Assessments										
Demography	X									
Full physical examination	X									
Height and weight	X	X						X		Height will be measured only at screening.
Vital signs[b]	X	X	X	X	X			X	X	SBP, DBP, and PR
Medical history and family history of CV disease	X									
History of substance usage	X									Substances: drugs, alcohol, tobacco, and caffeine
12-lead ECG	X									To be recorded in a resting supine state
Concomitant medication review	X	X	X	X	X	X	X	X	X	
AE/SAE/complaint handling		X	X	X	X	X	X	X	X	
Hypoglycemic events		X	X	X	X	X	X	X	X	
Completion or discontinuation of investigation			X	X	X	X	X	X	X	
FBG[c]		X	X	X	X					

Procedure	Screening	Treatment Period							Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8**	**9/ET**	
Week of Study	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Allowable Deviation +/- (days)		**3**	**7**	**7**	**7**	**7**	**7**	**7**		
7-point SMBG measurement[d]		X	X	X	X			X		
Laboratory Assessments										
Hematology, clinical chemistry, and urinalysis tests	X				X			X		See Appendix 2 for details. Estimated glomerular filtration rate will be measured only in subjects with a history of severe chronic kidney disease.
Pregnancy test (for WCBP only)	X	X								Serum pregnancy test at Visit 1 and urine pregnancy test at Visit 2 prior to being given the study drug
HIV, hepatitis B and C	X									
HbA1c measurement	X	X			X			X		
Subject-reported outcomes										
ITSQ			X					X		
Ancillary Supplies/Diaries/Study Drug										
Trainings on signs/symptoms of hypo/hyperglycemia and insulin reactions		X	X	X	X	X	X	X		This training is given at baseline and reinforced at every visit of the treatment period
Trainings on injection technique, use of glucometer and 7-point SMBG measurement	X	X	X	X	X			X		This training is given during screening and reinforced at every face-to-face visit of the treatment period

Procedure	Screening	Treatment Period							Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8**	**9/ET**	
Week of Study	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	
Allowable Deviation +/- (days)		**3**	**7**	**7**	**7**	**7**	**7**	**7**		
Self-titration training[e]		X	X	X	X	X	X	X		This training is given at baseline and reinforced at every visit of the treatment period
Dispense study diary	X	X								Pretreatment study diary will be dispensed at Visit 1 and comprehensive study diary will be dispensed at Visit 2
Dispense study drug		X	X	X	X					
Review study diary		X	X	X	X			X		Pretreatment study diary will be collected at Visit 2 and comprehensive study diary will be collected at Visit 8
Collect unused study drug			X	X	X			X		
Dispense glucometer	X									
Compliance to study drug administration		X	X	X	X	X	X	X		
Adjust insulin dose (if required)			X	X	X			X		Site personnel will review the Basaglar dose and FBG levels recorded in the subject diary. They may recommend change in dose of Basaglar if required.

Abbreviations: AE = adverse event; CV = cardiovascular; DBP = diastolic blood pressure; ECG = electrocardiogram; ET = early termination; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; ITSQ = Insulin Treatment Satisfaction Questionnaire; PR = pulse rate; SAE = serious adverse event; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; WCBP = women of child-bearing potential.

[a] Telephone visit.

[b] All vital signs should be recorded in the subject in a resting state. If there is a suspicion of postural hypotension or autonomic instability, the investigators at their discretion might decide to record the blood pressure in a supine state and then after standing for 2 minutes to detect any postural hypotension. Blood pressure measurements should be done in the left arm with sphygmomanometer held at the level of the heart. Blood pressure recording in both arms is at the investigators' discretion in selective cases of pulse volume inequality or pulse being absent in either of the arms.

[c] Subjects will be instructed to daily measure the FBG levels mandatorily using glucometer before the morning meal till Week 12 and record in the subject diary. Also, subjects will be instructed to measure and record the blood glucose levels using glucometer if they have symptoms of hypoglycemia (including nocturnal hypoglycemia) at any time of the day or night.

[d] Subjects will be instructed to perform 7-point SMBG level monitoring (glucose measurements before breakfast, lunch, and dinner; 2 hours after breakfast, lunch, and dinner; and at 3 am [± 1 hour]) 2-3 days in the week prior to Visits 2, 3, 4, 5, and 8, and record the values in the subject diary. Subjects will be instructed to carry the glucometers to the sites on Visits 2, 3, 4, 5, and 8.

[e] Subjects will be instructed to record the actual time and dose of Basaglar administration in the subject diary.

3. Introduction

3.1. Study Rationale

Basaglar® (LY2963016; Eli Lilly and Company [Lilly], Indianapolis, IN, USA, and Boehringer Ingelheim, Ingelheim Rheim, Germany) and LANTUS® (Sanofi Aventis, Paris, France) are basal insulin glargine analogs that have identical amino acid sequence and similar pharmacological profiles. Basaglar received marketing approval in India on 21 August 2017 for the treatment of patients with type 1 diabetes and type 2 diabetes mellitus (T2DM) above 2 years of age. As a clause towards marketing approval, the Drug Controller General of India (DCGI), in accordance to the biosimilar guidelines for India, recommended that Basaglar be studied in a minimum of 200 additional local subjects (there were 100 subjects from India in the ELEMENT 5 study) without specific guidance towards objective of the study from an efficacy or safety perspective.

Patients with T2DM who are unable to meet glycemic targets in spite of being on oral antihyperglycemic medications (OAMs) and/or glucagon-like peptide-1 receptor agonist (GLP-1 RA) and need to initiate basal insulin, are usually preferred for treatment with Basaglar. Hence, it was decided to conduct the study in these patients. The efficacy of the drug is well established based on results from 3 randomized controlled trials in patients with type 1 diabetes and T2DM. In this study, we would seek to understand the safety of this drug in the local Indian population in accordance with the biosimilar guidelines of India.

3.2. Background

Diabetes and its comorbidities present major health challenges to individuals and society at large by imposing an economic burden. Diabetes often turns fatal, thus, it has a detrimental impact on the economic burden of the society (Wild et al. 2004). The number of patients with T2DM is increasing rapidly. Of the current population burdened with T2DM, 60% are Asians (Hu 2011). Currently, India has an estimated 73 million people with diabetes, the second largest number for any individual country in the world. The projected growth between the period 2017 and 2045 in India is one of the highest in the world. By the year 2045, approximately 134 million people in India are projected to be suffering from diabetes as against 120 million in China (IDF 2017).

Insulins play an important role in the treatment of T2DM. Recent guidelines highlight the importance of initiation of basal insulin in patients with T2DM who fail to attain glycemic targets with non-insulin therapeutic options (Davies et al. 2018). Insulin initiation in India is often delayed, by almost a decade after diagnosis of diabetes. During this period, subjects are recommended various combinations of available OAMs and/or GLP-1 RA. Often, subjects are not able to achieve the glycemic targets in spite of these OAMs.

ELEMENT 5, a Phase 3, prospective, randomized, multinational, 2-arm, active-controlled, open-label, parallel-design study conducted in subjects with T2DM, showed that efficacy and safety profiles of Basaglar and LANTUS were similar (Pollom et al. 2019).

3.3. Benefit/Risk Assessment

There are different ways of insulin initiation in India – twice-daily neutral protamine Hagedorn insulin or once-daily LANTUS or premixed insulin. It is increasingly becoming easier to initiate subjects on long acting insulins due to its once-in-a-day dose. Evidence from several large randomized controlled trials showed that self-titration of insulin can help to reduce levels of glycated hemoglobin (HbA1c) and fasting blood glucose (FBG) without increasing the risk of hypoglycemia. This study involving glucometer-based blood glucose measurement can further substantiate the fact that subjects can self- titrate basal insulin in India without increased risk of hypoglycemia.

More detailed information about the known and expected benefits and risks of Basaglar may be found in the Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

Table ABEX.2 shows the objectives and endpoints of the study.

Table ABEX.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess risk of hypoglycemia in adult subjects with T2DM in India who will be administered Basaglar	• Incidence of total (symptomatic or asymptomatic with FBG level of ≤54 mg/dL [≤3.0 mmol/L]) hypoglycemic events at Week 24
Secondary	
• To assess adverse events and other safety parameters in adult subjects with T2DM in India	• SAEs and TEAEs • Rates per 30 days and per subject year of total (symptomatic or asymptomatic) hypoglycemic events • Incidence and rates per 30 days and per subject-year of nocturnal, severe, documented symptomatic and asymptomatic hypoglycemic events • Basal insulin dose (U/day and U/kg/day) • Change in weight and BMI at Week 24 from baseline
• To assess efficacy of Basaglar in adult subjects with T2DM in India	• Change in HbA1c at Week 12 and Week 24 from baseline • Percentage of subjects reaching HbA1c targets ≤6.5% or <7% • Change in FBG levels at Weeks 4, 8, and 12 from baseline • Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24 • Change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline • Intrasubject variability, as measured by SD of 7-point SMBG levels
• To assess outcomes reported by adult subjects with T2DM in India	• Change in Insulin Treatment Satisfaction Questionnaire scores at Week 24 from Week 4

Abbreviations: BMI = body mass index; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; SAE = serious adverse event; SD = standard deviation; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study I4L-IN-ABEX (ABEX) is a multicenter, open-label, single-arm, Phase 4 study to assess the safety of Basaglar in subjects with T2DM in India.

The study design includes the following periods:

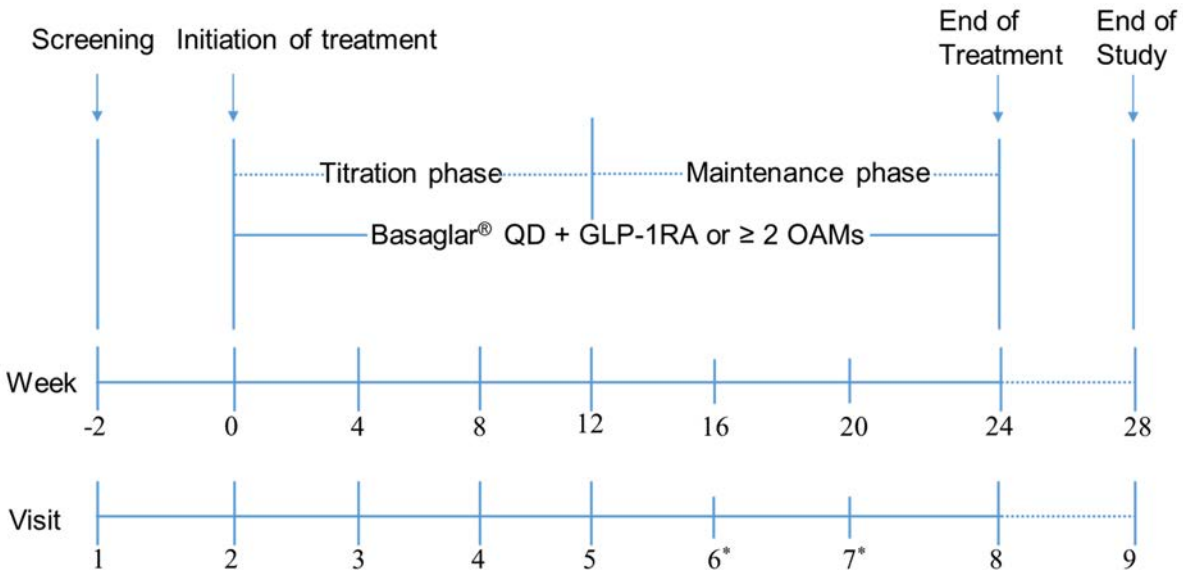
- Screening (Week -2 to Week 0)
- Treatment
  - Titration period (Week 0 to Week 12)
  - Maintenance period (Week 12 to 24)
- Safety Follow-up (Week 28)

Week 0 to Week 12 will be the titration phase followed by the maintenance phase till Week 24. Approximately 295 subjects will be screened as per the inclusion and exclusion criteria mentioned in Sections 6.1 and 6.2, respectively, so that 250 subjects can be enrolled in the study, with a target to have a minimum of 200 subjects completing the present study. Subjects will be screened at Visit 1 and eligible subjects will be administered with Basaglar once daily (QD) from Visit 2 for a period of 24 weeks.

The starting dose will be 10 units QD. All subjects will be trained at Screening (Visit 1) on insulin injection administration technique, use of glucometer, and 7-point SMBG measurement. These trainings will be reinforced at every face-to-face visit of the treatment period. Subjects will self-administer Basaglar at bedtime. The doses may be titrated by 2-4 units once or twice in a week until FBG levels are lowered to <100 mg/dL (5.6 mmol/L).

Study governance considerations are described in detail in Appendix 3.

Figure ABEX.1 illustrates the study design.



*Telephone visit
Abbreviations: GLP-1 RA = glucagon-like peptide-1 receptor agonist; OAM = oral antihyperglycemic medications; QD = once daily.

Figure ABEX.1. Illustration of study design for clinical protocol I4L-IN-ABEX.

5.1.1. Study Visits

Screening period (Week -2 to Week 0)

Multiple procedures will be done during the screening period to assess eligibility of subjects for inclusion in the study (Sections 6.1 and 6.2) as specified in the Schedule of Activities (Section 2). Subjects will be provided glucometers and study diaries at Screening (Visit 1).

Treatment period (Week 0 to Week 24)

Study participants found eligible during the screening period will begin their treatment at Visit 2. All measures to be performed at Visit 2 will be done prior to administration of Basaglar. All necessary trainings will be imparted at Visits 1 and 2 and will be reinforced at subsequent visits as outlined in Section 2.

Subjects will be instructed to carry the glucometers to the sites at Visits 2, 3, 4, 5, and 8. Subjects will be instructed to measure and record the FBG levels daily before the morning meal till Week 12. Also, subjects will be instructed to measure and record the blood glucose levels if they have symptoms of hypoglycemia at any time of the day or night. Subjects will be instructed to perform 7-point self-monitored blood glucose (SMBG) level monitoring (glucose measurements before breakfast, lunch, and dinner; 2 hours after breakfast, lunch, and dinner; and at 3 am [± 1 hour]) 2 to 3 days in the week prior to Visits 2, 3, 4, 5, and 8 and record the values in the subject diary (Section 2).

Subjects will self-administer Basaglar QD at bedtime. They will self-titrate once or twice in a week until FBG levels are lowered to <100 mg/dL (5.6 mmol/L).

Follow-up Visit (Week 28)

All subjects will have a follow-up visit 4 weeks after the last dose of Basaglar. Assessments at this visit will be done as detailed in Section 2. Subjects who withdraw from the study will also have assessments done similar to those at the follow-up visit.

5.2. Number of Participants

Assuming a 15% screen failure rate, approximately 295 subjects will be screened, so that 250 subjects can be enrolled. Assuming a drop-out rate of 20%, the target is to have a minimum of 200 subjects completing the present study.

In the India subpopulation of ELEMENT 5 study, 5 of the 46 insulin-naïve subjects experienced at least 1 hypoglycemic event (total hypoglycemia incidence with glucose levels ≤54 mg/dL [3.0 mmol/L]) during the overall study period. When considering the total ELEMENT 5 population, 146 out of 489 subjects (30%) experienced at least 1 hypoglycemic event during the overall study period. Based on these estimates, the precision with 250 and 200 subjects would be as outlined in Table ABEX.3 (95% confidence interval for proportion shown based on normality assumption).

Table ABEX.3. Estimated Precision Rates

Sample Size	Estimated Proportion	Standard Error	Width of Proportion to 95% Confidence Limit	Width of Interval (2 sides)	95% Lower Confidence Limit	95% Upper Confidence Limit
250	11%	2.0%	3.9%	7.80%	7.1%	14.9%
250	30%	2.9%	5.7%	11.40%	24.3%	35.7%
200	11%	2.2%	4.3%	8.60%	6.7%	15.3%
200	30%	3.2%	6.4%	12.80%	23.6%	36.4%

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

The ELEMENT 5 study has proven the noninferiority of Basaglar administered QD to LANTUS administered QD, as measured by change in HbA1c level from baseline to 24 weeks, when used in combination with OAMs. Basaglar received marketing approval as a basal insulin for the treatment of type 1 diabetes and T2DM in India in 2017 in subjects above 2 years of age. Biosimilar guidelines (effective August 2016) recommend the safety of the biosimilar to be

evaluated in at least 300 subjects. There were 100 subjects from India in the ELEMENT 5 study. As a clause towards marketing approval, the DCGI recommended that Basaglar be studied in a minimum of 200 additional local subjects without specific guidance towards objective of the study from an efficacy or safety perspective.

Patients with T2DM who are unable to meet glycemic targets in spite of being on OAMs and/or GLP-1 RA and need to initiate basal insulin, are usually preferred for treatment with Basaglar. Hence, it was decided to conduct the study in these patients.

Thus we designed a multicenter, open-label, single-arm, Phase 4 study to assess the safety and efficacy of Basaglar in subjects with T2DM who are on ≥2 OAMs and/or GLP-1 RA and are insulin-naïve with inadequate glycemic control.

5.5. Justification for Dose

The American Diabetes Association (2018) recommends initiation of basal insulin at 10 units or 0.1 to 0.2 unit/kg/day depending on the degree of hyperglycemia. Subjects can self-titrate once or twice in a week by 2 to 4 units or 10% to 15% to reach the target FBG level of <100 mg/dL (5.6 mmol/L). In case of hypoglycemia, the dose can be reduced by 4 units or 10% to 20%. The American Association of Clinical Endocrinologists consensus statement of 2018 recommends initiation of basal insulin based on HbA1c level of 8% (total daily insulin dose: 0.2 to 0.3 unit/kg). Thus, in this study the starting dose will be 10 units QD and the dose may be titrated every 2 to 3 days to reach the glycemic goal.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria at screening:

[1] have T2DM based on the disease diagnostic criteria from the World Health Organization (WHO) classification (Appendix 6) for at least 6 months before screening
[2] men or non-pregnant women aged more than 18 years and less than 75 years at the time of screening
[3] have been receiving GLP-1 RA or ≥2 OAMs at stable doses for 90 days prior to Visit 1
[4] have an HbA1c level ≥7.0% and <11.0%
[5] have never been treated with insulins except for short term treatment of acute conditions up to a maximum of 14 days
[6] are able and willing to provide signed informed consent to participate in this study in accordance with local regulations

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening:

[7] have any form of diabetes other than T2DM
[8] have hypersensitivity to the active substance of Basaglar or to any of the excipients
[9] have any clinically significant disorder, other than T2DM, that in the investigator's opinion, would preclude participation in the trial
[10] are receiving systemic glucocorticosteroids therapy or have excessive insulin resistance (total insulin dose >2 U/kg)
[11] have a history or diagnosis of human immunodeficiency virus infection, hepatitis B and C
[12] have comorbidities of unstable angina, cardiac failure (Stage III or IV as per New York Heart Association guidelines) or renal failure (estimated glomerular filtration rate <30 mL/min/m^2)
[13] are pregnant or intend to become pregnant during the course of the study; or are sexually active women of child-bearing potential not actively practicing birth control by a medically acceptable method as determined by the investigator
[14] is a woman who is breastfeeding
[15] are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted
[16] are Lilly employees or are employees of third party organizations involved in the study who require exclusion of their employees

[17] have participated within the last 30 days in a clinical trial involving an investigational product other than the Basaglar. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed
[18] have previously completed or withdrawn from this study or any other study investigating Basaglar. This exclusion criterion does not apply to subjects who are rescreened prior to baseline visit
[19] are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
[20] are unwilling or unable to comply with the use of a glucometer

6.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria [7], [8], [10], and [12] exclude medications or conditions that may cause HbA1c lowering not attributable to the regimens being studied or which could lead to misinterpretation of the results.

Exclusion criterion [9] permits investigators to exclude subjects who meet all other inclusion and exclusion criteria but may not be appropriate for this study.

Exclusion criterion [11] may prevent subjects from completing the protocol, may influence the effect or safety of study regimens.

Exclusion criteria [13] and [14] ensure the safety of unborn and newborn children.

Exclusion criteria [15] and [16] reduce potential bias due to conflict of interest.

Exclusion criteria [17], [18], [19], and [20] prevents a situation in which potential positive or negative outcomes may not be clearly attributable to the regimens in the study.

6.3. Lifestyle Restrictions

Patients will be suggested to continue their usual exercise habits and generally follow a healthy meal plan throughout the course of the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) at the initial visit may be later rescreened only once. The interval between screening and rescreening should be at least 4 weeks. A new informed consent form (ICF) must be signed at the time of rescreening and the study participant will be assigned a new identification number. A single repeat testing of suspected erroneous/spurious central laboratory results is allowed without rescreening the study participant. These will be done in consultation with the Lilly clinical research physician (CRP).

7. Treatments

7.1. Treatments Administered

Subjects will receive Basaglar QD at bedtime. The starting dose will be 10 units. Subjects can self-titrate as outlined in Table ABEX.4 once or twice weekly until FBG is lowered to <100 mg/dL (5.6 mmol/L). In case of hypoglycemia, the dose can be reduced by 4 units. Subjects will continue their pre-study anti-diabetic medications at the prescribed dosage throughout the study except for risks described in Section 7.7. It is recommended that doses of anti-diabetic medications being taken by the subjects is stable for 90 days prior to enrolling them in this study. However, the investigator can recommend that these doses be optimized to maximum tolerated dose during 2 weeks of the screening period. If the target FBG levels are not achieved at Visit 2, the subjects are included in the study and Basaglar is initiated.

Table ABEX.4. Recommendations for Dose Titrations

Fasting Blood Glucose (mg/dL)	Fasting Blood Glucose (mmol/L)	Dose Adjustments (Units)
<80	<4.4	-2
80-100	4.4-5.6	0
101-130	5.6-7.2	+2
131-160	7.3-8.9	+4
161-190	8.9-10.6	+6
>190	>10.6	+8

The investigator or his or her designee is responsible for

- explaining the correct use of the investigational agent to the subject
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection, and
- returning all unused medication to Lilly or its designee at the end of the study, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

Clinical study materials will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

Glucometers, test strips, and lancets will be provided to patients. Patients will be trained to use glucometers to self-monitor the blood glucose levels as specified in the Schedule of Activities (Section 2).

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to Basaglar treatment.

7.2.1. Selection and Timing of Doses

Subjects will self-administer the insulin every day at bedtime after dinner. Patients will record the actual time and dose of all administrations of Basaglar in the subject diary. Later, these data will be recorded in the subjects' electronic case report form (eCRF).

7.3. Blinding

This is an open-label study. The investigational product will be procured from commercially available Basaglar in India. The investigational product will be adequately labeled to indicate that it is only for use in the clinical study and is not for sale.

7.4. Dosage Modification

The doses may be titrated by 2 to 4 units once or twice in a week until FBG levels are lowered to <100 mg/dL (5.6 mmol/L) as tabulated in Table ABEX.4.

Investigators will be trained to assess when they need to intervene the treatment regimen of subjects who do not reach glycemic targets. If any of the FBG values for 2 consecutive weeks exceed the limits outlined below with no other possible cause of hyperglycemia, rescue medication (more OAMs or GLP-1 RA or bolus insulin; switching to a different basal insulin is not permitted as decided by the investigator) will be prescribed in addition to the ongoing treatment.

- FBG >270 mg/dL (>15.0 mmol/L) from baseline to Week 6 (4 values/week)
- FBG >240 mg/dL (>13.3 mmol/L) from Week 6 to Week 12 (4 values/week)
- FBG >200 mg/dL (>11.1 mmol/L) from Week 12 to end of trial (4 values/week)
- HbA1c ≥8.5% (≥69.4 mmol/mol) by and after Week 24

The dose and name of rescue medication must be properly documented in the eCRF. Subjects who had to use rescue medication during the study period will be excluded from the per protocol set (PPS) population.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his or her designee is responsible for

- confirming that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. The drug product should be stored at room temperature for no more than 28 days or under refrigerated conditions (2°C to 8°C) for long-term storage.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

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

- subject's glycemic control
- adherence to the visit schedule
- dosing-titration algorithm
- administration of study insulin, and
- any other parameters the investigator deems necessary.

Deviations from the prescribed dosage regimen should be recorded in the eCRF.

The subject will be considered significantly noncompliant if during the study he or she misses

- more than 3 consecutive days of study medication (full doses), or
- more than 15 cumulative days of study medication (full doses).

Similarly, a subject will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. All such subjects will be considered to have withdrawn from the study. The last observation carried forward (LOCF) replacement of these subjects will be taken under the supervision of Lilly or its designee if the target number of subjects (a minimum of 200) is at risk to be achieved.

7.7. Concomitant Therapy

All combination of OAMs or GLP-1 RAs are allowed in the protocol and can be continued with Basaglar. Subjects need to be on GLP-1 RA or at least 2 OAMs at the time of entering the study. For subjects on thiazolidinediones, the investigator may consider reducing the dose or discontinuing it, if there is risk of fluid retention in the subject or complaint of shortness of breath during rest. For subjects on sulphonylureas, the investigator may consider to modify the dose in cases of hypoglycemia.

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Not applicable.

7.8.2. Treatment after Study Completion

Basaglar will not be made available to subjects from the study team after conclusion of the study. The subject can continue to take commercially available Basaglar or any other basal insulin analog as recommended by the investigator. The access of the drug to the subjects can be confirmed in the follow-up visit.

7.8.3. Special Treatment Considerations

Following an event of severe hypoglycemia or in cases where subjects require assistance to recover from hypoglycemia, the subject may continue in the study depending on the decision of the investigator in consultation with Lilly CRP. This may require a reduction in dosage of basal insulin being administered and titration algorithm provided above can be referred to or at the discretion of the investigator.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Following are the possible reasons leading to permanent discontinuation of investigational product:

- **Subject decision**
  - The subject requests to discontinue investigational product.

- **Discontinuation due to a hepatic event or liver test abnormality**
  Subjects who are discontinued from the investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected in the eCRF.

  Discontinuation of the investigational product due to abnormal liver tests **should be** considered by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio >1.5
  - ALT or AST >3X ULN, with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN, with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Subjects discontinuing from the investigational product prematurely for any reason should complete adverse events (AEs) and other safety follow-up as per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable.

8.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the subject to continue on study treatment. If the investigator and Lilly CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from Lilly CRP to allow the inadvertently enrolled subject to continue in the study with or without treatment with Basaglar. Safety

follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Subjects will be discontinued from the study in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- investigator decision
  - the investigator decides that the subject should be discontinued from the study
  - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
  - if the subject has persistent hypoglycemia or increased risk of hypoglycemia
- subject decision
  - the subject or the subject's designee requests to be withdrawn from the study

Subjects discontinuing from the study prematurely for any reason should complete AEs and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A subject 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. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results.

9.1. Efficacy and Safety Assessments

9.1.1. Primary Safety Assessments

Hypoglycemia

Information on treatment-emergent hypoglycemic events starting from Visit 2 until the last study visit (Visit 9 or early termination [ET] visit) will be collected. Subjects will be trained about signs and symptoms of hypoglycemia. Subjects will be trained to check and record their blood glucose levels if they experience symptoms suggestive of hypoglycemia. For each hypoglycemic event, subjects should record the following data in the study diaries provided by the sponsor via the investigator:

- blood glucose levels
- associated symptoms
- treatment, and
- other pertinent information.

A hypoglycemic event is defined as any time a subject feels that he or she is experiencing a sign or symptom that is associated with hypoglycemia or has a FBG level of ≤54 mg/dL (3.0 mmol/L), even if it was not associated with signs, symptoms, or treatment consistent with current guidelines.

Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrates or glucagon or taking other corrective actions. Blood glucose concentrations may not be available during an event, but neurologic recovery following the return of blood glucose to normal levels is considered sufficient evidence that the event was induced by a low blood glucose concentration.

Nocturnal hypoglycemia: Any total hypoglycemic event that occurs after bedtime and prior to the first meal in the morning.

Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a blood glucose level of ≤54 mg/dL (≤3.0 mmol/L) as confirmed by blood glucose measurement.

Asymptomatic hypoglycemia: Any event not accompanied by typical symptoms of hypoglycemia but a measured a blood glucose level of ≤54 mg/dL (≤3.0 mmol/L) was observed.

9.1.2. Secondary Safety and Efficacy Assessments

- Serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)
- Rates per 30 days and per subject year of total hypoglycemic events (symptomatic or asymptomatic)
- Incidence and rates per 30 days and per subject-year of nocturnal, severe, documented symptomatic and asymptomatic hypoglycemic events
- Change in HbA1c levels at Weeks 12 and 24 from baseline
- Percentage of subjects reaching HbA1c targets ≤6.5% or <7%
- Change in FBG levels at Weeks 4, 8, and 12 from baseline
- Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24
- Change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline
- Intrasubject variability, as measured by the standard deviation (SD) of 7-point SMBG levels
- Basal insulin dose (U/day and U/kg/day)
- Change in weight and body mass index at Week 24 from baseline
- Change in Insulin Treatment Satisfaction Questionnaire (ITSQ) score at Week 24 from Week 4

9.1.3. Appropriateness of Assessments

All safety and efficacy assessments included in this study are generally regarded as reliable and accurate with respect to diabetes mellitus.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that

- are serious or otherwise medically important
- are considered related to the investigational product or the study, or
- cause the subject to discontinue the investigational product before completing the study.

The investigator will record all relevant AE/SAE information in the eCRF. The subject should be followed until the event

- resolves
- stabilizes with appropriate diagnostic evaluation, or

- is reasonably explained.

The frequency of any additional follow-up evaluations of AEs between site and telephonic visits is left at the discretion of the investigator.

After the ICF is signed, study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study in eCRFs. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and investigational product in the eCRFs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes or no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRFs clarifying, if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged insubject hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in insubject hospitalization, or the development of drug dependency or drug abuse.
- severe hypoglycemia

If the investigator believes that a reported SAE of hypoglycemia does not meet any of the specific criteria outlined above, the investigator should select the outcome of "considered significant by the investigator for any other reason" in the eCRF.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the subject has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor according to the SAE-reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study-site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Subjects with a serious hepatic AE should have additional data collected using eCRFs (Appendix 4).

Pregnancy does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects after they have discontinued (ET visit) and/or completed the study (follow-up visit), that is, the subject disposition eCRF has been completed. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Serious AEs occurring up to and including the subject's last study visit (or ET visit) will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor. The investigator will make a note of the relationship of the event with the drug. This information will be included in the narrative.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Investigator's Brochure (IB) and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

9.2.2. Adverse Event Monitoring with a Systematic Questionnaire

Not applicable.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to

- ensure the safety of study participants
- monitor quality, and
- facilitate process and product improvements.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or glucometer so that the situation can be assessed. A replacement instrument may be used as long as the procedures and the subsequent visits continue to fall within the allowable time frames.

The investigator or his or her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose, and
- faxing the completed product complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

9.3. Treatment of Overdose

Refer to Section 6.2.2.9 of the IB for information on management of insulin overdose.

9.4. Safety

9.4.1. Electrocardiograms

For each subject, 12-lead electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational product should be reported to Lilly or its designee as an AE via eCRF/electronic data entry/designated data transmission methods.

9.4.2. Vital Signs

For each subject, vital signs measurements will be conducted as mentioned in the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the subject receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRFs.

9.4.3. Laboratory Tests

For each subject, laboratory tests detailed in (Appendix 2) will be conducted according to the Schedule of Activities (Section 2).

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Any clinically significant findings from laboratory tests that result in a diagnosis, and that occur after the subject receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRFs.

9.4.4. Immunogenicity Assessments

Not applicable.

9.4.5. Other Tests

Not applicable.

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.6.1. Hepatic Safety Monitoring

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days, including

- ALT
- AST
- ALP
- TBL
- direct bilirubin
- gamma-glutamyl transferase, and
- creatine kinase.

These tests are performed to confirm the abnormality and to determine if the levels are increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate screening visit (Week -2) levels.

Hepatic Safety Data Collection

Additional safety data as mentioned in Appendix 4 should be collected via the eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)

- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests, and/or
- hepatic event considered to be a SAE.

9.5. Subject-Reported Outcomes

Subject-reported outcomes will be measured using the ITSQ at Week 4 and Week 24.

The ITSQ is a validated instrument containing 22 items that assesses treatment satisfaction for subjects taking insulin. Items are measured on a 7-point scale, in which lower scores reflect better outcomes. The items that constitute the 5 domains of satisfaction are categorized as:

- Inconvenience of Regimen (IR – 5 items)
- Lifestyle Flexibility (LF – 3 items)
- Glycemic Control (GC – 3 items)
- Hypoglycemic Control (HC – 5 items), and
- Insulin Delivery Device (DD – 6 items).

The individual raw and transformed domain scores are calculated as follows:

- Step 1: Calculate the raw domain score as the mean of the items in the domain for that subject.
- Step 2: Use the following formula to transform the raw domain scores on a scale from 0 to 100, where higher scores indicate better treatment satisfaction:

  Transformed domain score = 100[(7- raw domain score)/(6)]*

The individual raw and transformed overall scores are then calculated as follows:

- Step 1: Calculate the raw overall score as the mean of the items for that subject.
- Step 2: Use the following formula to transform the raw overall score on a scale from 0 to 100, where a higher score indicates better treatment satisfaction:

  Transformed overall score = 100[(7- raw overall score)/(6)]*

If an item score is missing for a subject and ≤20% of the items within the domain (or overall) are missing for that subject, then the mean of the items in the domain (or overall) will be imputed for the missing item score(s). If there are >20% missing items, the individual subject domain (or overall) score will be set to missing. Change at Week 24 from Week 4 will be analyzed using the general linear model, with the Week 4 value of the response variable as covariate.

9.6. Pharmacokinetics

Not applicable.

9.7. Pharmacodynamics

Not applicable.

9.8. Pharmacogenomics

9.8.1. Sample for Pharmacogenetic Research

Not applicable.

9.9. Biomarkers

Not applicable.

9.10. Health Economics and Medical Resource Utilization

Health Economics and Medical Resource Utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

As a clause towards marketing approval, the DCGI in accordance with the biosimilar guidelines for India recommended that Basaglar be studied in a minimum of 200 additional local subjects.

Assuming a 15% screen failure rate, approximately 295 subjects will be screened so that 250 subjects can be enrolled. Assuming a drop-out rate of 20%, the target is to have a minimum of 200 subjects complete the present study.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent form
Full Analysis Set (FAS)	All enrolled participants who take at least 1 dose of study treatment
Safety	Identical to FAS, as no randomization occurs (single arm trial)
Per Protocol Set (PPS)	All FAS subjects, who also meet the following criteria: a) have no violations of inclusion/exclusion criteria b) have not discontinued from the study prior to 24 weeks c) have not been off study medication for more than 14 consecutive days during the treatment period d) have not received chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, intra-ocular, and inhaled preparations)

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

All data will be entered, verified, and archived by a contract research organization (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. Statistical analysis of this study will be the responsibility of Lilly.

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 statistical analysis plan and/or in the clinical study report. Additional exploratory analyses will be conducted as deemed appropriate.

Safety and efficacy analyses will be conducted on the full analysis set (FAS) or safety set. These sets include all data from all enrolled subjects who take at least 1 dose of study treatment.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

The planned statistical method for the primary analysis is the calculation of the estimate and the 95% confidence interval for the incidence of total (symptomatic or asymptomatic with FBG level ≤54 mg/dL [3.0 mmol/L]) hypoglycemic events at Week 24.

10.3.1.1. Subject Characteristics

The demographic and baseline characteristics will be recorded and summarized for the FAS and PPS populations. For continuous measures, summary statistics will include

- sample size
- mean
- median
- maximum
- minimum
- interquartile range
- SDs, and
- number with missing values.

For categorical measures, summary statistics will include

- sample size
- frequency
- percentage, and
- number with missing values.

10.3.1.2. Disposition

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

10.3.1.3. Concomitant Therapy

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

10.3.1.4. Treatment Compliance

Subject compliance with study medication will be assessed at each visit of treatment period as mentioned in Section 7.6.

10.3.2. Safety Analyses

10.3.2.1. Hypoglycemic Events

The primary endpoint of this study is the incidence of total (symptomatic or asymptomatic with FBG level ≤54 mg/dL [3.0 mmol/L]) hypoglycemic events at Week 24. The events will be analyzed as following as number and percentage of subjects experiencing at least 1 event over the study period. A 95% confidence interval for the rate will be calculated using the normality assumption.

The rate of total (symptomatic or asymptomatic with FBG level ≤54 mg/dL [3.0 mmol/L]) hypoglycemic events will be analyzed as follows:

- Number of hypoglycemic events per subject over the study period will be analyzed as continuous variables as per Section 10.3.1 (mean, median, SD, standard error [SE], minimum, and maximum)
- The rate of hypoglycemic events per 30 days, and the rate per year, that is the number of hypoglycemic events per subject year (365.25 days), will be calculated.
    - The rate per 30 days between 2 time points (end of treatment/study vs. baseline) is defined as the total number of events between the time points divided by the actual number of days between the time points, and then multiplied by 30. A similar approach is then used for the number of events per subject-year (365.25 days).
    - These measures will be summarized for the overall study period and will be assessed using a negative binomial model with baseline HbA1c as covariate and the log of the study treatment exposure time as offset variable.

The following types of hypoglycemia (see Section 9.1.1) will be analyzed similarly (incidence and rates) as specified for total hypoglycemia:

- nocturnal hypoglycemia
- severe hypoglycemia
- documented symptomatic hypoglycemia, and
- asymptomatic hypoglycemia

All analyses for the hypoglycemic events will be repeated for the PPS population.

10.3.2.2. Laboratory Measurements

Continuous chemistry and hematology measures will be summarized by descriptive statistics at screening visit (Week -2) and at different visits (Section 2) for the FAS population.

Continuous chemistry and hematology measures will be summarized as change from screening visit (Week -2) to Week 24 using the general linear model, with the screening visit (Week -2) value of the response variable as covariate.

All laboratory measurements analyses will be repeated for the PPS population.

10.3.2.3. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be summarized by descriptive statistics (mean, median, SD, SE, minimum, and maximum) by visit for the FAS population. Additionally, change from baseline to each post baseline face-to-face visit for each parameter will be summarized by means of descriptive measures as described in Section 10.3.1. Change from baseline values to Week 24 will be analyzed using the general linear model, with the baseline value of the response variable as covariate after applying the LOCF method to missing values.

All vital signs analyses will be repeated for the PPS population.

10.3.2.4. Adverse Events Analyses

Adverse events will be listed by

- subject
- system organ class (SOC)
- Medical Dictionary for Regulatory Activities® preferred term (PT)
- severity, and
- relationship to the study disease, drug, device, or procedure for all subjects.

Adverse events (including injection site reactions and neoplasms) will be summarized as TEAEs for the FAS population. Treatment-emergent AEs 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. Treatment-emergent AEs 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.

10.3.3. Efficacy Analyses

10.3.3.1. Actual and Change from Baseline HbA1c

The actual and change in HbA1c level from baseline to Week 12 and Week 24 will be analyzed using descriptive statistics (mean, median, SD, SE, minimum, maximum, and number with missing values). For subjects requiring rescue medication (see Section 7.4), HbA1c values recorded after the first administration of rescue medication will not be considered for analysis, and these values will be considered as missing. 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.

Additionally, 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.

All the HbA1c analyses described will be repeated for the PPS population.

10.3.3.2. Subjects Reaching HbA1c Targets (≤6.5% or <7%) at Week 24

Subjects reaching HbA1c levels of ≤6.5% and <7% at Week 24 will be analyzed descriptively as binary variable, using number and percentage. The HbA1c values used to calculate this binary variable will be the LOCF value, that is, in case the Week 24 value is missing, the Week 12 value will be used. The denominator will be the total FAS population. Subject with missing HbA1c data at Week 12 and Week 24 will be considered as not having reached the target.

These analyses will be repeated for the PPS population.

10.3.3.3. Other Efficacy Parameters

The following parameters (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 PPS population:

- 7-point SMBG levels (mg/dL and mmol/L)
- body mass index (kg/m^2)
- body weight (kg), and
- basal insulin dose (U/day and U/kg/day).

Additionally, the change from baseline to the Week 24 for 7-point SMBG levels, body mass index, and body weight will be analyzed using the general linear model for the FAS population. The model will evaluate the change from baseline in HbA1c level as the dependent variable, with the baseline value of the variable as covariate, after applying the LOCF method to missing values.

All analyses will be repeated for the PPS population.

10.3.4. Analyses of Subject-Reported Outcomes

Subject responses to the ITSQ will be reported as overall and domain scores at Weeks 4 and 24. These scores will be summarized by descriptive statistics (mean, median, SD, SE, minimum, and maximum) by visit for the FAS population. Change at Week 24 from Week 4 will be analyzed using the general linear model, with the Week 4 value of the response variable as covariate, after applying the LOCF method to missing values.

These analyses will be repeated for the PPS population.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Subgroup Analyses

Not applicable.

10.3.8. Interim Analyses

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.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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.
CRO	contract research organization
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
DCGI	Drug Controller General of India
ECG	electrocardiogram
eCRF	electronic case report form
ERB	Ethical Review Board
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ET	early termination
FAS	full analysis set

FBG	fasting blood glucose
GCP	Good Clinical Practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form
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
ITSQ	Insulin Treatment Satisfaction Questionnaire
LOCF	last observation carried forward
OAM	oral antihyperglycemic medication
PPS	per-protocol set: The set of data generated by the subset of subjects 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, as per Medical Dictionary for Regulatory Activities (MedDRA)
QD	once daily
SAE	serious adverse event
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
SMBG	self-monitored blood glucose
SOC	system organ class, as per Medical Dictionary for Regulatory Activities (MedDRA)
SUSARs	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus

TBL	total bilirubin level
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
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry[a,b,c]**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Fasting blood glucose
Urinalysis[a,b,d]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	
Glucose	**Pregnancy Test (females only)[e]**
Ketones	
Blood	
Urine leukocyte esterase	

Abbreviations: CRO = contract research organization; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by CRO-designated laboratory agreed by Lilly.

[b] Screening visit (Week -2) and Week 24 results will be confirmed by the Central Laboratory.

[c] Refer to the Schedule of Activities: Abbreviated chemistry includes total bilirubin, direct bilirubin, ALT, BUN, and serum creatinine.

[d] Estimated glomerular filtration rate may also be measured but only in subjects with a history of severe chronic kidney disease

[e] Local- or investigator-designated laboratory.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study, and sharing in a timely manner any new information that may be relevant to the subjects' willingness to continue his or her participation in the study
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Eli Lilly and Company (Lilly) or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current IB or Patient Information Leaflet, Package Insert, or Summary of Product Characteristics and updates during the course of the study
- ICF, and
- other relevant documents (for example, curricula vitae, advertisements).

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the

- consensus ethics principles derived from international ethics 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.

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in family practice, internal medicine, or endocrinology, who are experienced in treating subjects with diabetes mellitus with basal insulin may participate as investigators in this clinical trial, provided they can demonstrate adequate experience in the conduct of clinical research studies.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The coordinating investigator will sign the final clinical study report (CSR) for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified/analyzable/enrolled subjects will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the electronic case report forms (eCRFs), and study procedures.

- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection, and
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site will maintain a separate source for the data entered by the site into the sponsor-provided electronic data capture system. Electronic case report form 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. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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 and Insulin Treatment Satisfaction Questionnaires to collect patient-reported outcome measures. Data from these paper documentations will be transcribed to eCRFs at the sites.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee, judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication to a peer-reviewed journal.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly's or its designee's clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

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

Note: These tests will be implemented in accordance with the most current guidance provided by the Eli Lilly Liver and Gastrointestinal Safety Advisory Committee with respect to the assessment of hepatic safety and collection of hepatic safety data.

Appendix 5. Sampling Summary

This table summarizes the approximate number of blood samples and volumes for all sampling and tests during the study.

Protocol ABEX Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Screening tests[a]	Blood	4.5 mL	1	4.5 mL
Standard laboratory tests[a]	Blood	2 mL	1	2 mL
Total [rounded to nearest 10]		6.0 mL	-	6.0 mL
Hepatic Monitoring[b]	Blood	3-30 mL	-	-

[a] Additional samples may be drawn if needed for safety purposes.

[b] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of subject follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 6. World Health Organization Classification of Diabetes

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, and weight loss); despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes, but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) because of an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some subjects with type 2 diabetes later progress to a state of absolute insulin deficiency.

Appendix 7. Protocol Amendment 14L-IN-ABEX(b) Summary – A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India

Overview

Protocol I4L-IN-ABEX – A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India 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 the rationale for the changes made to this protocol are as follows:

1. The protocol title was changed from "Safety Evaluation of Basaglar in Adult Subjects with Type 2 Diabetes Mellitus in India: A Postmarketing Study" to "A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India" per request from Indian Ministry of Health.
2. The statistical analysis model was changed from "ANCOVA" to "general linear" model to match the statistical analysis plan.
3. Typographical errors with respect to the study identifier were corrected.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Cover Page: Protocol Title

Protocol I4L-IN-ABEX(b~~a~~)
A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India~~Safety Evaluation of Basaglar in Adult Subjects with Type 2 Diabetes Mellitus in India: A Postmarketing Study~~

1. Synopsis

Title of Study:
A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India~~Safety Evaluation of Basaglar in Adult Subjects with Type 2 Diabetes Mellitus in India: A Postmarketing Study~~

Summary of Study Design:

Study I4L-IN~~MC~~-ABEX is a multicenter, open-label, single-arm study, that will enroll insulin-naïve subjects with T2DM. The study period consists of a screening period (Week -2 to Week 0), a treatment period (Week 0 to Week 24), and a safety follow-up visit at Week 28.

Statistical Analysis:

Statistical Methodology:

Secondary outcomes: Actual values and change in glycated hemoglobin (HbA1c) level from baseline to Week 12 and Week 24 will be analyzed in a descriptive manner on non-missing values and last observation carried forward-imputed values. Additionally, a general linear model ~~analysis of covariance (ANCOVA) model~~ will be performed on the full analysis set (FAS), with change from baseline in HbA1c level as the dependent variable and the baseline value of HbA1c as a covariate.

The number of hypoglycemic events per subject, the rate of hypoglycemic events per 30 days, and the rate per year, that is, the number of hypoglycemic events per subject year (365.25 days) will be assessed using a negative binomial model, with baseline HbA1c as a covariate and the log of the study treatment exposure time as an offset variable.

The analysis for other continuous secondary efficacy and safety measurements and continuous laboratory measures will use the ~~ANCOVA~~ general linear model for the FAS population with the baseline value of the response variable as a covariate.

5.1. Overall Design

Study I4L-IN~~MC~~-ABEX (ABEX) is a multicenter, open-label, single-arm, Phase 4 study to assess the safety of Basaglar in subjects with T2DM in India.

9.5. Subject-Reported Outcomes

If an item score is missing for a subject and ≤20% of the items within the domain (or overall) are missing for that subject, then the mean of the items in the domain (or overall) will be imputed for the missing item score(s). If there are >20% missing items, the individual subject domain (or overall) score will be set to missing. Change at Week 24 from Week 4 will be analyzed using the ~~analysis of covariance (ANCOVA)~~general linear model, with the Week 4 value of the response variable as covariate.

10.3.2.2. Laboratory Measurements

Continuous chemistry and hematology measures will be summarized by descriptive statistics at screening visit (Week -2) and at different visits (Section 2) for the FAS population.

Continuous chemistry and hematology measures will be summarized as change from screening visit (Week -2) to Week 24 using the ~~ANCOVA~~ general linear model, with the screening visit (Week -2) value of the response variable as covariate.

10.3.2.3. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be summarized by descriptive statistics (mean, median, SD, SE, minimum, and maximum) by visit for the FAS population. Additionally, change from baseline to each post baseline face-to-face visit for each parameter will be summarized by means of descriptive measures as described in Section 10.3.1. Change from baseline values to Week 24 will be analyzed using the ~~ANCOVA~~ general linear model, with the baseline value of the response variable as covariate after applying the LOCF method to missing values.

10.3.3.1. Actual and Change from Baseline HbA1c

Additionally, the change in HbA1c level from baseline to Week 24 will be analyzed using the ~~ANCOVA~~ general linear model for the FAS population. The ~~ANCOVA~~ general linear model will evaluate the change from baseline in HbA1c level as the dependent variable and the baseline value of HbA1c as covariate.

10.3.3.3. Other Efficacy Parameters

Additionally, the change from baseline to the Week 24 for 7-point SMBG levels, body mass index, and body weight will be analyzed using the ~~ANCOVA~~ general linear model for the FAS population. The model will evaluate the change from baseline in HbA1c level as the dependent variable, with the baseline value of the variable as covariate, after applying the LOCF method to missing values.

10.3.4. Analyses of Subject-Reported Outcomes

Subject responses to the ITSQ will be reported as overall and domain scores at Weeks 4 and 24. These scores will be summarized by descriptive statistics (mean, median, SD, SE, minimum, and maximum) by visit for the FAS population. Change at Week 24 from Week 4 will be analyzed using the ~~ANCOVA~~ general linear model, with the Week 4 value of the response variable as covariate, after applying the LOCF method to missing values.

Appendix 1. Abbreviations and Definitions

Term	Definition
~~ANCOVA~~	~~analysis of covariance~~

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