Statistical Analysis Plan Version 1 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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STATISTICAL ANALYSIS PLAN

Protocol title: A Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Basaglar in Subjects with Type 2 Diabetes Mellitus in India	
Protocol number: I4L-IN-ABEX(b)	**Applicable Protocol Version:** b
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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
ENRL	Enrolled Population Set
ET	Early Termination
FAS	Full Analysis Set
FBG	Fasting Blood Glucose
HbA1c	Glycated Haemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IMP	Investigational product
IQR	Inter Quartile Range
ITSQ	Insulin Treatment Satisfaction Questionnaire
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
N	Sample size
ODS	Output delivery system
PR	Pulse Rate
PPS	Per-Protocol Set
PT	Preferred term
QD	once daily
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMBG	Self-Monitored Blood Glucose
SOC	System organ class
SUSARs	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures
WCBP	Women of Child-Bearing Potential

WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of a Phase 4, multicentre, open-label, non-randomized, single-arm study to access the Safety of Basaglar in Adult Subjects with Type 2 Diabetes Mellitus (T2DM) in India.

This statistical analysis plan (SAP), is based on protocol I4L-IN-ABEX(b),Version b, dated 04-Oct-19.

2. Trial objectives

The following objectives are those stated in the protocol.

2.1 Primary objectives

- To assess risk of hypoglycemia in adult subjects with T2DM in India who will be administered Basaglar.

2.2 Secondary objectives

- To assess adverse events and other safety parameters in adult subjects with T2DM in India
- To assess efficacy of Basaglar in adult subjects with T2DM in India
- To assess outcomes reported by adult subjects with T2DM in India

3. Endpoints

3.1 Primary endpoints

- Incidence of total (symptomatic or asymptomatic with FBG level of ≤54 mg/dL [≤3.0 mmol/L]) hypoglycemic events at Week 24

3.2 Secondary endpoints

- 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
- Basal insulin dose (U/day and U/kg/day)
- Change in weight and body mass index at Week 24 from baseline
- Change in HbA1c levels at Weeks 12 and 24 from baseline
- Percentage of subjects reaching HbA1c targets ≤6.5% and <7% at week 24
- 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
- Change in Insulin Treatment Satisfaction Questionnaire (ITSQ) score at Week 24 from Week 4

4. Trial design

4.1 Design overview

This is a multicenter, open-label, single-arm, phase 4 study to assess the safety of Basaglar in insulin-naïve subjects with T2DM in India. 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 period contains 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,(in protocol) and 6.2,(in protocol) 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. 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. Subjects will self-administer Basaglar once daily at bedtime (starting dose will be 10 units). Subjects can self-titrate (as per outlined in table 4.1) 2-4 units once or twice in weekly until FBG levels are 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 concomitant medications.

This is a single-arm study and enrolled subjects will be treated with Basaglar using a self-titration scheme as outlined in below table 4.1.

Table 4.1

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

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.

4.2 Schedule of events

The schedule of evaluations and procedures to be performed at specific time points is described in the following table 4.2.

Table 4.2

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										
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	X	X	X	X	X	X	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					
7-point SMBG measurement[d]		X	X	X	X			X		
Laboratory Assessments										

Hematology, clinical chemistry, and urinalysis tests	X				X			X		See Appendix 2 of protocol for details. Estimated glomerular filtration rate will be measured only in subjects with a history of severe chronic kidney disease.
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**		
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
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 drug and study diary		X	X	X	X					
Collect unused study drug and study diary			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 3, 4, 5, and 8.
e. Subjects will be instructed to record the actual time and dose of Basaglar administration in the subject diary.

5. Changes/deviations from the planned analysis

Any deviation in implementing original statistical plan will be described and justified in the final clinical study report.

6. Analysis populations

Agreement and authorization of participants included/excluded from each analysis population will be reached prior to final database hard lock. Sponsor will supply a list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations.

6.1 Enrolled Population Set (ENRL)

This analysis population will include all participants who sign informed consent form.

- "Y" for subjects who have signed ICF, Else set to "N".

6.2 Full Analysis Set (FAS) / Safety Analysis Set (SAF)

FAS and SAF are identical to each other as this is single arm trial and no randomization occurs. So, we will indicate this population as FAS for analysis purpose.

This population will include all enrolled participants who take at least 1 dose of study treatment.

- "Y" for subjects who received at least one dose of the investigational product (IMP). Else set to "N".

6.3 Per-Protocol Analysis Set (PPS)

This analysis population will include 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)

- Set to 'Y' if
  1. For all FAS subjects = "Y" and

2. Date of completion/discontinuation is not less than date of visit 8 (week 24)
3. within a subject there is no DV.DVCAT = "MAJOR"

7. General considerations

7.1 Visit and date conventions

Visit day will be calculated from the reference start date which will be used to present start/stop day of assessments and events. The *reference start date* is defined as the date of first IMP administration. The following conventions will be used for event references:

Date of event less than reference treatment start date

- $Event\ day = date\ of\ event - reference\ treatment\ start\ date$

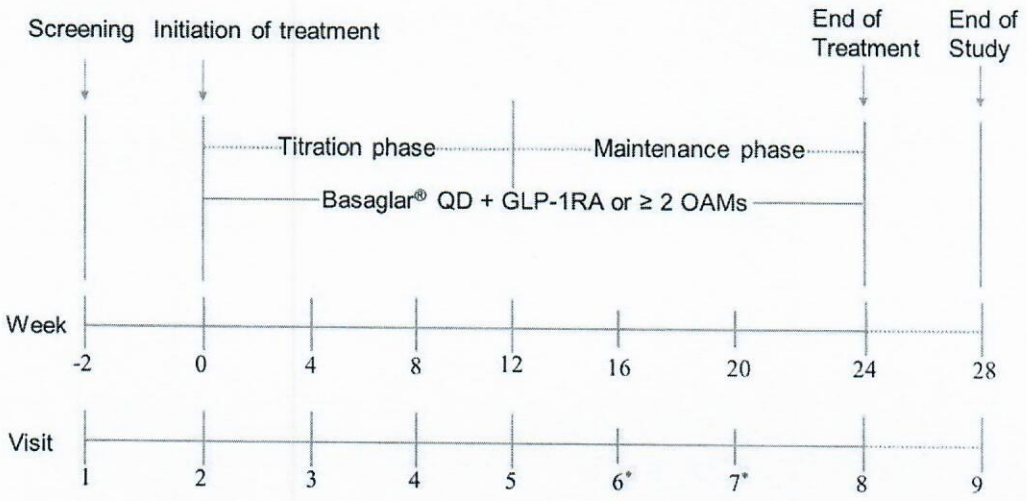
Date of event greater than equal to reference treatment start date

- Event $day = date\ of\ event - reference\ treatment\ start\ date + 1$

Above two formulae will be use for the calculation of the duration (in days) for the respective events (i.e. AEs etc).

Visit windowing (i.e. remapping of visits based on visit windows) will be performed for this trial. The assigned nominal visit will be used for by-visit summaries. In the situation where the assessment/event date is partial or missing, visit day/week, and any corresponding durations will appear missing in the data listings. Unscheduled measurements will not be included in by-visit summaries. Data listings will include scheduled, unscheduled, and early discontinuation data. The following figure 7.1 illustrates the study design.

Figure 7.1



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

The study design includes the following periods:

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

Trial visit will be assigned as delineated in Table 7.1:

Table 7.1

	Screen	**Treatment Period**							**Follow-up**
Visit Day	-14 to 0	0	28	56	84	112	140	168	196
Visit Week	-2	0	4	8	12	16	20	24	28
Visit No.	1	2	3	4	5	6	7	8	9 /ET
Allowable Deviation +/- (days)		3	7	7	7	7	7	7	

The below detail mentioned procedures will be completed at each visit:

Screening period (Week -2 to Week 0) i.e. Visit 1

The following procedures will be completed for each study participant:

- Informed consent
- Inclusion / Exclusion Criteria
- Demographic information
- HIV and Hepatitis testing
- Physical Examination
- Vital Signs
- Medical History and family history of CV disease
- History of substance usage
- 12-lead ECG
- Laboratory Sample Collection
- Trainings on injection technique, use of glucometer and 7-point SMBG measurement
- Dispense study diary
- Dispense glucometer
- Concomitant medication review

Treatment period (Week 0 to Week 24) i.e. Visit 2, 3, 4, 5, 6, 7 and 8

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. At these visits, participants will undergo the following procedures and evaluations.

- Vital Signs (for visit 2,3,4,5, 8 and 9 only)
- Concomitant medication review
- Dispense study diary (for visit 2 only) Hypoglycemia Events Summary
- FBG (for visit 2,3 and 4 only)
- Adverse events and Serious adverse events
- Blood Glucose Monitoring (7-point reading) (for visit 2,3,4,5 and 8 only)
- Treatment exposure
- Urine Pregnancy Test (for visit 2)
- HbA1c measurement (for visit 2,5 and 8)
- Insulin Treatment Satisfaction Questionnaire (ITSQ) (for visit 3 and 8)
- Hematology, clinical chemistry, and urinalysis tests (for visit 5 and 8)

- Hepatic Monitoring Tests
- Trainings on signs/symptoms of hypo/hyperglycemia and insulin reactions
- Trainings on injection technique, use of glucometer and 7-point SMBG measurement (for visit 2,3,4,5 and 8 only)
- Self-titration training
- Dispense study drug (for visit 2,3,4 and 5 only)
- Review study diary (for visit 2,3,45 and 5 only)
- Substance use - Alcohol (Initial/Historical)
- Substance use - Recreational Drug (Initial/Historical)

Follow-up Visit (Week 28) i.e. Visit 9

- Vital Signs
- Concomitant medication review
- Adverse events and Serious adverse events
- Hypoglycemia Events Summary
- Completion or discontinuation of investigation

7.2 Baseline

Unless stated otherwise, baseline is defined as the last non-missing observation made prior to the first administration of IMP. if multiple values pre-treatment exists then the value closes to first treatment administration will be considered as baseline.

7.3 Stratifications

For analysis purposes, we are not doing any stratification and we will provide summary by treatment (i.e. Basaglar).

7.4 Statistical tests

This is the single arm study so no comparison tests will be performed.

The incidence of hypoglycemia will be analysed using the exact binomial method (Clopper-Pearson method) for single proportions. The change from baseline (e.g. for HbA1c, FBG levels etc) will be analysed using the general linear model and the baseline visits of the respective parameter will be considered as covariate. The rates

of hypoglycemia will be analysed using the Negative Binomial Model without categorical variable i.e. the generalized linear model and the baseline visit of HbA1c will be considered as covariate.

7.5 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value), where the baseline value is defined as the last non-missing observation taken prior to first exposure to IMP.

7.6 Software

All analyses will be conducted using SAS® Version 9.4 and above.

8. Statistical considerations

8.1 Multicentre studies

Approximately 295 subjects will be screened, so that 250 subjects can be enrolled. the target is to have a minimum of 200 subjects completing the present study and the study visits will be conducted at different sites in India.

8.2 Missing data

1) **Vital Signs:** we will use the last observation carry forward (LOCF) method for the missing values.
2) **Actual and Change from Baseline HbA1c:** For subjects requiring rescue medication, 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.
3) **Subjects Reaching HbA1c Targets (≤6.5% and <7%) at Week 24:** 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.

   For other efficacy parameters 7-point SMBG levels (mg/dL and mmol/L), body mass index (kg/m^2), body weight (kg), basal insulin dose (U/day and U/kg/day) we will apply the LOCF method for missing data.

4) **ITSQ score:** 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 scores 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. that is here we will use the mean imputation method.

Change at Week 24 from Week 4 for ITSQ score (Transformed overall and domain scores): we will use the last observation carry forward (LOCF) method for the missing values.

5) **Laboratory data:** we will use the last observation carry forward (LOCF) method for the missing values.

For all other cases the missing data will not be imputed for this trial.

9. Output presentations

This is single arm study; we are not doing any stratification we will present the summary table for single treatment group i.e. Basaglar.

The Section 23, Appendix 1 describe the format and content for presentation of tables, listings and figures (TLFs).

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all participants, unless otherwise specified.

In general, if we have no response or record for respective parameter in data (i.e. n=0) then while presenting statistics in table only n will be presented as "0" and other statistics will be left blank. In case, we have only one response or record for respective parameter (i.e. n=1) in data then statistic (S.D) in table will be presented blank.

By default, for continuous measures, summary statistics will include, unless otherwise specified:

- Sample Size (N)
- n
- Mean
- Median
- Maximum
- Minimum
- Interquartile Range
- SDs, and
- Frequency of Missing Values.

For categorical measures, summary statistics will include, unless otherwise specified:

- Sample Size (N)
- Frequency of non-missing values
- Percentage, and

- Frequency of Missing Values.

For efficacy tables, below statistics will be included, unless otherwise specified:

- Estimate
- 95 % Confidence Interval
- P-value

10. Participant disposition and withdrawal

10.1 Variables and derivations

The trial classifications are defined as follows:

- Screening failure:

  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.

- Completed treatment:

  All the subject who have taken all the treatment as per protocol.

- Completed trial:

  Participants who completed the trial, as indicated on the [End of Study] page of the (eCRF), will be assumed to have completed trial.

- 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.

- Early withdrew from trial:

  Participants who discontinued from the trial, as indicated on the [End of Study] page of the (eCRF), will be assumed to have withdrew early from trial.

The following parameters will be summarised for the subject's disposition table as per eCRF:

- Number of screening failure subjects (This will be applicable for ENRL set table only.)
- Number of subject's completed trial
- Number of subject's completed treatment
- Number of subjects withdrew early from trial

- Number of Subject's in ENRL set
- Number of Subject's in FAS set
- Number of Subject's in PP set

The following parameters will be summarised for the early withdrawals table as per eCRF Subject's primary reason for discontinuation (reasons mentioned in eCRF "End of the Study" form) which is as follows:

- ADVERSE EVENT
- DEATH
- SCREEN FAILURE
- WITHDRAWAL BY SUBJECT
- PHYSICIAN DECISION
- NON-COMPLIANCE WITH STUDY DRUG
- PROTOCOL DEVIATION
- STUDY TERMINATED BY IRB OR ERB
- STUDY TERMINATED BY SPONSOR
- LOST TO FOLLOW-UP
- LACK OF EFFICACY
- OTHER

Derivations:

- In eCRF at End of the study form primary reason for discontinuation is indicated as "SCREEN FAILURE" to ensure that subject is screen failure.
- In eCRF at End of Study form Subject status is indicated as "COMPLETED" to ensure that subject is completed trail.
- If the date of last dose of study treatment < Date of Visit (Visit 8(Week 24)) and date of last dose of study treatment > Date of Visit (visit 7(week 20)) to ensure that subjects is completed treatment.
- In eCRF at End of Study form Subject status is indicated as "DISCONTINUED" to ensure that subjects withdrew early from trial.
- In eCRF at End of Study form the subject's primary reason for discontinuation is indicated as "LOST TO FOLLOW-UP" to ensure that subjects lost to follow-up form trial.

The following variables will be listed for the subject's disposition:

- Subject Number
- Informed consent date
- Last dose administration date
- Subject study status
- Date of completion/discontinuation
- Subject's primary reason for discontinuation
- Death date

10.2 Analysis

Population:	ENRL and FAS
Stratification:	Table: NA Listing: By subject
Statistics:	Participants disposition and Withdrawal will be summarised frequency and percentages and the screening failure subjects will be summarised (frequency) by total for table. The listing will be provided.

11. Participant demographics and other baseline characteristics

11.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized:

- Age (in Years) (Calculated relative to date of informed consent in eCRF)
- Gender
- Race
- Height (cms) at Screening
- Weight (kgs) at Screening
- BMI (kg/m^2) at Screening

Note: For Age Calculation according to Lily standards for the Date of birth only year field will population in the dataset, and day and month will come as unknown so, we will consider it as 01JUL for back end calculation.

Age (Years) and BMI (kg/m^2) will be calculated as follows:

- $Age\ (Years) = floor\ [\frac{Date\ of\ informed\ consent - Date\ of\ birth}{365.25}]$
- $BMI\ (kg/m^2) = \frac{weight\ (kgs)}{[\frac{height\ (cms)}{100}]^2}$

The following demographic and baseline characteristics will be listed:

- Subject number
- Informed consent date
- Year of birth
- Age (in years)
- Gender
- Race
- BMI

Below parameters will be provided in septate listing:

- 12 Lead ECG

- Serum Pregnancy Test
- HIV and Hepatitis testing

11.2 Analysis

Population: FAS and PPS populations

Stratification: Table: NA

Listing: By subject

Statistics: Baseline and Demographic variables will be summarized and listed. Overall summaries will include descriptive statistics for continuous measures (N=sample size, n=number of subjects with respective parameter, mean, median, maximum, minimum, interquartile range (IQR), standard deviation and frequency of missing values) and for categorical measures (N=sample size, frequency, percent, frequency of missing values).

12. Exposure to IMP

12.1 Variables and derivations

In eCRF exposure form we are capturing the treatment dosing related data and the dates of first IMP administration will be derived as the first date of dosing from the Exposure form in eCRF. The date of last IMP administration will be derived as the date of last dose of IMP from the End of the Study form in eCRF page.

Note: Total amount of missed dose on 3 consecutive or 15 days in total within the 6 months' time frame is considered as per standard definition per sponsor, the same definition has beens used in all previous insulin studies.

The following variables will be listed for exposure to IMP:

- Subject Number
- Date of treatment administration
- Total amount of dose consumed
- Number of missed doses
- Duration of exposure(days)

The duration of exposure, which will be derived as follows:

- $Duration\ of\ exposure\ (days) =$
  $(Date\ of\ last\ IMP\ administration - Date\ of\ first\ IMP\ administration) + 1$

12.2 Analysis

Population:	FAS and PPS populations
Stratification:	Table: NA Listing: By Subject
Statistics:	Listing will be provided for daily dosing treatment exposure data for each subject.

13. IMP compliance

13.1 Variables and derivations

The compliance to IMP will be calculated based on information obtained from the exposure form in eCRF at each visit (i.e. for treatment period) as per mentioned in protocol section 7.6.

Compliance will be derived and reported by visit (i.e. for treatment period) and overall as follows:

For visit:

- Compliant" if, the response to the question "Were there any missed doses" is answered "No" or, if the answered is "Yes" and the response to the question "Did the subject miss more than 3 consecutive days of study medication" is answered as "No".
- "Not Compliant" if, the response to the question "Were there any missed doses" is answered "Yes" and, the response to the question "If yes, indicate the number of missed doses" is equal or more than 3,
- "Unknown" otherwise

For overall

- "Compliant" if, the response to the question "Were there any missed doses" is answered "No" or, if the answered is "Yes" and the response to the question "Did the subject miss more than 3 consecutive days of study medication" is answered as "No" or the total of all missed doses in the treatment period is less than equal to 15.
- "Not Compliant"
    - if, the response to the question "Were there any missed doses" is answered "Yes" and, the response to the question "If yes, indicate the number of missed doses" is equal or more than 3 and,
    - The response of the question "Did the subject miss more than 3 consecutive days of study medication" is answered "Yes" then if the total of all missed doses in the treatment period is more than 15.

- "Unknown" otherwise.

The following mentioned parameters will be summarised in table:

- IMP compliance categories by each visit and overall

The following variables will be provided in the listing:

- Subject Number
- Visit
- Start date of study drug administration
- Date of dose on last day prior to visit
- Compliance status

13.2 Analysis

Population:	FAS and PPS
Stratification:	Table: By visit Listing: By subject and visit
Statistics:	The treatment compliance will be summarised (frequency and percentages) for table and the listing will be presented.

14. Medical and treatment history

14.1 Variables and derivations

Medical history will be coded using the MedDRA central coding dictionary Version (refer to DMP for dictionary version).

Partial date imputation is not done for Medical and treatment history.

The following parameters will be summarised for the subject's Medical history as mentioned in eCRF:

- Number of subjects with at least one medical history
- Number of subjects for each medical history by SOC and PT

The following variables will be listed:

- Subject number
- System organ class/ Preferred terms / Reported terms
- Severity of medical history
- Start date of medical history
- End date of medical history

14.2 Analysis

Population:	FAS and PPS
Stratification:	Table: By Primary SOC and PT in decreasing order Listing: By subject
Statistics:	Medical and treatment history will be summarised (frequency and percentages) for table and listing also be provided.

15. Concomitant and other medications

15.1 Variables and derivations

In eCRF "Concomitant Medications: General Use" form we are capturing the concomitant medication related data.

Concomitant medications are defined as any medication taken after first administration of the IMP till the end of the trial.

All medications will be coded using the WHO-DD, dated (refer to DMP for dictionary date) All concomitant therapies that was originally mapped using the WHO Drug Dictionary in the ClinTrial database will be further classified using Anatomical Therapeutic Chemical (ATC) codes for reporting purposes.

The following parameters will be summarised separately for the subject's with concomitant medication and Special Interest Hyperglycaemia related concomitant medication:

- Number of subjects with at least one concomitant medication and Special Interest Hyperglycaemia related concomitant medication
- Number of subjects for each concomitant medication and Special Interest Hyperglycaemia related concomitant medication by ATC and PT.

The following variables will be listed concomitant and other medications:

- Subject Number
- Medication class/ Standardized medication name/ Reported term
- Dose and unit
- Frequency
- Route
- Start date of medication
- End date of medication

Rescue Medication:

The rescue medication related data will be captured in "Concomitant Therapy: Special Interest Hyperglycaemia" special form in eCRF.

The rescue medication we will identify using following variables:

- Date of first dose administration
- First Rescue medication date

Derivations:

All concomitant medication and Special Interest Hyperglycaemia related concomitant medication, which are identifies as follows:

- If start date of concomitant medication >= Date of first dose administration, then we will consider it as "concomitant medication".

For identification of rescue medication visit wise we will use the following derivation:

- (First Rescue Medication Date – Date of First Dose Administration) +1

15.2 Analysis

Population:	FAS and PPS
Stratification:	Table: by ATC and PT Listing: By subject
Statistics:	Concomitant medication and Special Interest Hyperglycaemia related concomitant medication will be summarized separately as (frequency, percentages) for table and listing will be presented for concomitant medication and Special Interest Hyperglycaemia related concomitant medication. The rescue medication will be summarized as (frequency and percentage) by visit (i.e. Week 4, 8, 12, 16, 20 and 24) for FAS population. By using formula mentioned in derivation section for rescue medication, we will get the Day at which the rescue medication will be started per subject, then we will convert these days to respective visits.

e.g. if, subject in the trial who needs rescue medication on day 30 (Day 30 is calculated using derivation mentioned above for rescue medication) then this subject will be counted under week 4 visit (as Day 30 comes under the week 0 to week 4 visit).

Denominators for "n" are per visit, for "n-cumulative" it will be the number of subjects with at least 1 visit up to respective visit.

16. Adverse events

16.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version (refer to DMP for dictionary version).

Adverse events (AE) and Serious adverse event (SAE) are defined as events that are reported after the signing the inform consent form (ICF).

Treatment-emergent adverse events (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. In the case where it is impossible to define an AE as treatment-emergent or not, the AE will be classified by the worst case assigned, i.e. a TEAE.

In section 24 Appendix 2 the algorithm is given for calculation of partial date imputation for adverse events (AEs) and it will be used for partially missing adverse event start and end date imputation.

Each adverse event will be described by following in listing:

- Subject Number
- Description (AE term) i.e. System organ class/ Preferred terms / Reported terms
- Duration (start and end dates)
- Severity of event
- Relationship to the investigational product
- Relationship to non-study drug treatment
- Relationship to the study procedure
- Action taken with the study treatment
- Outcome
- Whether SAE or not

Each serious adverse event will be described by following in listing:

- Subject Number

- Description (SAE term) i.e. System organ class/ Preferred terms / Reported terms
- Duration (start and end dates)
- Seriousness criteria
- Toxicity grade
- Severity
- Causality
- Outcome

The following parameters will be summarised for the subject's adverse events as mentioned in eCRF

- Number of participants with at least one TEAEs
- Number of participants with at least one drug related TEAEs
- Number of participants with at least one serious TEAEs
- Number of participants with at least one drug related serious TEAEs
- TEAE by Severity
- TEAEs leading to Death
- Drug-related TEAEs leading to Death
- TEAEs leading to early withdrawn of study
- Injection site Adverse events

Derivations:

- If adverse event start date ≥ Study drug administration start date, then we will consider it as TEAE.
- If adverse event start date ≥ Study drug administration start date and adverse event related to study treatment = "YES", then we will consider it as drug related TEAEs.
- If adverse event start date ≥ Study drug administration start date and adverse event serious = "YES", then we will consider it as serious TEAEs.
- If adverse event start date ≥ Study drug administration start date and adverse event serious = "YES" and adverse event related to study treatment = "YES", then we will consider it as drug related serious TEAEs.

- If adverse event start date ≥ Study drug administration start date and subject's primary reason for discontinuation = "DEATH", then we will consider it as TEAEs leading to Death.
- If adverse event start date ≥ Study drug administration start date and subject's primary reason for discontinuation = "DEATH" and adverse event related to study treatment = "YES", then we will consider it as Drug-related TEAEs leading to Death.
- If adverse event start date ≥ Study drug administration start date and subject's primary reason for discontinuation = "ADVERSE EVENT", then we will consider it as TEAEs leading to early withdrawn of study.
- If the question "were the injection site reaction(s) recorded in AE form" is answered as "YES" in eCRF "Injection Site Reaction" form, then we will consider it as Injection site Adverse events

16.2 Analysis

16.2.1 Treatment emergent AEs

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented as treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	Treatment emergent AEs will be listed and summarized as (frequency, percentages) for table.

16.2.2 Drug-related TEAEs

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented as treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	Drug-related TEAEs will be listed and summarized as (frequency, percentages) for table.

16.2.3 Serious TEAEs

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented as treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	Serious TEAEs will be listed and summarized as (frequency, percentages) for table.

16.2.4 Drug related Serious TEAEs

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	Drug related Serious TEAEs will be listed and summarized as (frequency, percentages) for table.

16.2.5 TEAEs by severity

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	TEAEs by severity will be listed and summarized as (frequency, percentages) for table.

16.2.6 TEAEs leading to death

Population:	FAS and PPS
Stratification:	Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order. Listing: By subject
Statistics:	TEAEs leading to death will be listed and summarized as (frequency, percentages) for table.

16.2.7 Drug-related TEAEs leading to death

Population: FAS and PPS

Stratification: Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order.
Listing: By subject

Statistics: Drug-related TEAEs leading to death will be listed and summarized as (frequency, percentages) for table.

16.2.8 TEAEs leading to early withdrawal from study

Population: FAS and PPS

Stratification: Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order.
Listing: By subject

Statistics: TEAEs leading to early withdrawal from study will be summarized as (frequency, percentages) for table.

16.2.9 Serious AEs

Population: FAS and PPS

Stratification: Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order.
Listing: By subject

Statistics: Serious AEs will be listed and summarized as (frequency, percentages) for table.

16.2.10 Serious TEAEs by severity (Grade 3-5)

Population: FAS and PPS

Stratification: Table: In the overview table will be presented by treatment i.e. Basaglar and rest by Primary SOC and PT in decreasing order.
Listing: By subject

Statistics: Serious TEAEs by severity (Grade 3-5) will be listed and summarized as (frequency, percentages) for table.

17. Safety laboratory tests

17.1 Variables and derivations

For safety laboratory data, baseline will be defined as the last observation made prior to the first administration of IMP (see section 7.2).

The following Clinical Laboratory Tests (haematology, clinical chemistry and urinalysis measured at Visit 1, 5 and 8) to be included in the analysis:

- Haematology:
  - Hemoglobin
  - Hematocrit
  - Erythrocyte count (RBC)
  - Mean cell volume
  - Mean cell hemoglobin concentration
  - Leukocytes (WBC)
  - Neutrophils, segmented
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets
- Clinical Chemistry:
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Blood
  - Urine leukocyte esterase
- Urinalysis:
  - Sodium
  - Potassium
  - Total bilirubin
  - Direct bilirubin

- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Calcium
- Fasting blood glucose
- Albumin
- Cholesterol
- Creatine kinase (CK)

The following Hepatic Monitoring Tests (Hepatic Haematology, Hepatic Chemistry, Hepatic Coagulation and Hepatic Serologies measured at Visit 3, 4, 5 and 8) to be included in the analysis:

- Hepatic Haematology
  - Haemoglobin
  - Haematocrit
  - RBC
  - WBC
  - Neutrophils (segmented)
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets result
- Hepatic Chemistry
  - Total bilirubin result
  - Direct bilirubin result
  - Alkaline phosphatase result
  - Alanine Aminotransferase (ALT) result
  - Aspartate Aminotransferase (AST) result
  - Gamma-Glutamyl Transferase (GGT) result
  - Creatine phosphokinase (CPK) result

- Haptoglobin result

- Hepatic Coagulation
  - Prothrombin time result
  - Prothrombin time, INR result
- Hepatic Serologies
  - Hepatitis A antibody, total – result
  - Hepatitis A antibody, IgM – result
  - Hepatitis B surface antigen – result
  - Hepatitis B surface antibody – result
  - Hepatitis B core antibody – result
  - Hepatitis C antibody – result
  - Hepatitis E antibody, IgG – result
  - Hepatitis E antibody, IgM – result
  - Anti-nuclear antibody result
  - Alkaline Phosphatase Isoenzymes result
  - Anti-smooth muscle antibody (or anti-actin antibody) result

17.2 Analysis

Population: FAS and PPS

Stratification: Table: By visit

Listing: By subject, visit and each laboratory test parameter

Statistics: Summaries of all the clinical laboratory tests (haematology, clinical chemistry and urinalysis) will include descriptive statistics of the following:

- Actual and change from baseline (n, mean, standard deviation, standard error median, minimum, maximum) (for quantitative measurements)
- Frequencies and percentages (n and %) (for qualitative measurements)

Continuous clinical laboratory chemistry and haematology measures will be summarized as change from screening visit (Week -2) to Week 24 using the general linear model , with the change from

week -2 to week 24 in respective laboratory parameter as dependent variable and the screening visit (Week -2) value of the respective response variable as covariate.

Missing data imputation will be performed as mentioned in section 8.2 point 5.

Efficacy tables will be presented for with and without imputed values separately for each population set.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The regression line for the general linear model without categorical variable is as follows:

$Y = \alpha + \beta (X)$

Where,

Y= The response change in respective laboratory parameter.

α =Intercept

β =slope

X= Covariate i.e. Baseline (i.e. week -2) respective laboratory parameter

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in respective laboratory parameter at week 24 from screening visit (Week -2) depending on the Baseline (i.e. week -2) respective laboratory parameter.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in respective laboratory parameter at week 24 from screening visit (Week -2) depending on the Baseline (i.e. week -2) respective laboratory parameter.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value ≥ 0.05 then we will conclude that there is no statistically significant change in respective laboratory parameter at week 24 from screening visit (Week -2) i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
   model Y= X / s cl;
   estimate "Model with Mean baseline lab parameter" int 1 lab parameter baseline mean /CL;
   ods output estimates=output dataset;
run;
quit;
```

Quantitative all the clinical laboratory tests (haematology, clinical chemistry and urinalysis) will be compared with the relevant laboratory reference ranges and categorised as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range

i.e. Shift tables (low, normal, high) will be presented for all parameters by treatment and visit.

Data for all the clinical laboratory tests (haematology, clinical chemistry) will also be presented graphically as a function of time. These will include line plots of mean ± standard deviation and median ± range of individual participant's data by treatment and visit.

Note: if we get continuous laboratory test results as < or > value then worst-case scenario will be considered (i.e. for ex. if parameter values are < 40 then it will be considered as 40).

All the hepatic monitoring tests (Hepatic Haematology, Hepatic Chemistry, Hepatic Coagulation and Hepatic Serologies) will be summarised as n, mean, standard deviation, standard error median, minimum, maximum for quantitative measurements also

frequencies and percentages (n and %) for qualitative measurements.

All the clinical laboratory tests and hepatic monitoring tests will be listed by subject, visit and each laboratory test parameter.

Note: This Hepatic test present on the case that the patient suffers from hepatic event.

18. Vital signs

The vital sings will be measured on scheduled visits i.e. visit 1 through visit 9 (EOS) except Visit 6 and 7 (telephonic visits).

18.1 Variables and derivations

For vital signs, baseline is defined as the last observation made prior to the first administration of IMP (See the section 7.2).

The following vital signs will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats per minute)

18.2 Analysis

Population:	FAS and PPS
Stratification:	Table: By visit Listing: By subject
Statistics:	Descriptive statistics (n, mean, standard deviation, standard error, median, minimum, maximum) will be calculated for all the vital signs variables (Actual and change from baseline) for table. Listing will be presented for all the vital signs parameter by subject. The change from baseline values to Week 24 will be analysed using the general linear model, with the baseline value of the response variable as covariate after applying the LOCF method to missing values. Missing data imputation will be performed as mentioned in section 8.2 point 1. Efficacy tables will be presented for with and without imputed values separately for each population. The estimate, 95% confidence interval and p-value will be summarised for efficacy table. The regression line for the general linear model without categorical variable is as follows:

$Y = \alpha + \beta (X)$

Where,

Y= The response change in respective vital signs parameter.

α =Intercept

β =slope

X= Covariate i.e. Baseline of respective vital signs parameter

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in respective vital signs parameter at week 24 from baseline depending on the Baseline of respective vital signs parameter.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in respective vital signs parameter at week 24 from baseline depending on the Baseline of respective vital signs parameter.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value ≥ 0.05 then we will conclude that there is no statistically significant change in respective vital signs parameter at week 24 from baseline i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
   model Y= X / s cl;
   estimate "Model with Mean of baseline respective vital signs parameter " int 1 vital signs parameter baseline mean /CL;
   ods output estimates=output dataset;
run; quit;
```

19. Primary efficacy assessments

The primary endpoint parameter is mention below

19.1 Variables and derivations

19.1.1 Incidence of total (symptomatic or asymptomatic with FBG level of ≤54 mg/dL [≤3.0 mmol/L]) hypoglycaemic events at Week 24

Variables:

- What was the blood glucose level (mg/dL) prior to treating the event? (In eCRF "Hypoglycemia Events" form)
- Were signs/symptoms of hypoglycemia present, other than the blood glucose reading? (In eCRF "Hypoglycemia Events" form)
- Hypoglycemic event start date
- Date of Visit 2 (Week 0)
- Date of Visit 8 (Week 24)

Derivation:

- Hypoglycemic event start date ≥ Date of Visit 2 (Week 0) and Hypoglycemic event start date ≤ Date of Visit 8 (Week 24) for accessing the hypoglycemic events from Day 0 to week 24.

- "Symptomatic Hypoglycaemic events" if, the question "What was the blood glucose level (mg/dL) prior to treating the event" result is less or equal to 54 mg/dL and the question "Were signs/symptoms of hypoglycemia present, other than the blood glucose reading" is answered as "YES".

- "Asymptomatic Hypoglycaemic events" if, the question "What was the blood glucose level (mg/dL) prior to treating the event" result is less or equal to 54 mg/dL and the question "Were signs/symptoms of hypoglycemia present, other than the blood glucose reading" is answered as "NO" or "UNKNOWN.

19.2 Analyses

19.2.1 Primary analysis

Population: FAS and PPS

Stratification: Table: NA

Listing: By subject

Statistics: The total hypoglycaemic event will be analysed as number and percentage (n and %) of subjects experiencing at least 1 event from Day 0 to Week 24.

The estimate and 95% confidence interval will be presented by using exact binomial method (Clopper-Pearson method) for single proportions for the incidence of total hypoglycaemic events from Day 0 to Week 24.

The listing will be presented for all the hypoglycaemic events.

20. Secondary efficacy assessments

20.1 Variables and derivations

20.1.1 Serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)

Variables:

- First Study drug administration Date
- Serious AE start Date
- Inform consent date
- Adverse Event Serious i.e. (AESER)

Derivations:

- If Adverse Event Serious i.e. (AESER) = "YES" and Serious AE start Date >= Inform consent date, then we will consider it as serious adverse event (SAE)
- If AE start Date >= First Study drug administration date, then we will consider it as treatment-emergent adverse events (TEAEs)

20.1.2 Rates per 30 days and per subject year of total hypoglycemic events (symptomatic or asymptomatic)

Variables:

- What was the blood glucose level (mg/dL) prior to treating the event? (In eCRF "Hypoglycemia Events" form)
- Were signs/symptoms of hypoglycemia present, other than the blood glucose reading? (In eCRF "Hypoglycemia Events" form)
- Hypoglycemic event start date
- Date of Visit 2 (Week 0)
- Date of Visit 8 (Week 24)
- Date of Visit 9 (Week 28)
- Date of first IMP dose administration (In eCRF "Exposure" form)
- Date of last IMP administration (In eCRF "End of Study" form)

Derivations:

- The symptomatic and asymptomatic i.e. total hypoglycemic events will be identified based on derivation mentioned in section 19.1.1.
- Hypoglycemic event start date ≥ Date of Visit 2 (Week 0) and Hypoglycemic event start date ≤ Date of Visit 8 (Week 24) for accessing the hypoglycemic events from Day 0 to week 24.
- Hypoglycemic event start date ≥ Date of Visit 2 (Week 0) and Hypoglycemic event start date ≤ Date of Visit 9 (Week 28) for accessing the hypoglycemic events from Day 0 to week 28.

The formula used for calculation for rates per 30 days and per subject year (365.25 days) of total hypoglycemic events mentioned below:

The rate of hypoglycemic events per 30 days	$= \frac{\text{"The total number of events between the time points"}}{\text{"Actual number of days between the time points"}} * 30$
The rate of hypoglycemic events per year (365.25 days)	$= \frac{\text{"The total number of events between the time points"}}{\text{"Actual number of days between the time points"}} * 365.25$
Offset variable for per 30 days	$= log\left(\frac{\text{"The Duration of treatment exposure"}}{30}\right)$
Offset variable per year (365.25 days)	$= log\left(\frac{\text{"The Duration of treatment exposure"}}{365.25}\right)$

Note: For the duration of treatment exposure see formula mentioned in section 12.1

20.1.3 Incidence and rates per 30 days and per subject-year of nocturnal, severe, documented symptomatic and asymptomatic hypoglycemic events

Variables:

- What was the blood glucose level (mg/dL) prior to treating the event? (In eCRF "Hypoglycemia Events" form).
- Were signs/symptoms of hypoglycemia present, other than the blood glucose reading? (In eCRF "Hypoglycemia Events" form).
- When did the hypoglycemic event occur? (In eCRF "Hypoglycemia Events" form).
- Did the subject experience a severe hypoglycemic episode with neurological (cognitive) impairment requiring assistance from another person? (In eCRF "Hypoglycemia Events" form).
- Hypoglycemic event start date
- Date of Visit 2 (Week 0)
- Date of Visit 8 (Week 24)
- Date of Visit 9 (Week 28)
- Date of first IMP dose administration (In eCRF "Exposure" form)
  Date of last IMP administration (In eCRF "End of Study" form)

Derivation:

- Hypoglycemic event start date ≥ Date of Visit 2 (Week 0) and Hypoglycemic event start date ≤ Date of Visit 8 (Week 24) for accessing hypoglycemic events from Day 0 to week 24 (for the incidence and rate of hypoglycemic events endpoint).
- Hypoglycemic event start date ≥ Date of Visit 2 (Week 0) and Hypoglycemic event start date ≤ Date of Visit 9 (Week 28) for accessing hypoglycemic events from Day 0 to week 28 (only for the rate of hypoglycemic events endpoints).
- If in eCRF "Hypoglycemia Events" form the question if, the question "What was the blood glucose level (mg/dL) prior to treating the event hypoglycaemic event occur" result is less or equal to 54 mg/dL and the question "when did the hypoglycemic event occur" is answered as "BETWEEN BEDTIME AND PRIOR TO FIRST MEAL IN MORNING" then we will consider it as nocturnal hypoglycemia.
- If in eCRF "Hypoglycemia Events" form the question "What was the blood glucose level (mg/dL) prior to treating the event hypoglycaemic event occur" result is less or equal to 54 mg/dL and the question "Did the subject experience

a severe hypoglycemic episode with neurological (cognitive) impairment requiring assistance from another person" is answered as "YES" then we will consider this as severe hypoglycemia.

- For Documented symptomatic hypoglycemia and documented asymptomatic hypoglycemia see the derivation mentioned in section 19.1.1.

20.1.4 Change in HbA1c levels at Weeks 12 and 24 from baseline

Variables:

- HbA1c Results (we will get this data from laboratory in results forms)
- Start date of concomitant medication (From eCRF form: "Concomitant Therapy: Special Interest Hyperglycaemia (For rescue medication)")
- Date of first dose administration
- Date of collection of HbA1c at week 24

Derivations:

- Change in HbA1c = Post visit – Baseline visit
- If start date of concomitant medication (Special form) > Date of first dose administration, then this HbA1c result data will not be considered for analysis and we will consider this value as missing.
- If week 24 (HbA1C results) = missing or start date of concomitant medication (Special form) < Date of collection of HbA1c at week 24, then we will use LOCF i.e. previous visit value we will carry forward to visit (week 24).

20.1.5 Percentage of subjects reaching HbA1c targets ≤6.5% and <7% at week 24

Variables:

- HbA1c Results at week 24 (we will get this data from laboratory in results forms)

Derivations: Criteria for identifying the subjects reaching target level is mentioned below for both cases,

- HbA1c level ≤ 6.5%
- HbA1c level ≤ 7%

20.1.6 Change in FBG levels at Weeks 4, 8, and 12 from baseline

Variables:

- The question "Blood glucose concentration (mg/dL) before breakfast" in eCRF "Blood Glucose Monitoring (7-point reading)" form
- Start date of concomitant medication (From eCRF form: "Concomitant Therapy: Special Interest Hyperglycaemia (For rescue medication)")
- Date of first dose administration
- Date of collection of FBG at week 12.

Derivations:

- Change in FBG level = Post visit – Baseline visit
- If start date of concomitant medication (Special form) > Date of first dose administration, then this FBG result data will not be considered for analysis and we will consider this value as missing.
- If week 12 (FBG results) = missing or start date of concomitant medication (Special form) < Date of collection of FBG at week 12, then we will use LOCF i.e. previous visit value we will carry forward to visit (week 12).

20.1.7 Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24

Variables:

Below each Self-monitored 7-point SMBG level will be captured in eCRF "Blood Glucose Monitoring (7-point reading)" form

- Blood glucose concentration (mg/dL) before breakfast
- Blood glucose concentration (mg/dL) 2 hours after morning meal
- Blood glucose concentration (mg/dL) before midday meal
- Blood glucose concentration (mg/dL) 2 hours after midday meal
- Blood glucose concentration (mg/dL) before evening meal
- Blood glucose concentration (mg/dL) 2 hours after evening meal

- Blood glucose concentration (mg/dL) at 3AM (± 1 hour)

Derivations: Not Applicable

20.1.8 Change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline

Variables:

- All in above secondary endpoint (section 20.1.7) mentioned variables are applicable for this endpoint.
- Start date of concomitant medication (From eCRF form: "Concomitant Therapy: Special Interest Hyperglycaemia (For rescue medication)")
- Date of first dose administration
- Date of collection of 7-point SMBG levels at week 24.

Derivations:

- Change in 7-point SMBG levels = Post visit – Baseline visit
- If start date of concomitant medication (Special form) > Date of first dose administration, then this 7-point SMBG levels will not be considered for analysis and we will consider this value as missing.
- If week 24 (7-point SMBG results) = missing or start date of concomitant medication (Special form) < Date of collection of 7-point SMBG levels at week 24, then we will use LOCF i.e. previous visit value we will carry forward to visit (week 24).

20.1.9 Intrasubject variability, as measured by the standard deviation (SD) of 7-point SMBG levels

Variables:

- All in above secondary endpoint (section 20.1.7) mentioned variables are applicable for this endpoint.

Derivations:

Intrasubject variability, measured by SD (%) $= \frac{\text{S.D}}{\text{Mean}} * 100(\%)$

20.1.10 Basal insulin dose (U/day and U/kg/day)

Variables:

- Amount of Dose (Units) (In eCRF "Exposure Form")

Derivations:

- Basal insulin dose (U/kg/day) = $\frac{\text{Basal insulin dose (U/day)}}{\text{Weight (kgs)}}$

Note: Weight at corresponding visit will be used.

20.1.11 Change in weight and body mass index at Week 24 from baseline

Variables:

- Weight (In eCRF "DEMOGRAPHICS" form)
- Body Mass Index (BMI) (In eCRF "DEMOGRAPHICS" form)

Derivations:

- Change in weight = Post visit – Baseline visit
- Change in body mass index = Post visit – Baseline visit

20.1.12 Change in Insulin Treatment Satisfaction Questionnaire (ITSQ) score at Week 24 from Week 4

Variables:

- ITSQ score (for each subject we have 22 questions each question with 7 point scale in eCRF "Insulin Treatment Satisfaction Questionnaire (ITSQ)" form)

Derivations:

Transformed score domain $= 100 * \frac{7-\text{Raw Doamin score}}{6}$

Where, Raw domain score= mean of the items score in the domain for that subject

Transformed score Overall $= 100 * \frac{7-\text{Raw Overall score}}{6}$

Where, Raw overall score =mean of the items score for that subject

20.2 Analyses

20.2.1 Serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs)

Population: FAS and PPS

Stratification: Table: NA

Listing: NA

Statistics: The SAE and TEAE will be identified by using derivation mentioned in section 20.1.1. Summary statistics for SAEs and TEAEs will be presented as frequency and percentage (n and %) for table.

20.2.2 Rates per 30 days and per subject year of total hypoglycemic events (symptomatic or asymptomatic)

Population: FAS and PPS

Stratification: Table: NA

Listing: NA

Statistics: The rate that is the number of hypoglycemic events per subject over the study period i.e. Day 0 to week 24/week 28 will be summarised as continuous variables as (n, mean, standard deviation, standard error, median, minimum, maximum).

By using the formula mentioned in section 20.1.2, we will get the Rates per 30 days and per subject year (365.25 days) between two time points (i.e. baseline to end of treatment/study) and This Rates per 30 days and per subject year (365.25 days) will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum).

Summary statistics and efficacy table will be presented separately for baseline to end of treatment and baseline to end of the study.

The Negative Binomial Model without categorical variable i.e. the generalized linear model will be used with HbA1c as covariate and the log of the study treatment exposure time as offset variable.

The estimate, 95% confidence interval and p-value will be provided for efficacy table.

The Negative binomial regression equation is as follows:

$Y = \text{Offset variable} + \alpha + \beta (X)$

Where,

Y= The response rate of 30 days and per subject year for total hypoglycaemic events.

Offset variable = The log of study treatment exposure time for rates per 30 days and per subject year (See section 20.1.2 for formula)

α =Intercept

β =slope

X= Covariate i.e. Baseline HbA1c results

The hypothesis is as follows

H0: $\beta = 0$

i.e. The Rate of per 30 days and per subject year of total hypoglycaemic events not significantly differs depending on the Baseline HbA1c..

V/s

H1: $\beta \neq 0$

i.e. The Rate of per 30 days and per subject year of total hypoglycaemic events significantly differs depending on the Baseline HbA1c. events.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value $\geq$ 0.05 then we will conclude that there is no statistically significant change in rates per 30 days and per subject year of total hypoglycaemic events. i.e. Ho is accepted.

The sample SAS programme is as follows for negative binomial model:

```
proc genmod data=Dataset;
   model Response Rate=Baseline_HbA1c / cl dist=NB
link=log offset= offset variable;
   estimate "Model with Mean baseline HbA1C for rate per 30
days and per year" int 1 Baseline HbA1c observed mean /
exp;
   ods output estimates=Output dataset;
run;
quit;
```

20.2.3 Incidence and rates per 30 days and per subject-year of nocturnal, severe, documented symptomatic and asymptomatic hypoglycemic events

Population: FAS and PPS

Stratification: Table: NA

Listing: NA

Statistics: By using the formula mentioned in section 20.1.2, we will get the Rates per 30 days and per subject year (365.25 days) between two time points (i.e. baseline to end of treatment/study) for each hypoglycaemic events category separately.

The incidence and rates per 30 days and per subject-year for each below mentioned hypoglycemic events will be analysed similarly as mentioned in section 19.2.1 for incidence and section 20.2.2 for rates of hypoglycemic events.

- Nocturnal hypoglycemia
- Severe hypoglycemia
- Documented symptomatic hypoglycemia, and
- Asymptomatic hypoglycemia

20.2.4 Change in HbA1c levels at Weeks 12 and 24 from baseline

Population: FAS and PPS

Stratification: Table: By visit

Listing: by subject

Statistics: The actual and change from baseline data of HbA1c levels will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum and number with missing values).

The change from baseline variable and the missing HbA1c results imputation i.e. LOCF will be done by using derivations mentioned in section 20.1.4 and the efficacy tables will be presented for with and without imputed values separately for each population set.

The change in HbA1c level from baseline to Week 12 and baseline to week 24 will be analysed using the general linear model.

The change from baseline in HbA1c level as dependent variable and the baseline value of HbA1c as covariate.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The regression line for the general linear model without categorical variable is as follows:

$Y= \alpha + \beta (X)$

Where,

Y= The response change in HbA1c levels.

α =Intercept

β =slope

X= Covariate i.e. Baseline HbA1c results

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in HbA1c levels at week 12 and 24 from baseline depending on the baseline HbA1c.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in HbA1c levels at week 12 and 24 from baseline depending on the baseline HbA1c.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value $\geq$ 0.05 then we will conclude that there is no statistically significant change in HbA1c levels at week 12 and 24 from baseline i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
   model Y= X / s cl;
        estimate "Model with Mean baseline HbA1C" int 1
HbA1c_baseline mean /CL;
        ods output estimates=output dataset;
run; quit;
```

The listing of the HbA1c data will be provided containing the additional variable for identification of the HbA1C results measured after intake of rescue medication.

20.2.5 Percentage of subjects reaching HbA1c targets ≤6.5% and <7% at week 24

Population: FAS and PPS

Stratification: Table: NA

Listing: NA

Statistics: Subjects reaching HbA1c levels of ≤6.5% and <7% at Week 24 will be identified as derivation mentioned in section 20.1.5. we will analyse this endpoint descriptively as binary variable. Binary variable is as follows,

- Response=1, if HbA1c (%) meets target level
- Response=0, if HbA1c (%) does not meets target level

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. Subject with missing HbA1c data at Week 12 and Week 24 will be considered as not having reached the target (i.e. response =0 for binary variable).

This endpoint will be summarised for subject reaching the HBA1c target level for both cases as number and percentage (n and %) at week 24.

20.2.6 Change in FBG levels at Weeks 4, 8, and 12 from baseline

Population: FAS and PPS

Stratification: Table: NA

Listing: By Subject

Statistics: The actual and change from baseline data of FBG levels will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum and number with missing values) and the listing will be presented.

The change from baseline of FBG level variable will be calculated by using formula mentioned in section 20.1.6.

The change from baseline variable and the missing FBG results imputation i.e. LOCF will be done by using derivations mentioned in section 20.1.6 and the efficacy tables will be presented for with and without imputed values separately for each population set.

The change in FBG level from baseline to Week 4,8 and 12 will be analysed using the general linear model.

The change from baseline in FBG level as dependent variable and the baseline value of FBG level as covariate.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The regression line for the general linear model without categorical variable is as follows:

$Y = \alpha + \beta (X)$

Where,

Y= The response change in FBG levels.

α =Intercept

β =slope

X= Covariate i.e. Baseline FBG results

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in FBG levels at Week 4,8 and 12 from baseline depending on the baseline FBG level.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in FBG levels at Week 4,8 and 12 from baseline depending on the baseline FBG level.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value ≥ 0.05 then we will conclude that there is no statistically significant change in FBG levels at Week 4,8 and 12 from baseline i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
   model Y= X / s cl;
        estimate "Model with Mean baseline FBG" int 1 FBG
baseline variable mean /CL;
        ods output estimates=output dataset;
run;
quit;
```

Note: For the Change from FBG levels endpoint we are using the "7-point SMBG levels blood glucose parameter i.e. "Blood glucose concentration (mg/dL) upon awakening before breakfast (Fasting)" also, we have change form 7-point

SMBG level endpoints (See section 20.2.8) i.e. we will get same results from both parameters.

20.2.7 Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24

Population: FAS and PPS

Stratification: Table: By visit
Listing: By subject

Statistics: Self-monitored 7-point SMBG levels at baseline, Weeks 4, 8, 12, and 24 will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum) for table and the listing will be presented.

20.2.8 Change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline

Population: FAS and PPS

Stratification: Table: By Visit
Listing: NA

Statistics: The change in 7-point SMBG levels at Weeks 4, 8, 12, and 24 from baseline will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum).

The change from baseline of 7-point SMBG levels variable will be calculated by using formula mentioned in section 20.1.8.

The change from baseline variable and the missing 7-point SMBG results imputation i.e. LOCF will be done by using derivations mentioned in section 20.1.8 and the efficacy tables will be presented for with and without imputed values separately for each population set.

The change in 7-point SMBG levels from baseline to Week 4,8 and 12 will be analysed using the general linear model.

The change from baseline in 7-point SMBG levels as dependent variable and the baseline value of 7-point SMBG levels as covariate.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The regression line for the general linear model without categorical variable is as follows:

$Y= \alpha + \beta (X)$

Where,

Y= The response change in 7-point SMBG levels.

α =Intercept

β =slope

X= Covariate i.e. Baseline 7-point SMBG levels.

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in 7-point SMBG levels at Week 4,8,12 and 24 from baseline depending on the baseline 7-point SMBG level.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in 7-point SMBG levels at Week 4,8,12 and 24 from baseline depending on the baseline 7-point SMBG level.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value $\geq$ 0.05 then we will conclude that there is no statistically significant change in 7-point SMBG levels at Week 4,8,12 and 24 from baseline i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
   model Y= X / s cl;
        estimate "Model with Mean baseline 7-point SMBG
levels " int 1 SMBG baseline variable mean /CL;
        ods output estimates=output dataset;
run;
```

quit;

20.2.9 Intrasubject variability, as measured by the standard deviation (SD) of 7-point SMBG levels

Population: FAS and PPS

Stratification: Table: By visit
Listing: NA

Statistics: Intrasubject variability will be calculated by using formula mentioned in section 20.1.9 and this intrasubject variability will be presented for table.

20.2.10 Basal insulin dose (U/day and U/kg/day)

Population: FAS and PPS

Stratification: Table: By visit
Listing: NA

Statistics: The basal insulin dose (U/day and U/kg/day) will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum) for table.

20.2.11 Change in weight and body mass index at Week 24 from baseline

Population: FAS and PPS

Stratification: Table: By visit
Listing: By subject

Statistics: The change in weight and body mass index at week 24 from baseline will be summarised as (n, mean, standard deviation, standard error, median, minimum, maximum) and the listing will be presented.

The change from baseline of weight and body mass index variable will be calculated by using formula mentioned in section 20.1.11.

If the Week 24 result value for weight and body mass index is missing, then nearest previous visit value will be carried forward to week 24 results i.e. LOCF and Efficacy tables will be presented for with and without imputed values separately for each population set.

The change in weight and body mass index from baseline to Week 24 will be analysed using the general linear model.

The change from baseline in weight and body mass index as dependent variable and the baseline value of respective weight and body mass index as covariate.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The percentage change from baseline of weight in kg will also be summarised and efficacy table will be presented.

The regression line for the general linear model without categorical variable is as follows:

$Y= \alpha + \beta (X)$

Where,

Y= The response change in weight and body mass index.

α =Intercept

β =slope

X= Covariate i.e. Baseline weight and body mass index.

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in weight and body mass index at Week 24 from baseline depending on the Baseline weight and body mass index.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in weight and body mass index at Week 24 from baseline depending on the Baseline weight and body mass index.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value ≥ 0.05 then we will conclude that there is no statistically significant change in weight and body mass index at Week 4,8,12 and 24 from baseline i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
    model Y= X / s cl;
 estimate "Model with Mean baseline weight and body mass
index " int 1 weight and BMI baseline variable mean /CL;
          ods output estimates=output dataset;
run; quit;
```

20.2.12 Change in Insulin Treatment Satisfaction Questionnaire (ITSQ) score at Week 24 from Week 4

Population: FAS and PPS

Stratification: Table: By visit

Listing: By subject

Statistics: The listing will be presented for ITSQ score and the subject responses to the ITSQ will be reported as transformed overall and domain scores at Weeks 4 and 24 separately.

The domains are categorised as mentioned below:

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

Transformed domain and overall scores will be calculated based on formula mentioned in section 20.1.12. The transformed domain and overall scores will be summarized

by descriptive statistics (n, mean, median, SD, SE, minimum, and maximum) for table.

Missing data imputation will be performed as mentioned in section 8.2 point 4 and Efficacy tables will be presented for with and without imputed values separately for each population set.

The change in transformed domain and overall ITSQ scores score from week 4 to Week 24 will be analysed the general linear model. The change from week 4 in transformed domain and overall ITSQ scores as dependent variable and the week 4 value of transformed domain and overall ITSQ scores as covariate.

The estimate, 95% confidence interval and p-value will be summarised for efficacy table.

The regression line for the general linear model without categorical variable is as follows:

$Y= \alpha + \beta (X)$

Where,

Y= The response change in transformed domain and overall ITSQ scores.

α =Intercept

β =slope

X= Covariate i.e. week 4 transformed domain and overall ITSQ scores.

The hypothesis is as follows

H0: $\beta = 0$

i.e. There is no statistically significant change in transformed domain and overall ITSQ scores at Week 24 from week 4 depending on the week 4 transformed domain and overall ITSQ scores.

V/s

H1: $\beta \neq 0$

i.e. There is statistically significant change in transformed domain and overall ITSQ scores at Week 24 from week 4

depending on the week 4 transformed domain and overall ITSQ scores.

The above hypothesis will be tested based on α (alpha)=0.05, if the p-value ≥ 0.05 then we will conclude that there is no statistically significant change in transformed domain and overall ITSQ scores at week 24 from week 4 i.e. Ho is accepted.

The sample SAS programme is as follows:

```
proc mixed data=dataset;
    model Y= X / s cl;
        estimate "Model with Mean transformed domain and overall ITSQ scores" int 1 transformed domain and overall ITSQ scores baseline variable mean /CL;
        ods output estimates=output dataset;
run;
quit;
```

21. Other assessment

The Physical examination assessment will be presented in data listings and summarised as number and percentage (n and %) for the FAS and PP population set.

Physical examination data will be classified as follows:

- NORMAL
- ABNORMAL

22. Revision history

Version	Date	Change
1	02-Dec-19	Initial Version

23. Appendix 1: Programming Conventions for Tables, Data Listings and Figures (TLFs)

23.1 Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated in Table 20.1 will be used for the presentation of all TLFs.

Table 23.1: Output margin, page size and line size specifications

	Landscape
Margins (Inches):	
Top	1
Bottom	1
Left	1
Right	1
SAS® specifications:	
PAGESIZE	46
LINE SIZE	134

23.2 Fonts

The font type "Arial", "Courier", "Courier New" or "Times New Roman" must be used for tables, listings and figures, with a font size of minimum 9 and it should be consistent for the whole report. The font color must be black for tables, listings and figures.

Colors are allowed for figures as long as the data series can be distinguished clearly if printed in black and white paper.

23.3 Header and Footer Information

Headers and Footer should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- Prop case should be used for titles and column names in header.
- Titles should not contain quotation marks or footnote references.
- The sponsor name should appear in left-aligned, the purpose of the analysis indicated in SAP in center aligned in row 1 of header.

- The protocol number should appear in left-aligned, if available cutoff date in SAP in center aligned in row 2 of header.
- The TLF identification number should appear in row 3, centered in header.
- The TLF title should start in row 4, centered in header.
- The TLF population should appear in row 5, centered in header. The population will be spelled out in full, e.g. Safety analysis population in preference to Safety analysis population.
- Row 6 in header should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- In general, the analysis population count should appear in the column header in the form "(N=XX)" and column headings containing numbers should be centered.
- The page footnotes should provide the following information: the source (ADAM dataset with timestamp as date time, SDTM dataset with timestamp as date if applicable), the program (Program name with timestamp as date time) in two lines left aligned with a separation solid line above.
- The word "CONFIDENTIAL" should appear in row 1, centered aligned at footer in compiled file only.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right aligned at Footer for compiled TLFs if required.

23.4 Table and Data Listing Table, Listing and Figure (TLF) Conventions

23.4.1 General

- The first row in the body of the table or data listing will be blank.
- The left-hand column should start in Column 1.
- Rounding will be done with the SAS® function ROUND if applicable.
- Numerical values in tables should be rounded and not truncated as per section (23.4.2.1) for respective statistics.
- Numerical values will be center aligned.

- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug will be appeared first in tables with treatment group as columns.
- The width of the TLF should match the line size.

23.4.2 Univariate statistics

23.4.2.1 Continuous variables statistics

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, SE, IQR, minimum, median and maximum).
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum, maximum: N.
  - CV (%): N+2.
  - Mean and median: N +1.
  - SD: N + 2.
  - SE: N+2.
  - IQR: N+2.

23.4.2.2 Categorical variables statistics (Frequencies and percentages [n and %])

- The percentages should be reported inside parentheses, with one space between the count and the left parenthesis of the percentages. An example is given below:
  - 124 (645)
- Percentages will be reported to one decimal place, except percentages <100.0 but >99.9 will be presented as '>99.9' (e.g., 99.99 is presented as >99.9); and percentages <0.1 will be presented as '<0.1' (e.g., 0.08 is presented as <0.1). Rounding will be applied after the <0.1 and >99.9 rule.
  - (<0.1)
  - (6.8)
  - (>99.9)
- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

- Where counts are zero, then counts and percentages will be represented as "0 (0.0)" respectively in the table.

23.4.3 Confidence intervals (CIs)

- CIs should be presented with one additional decimal place as that of the raw data.
- CIs will be presented as (lower bound, upper bound).

23.4.4 P-values

- P-values should be reported to four decimal places.

23.4.5 Ratios

- Ratios should be reported with one additional decimal place as that of the raw data.

23.4.6 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

23.4.7 Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in data listings.

23.5 Tables, Listings and Figure output conventions

The compiled final file will be presented in PDF format with TOC for listing and table/figures separately. The Table, Listing and Figures will be provided in RTF (if requested form sponsor) and PDF files using the SAS® Output Delivery System (ODS).

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all participants treated, unless otherwise specified.

By default, descriptive statistics for quantitative measurements will include the number of participants (n), mean, standard deviation (SD), minimum, median and maximum

23.6 Dates and times

In footer of the TLFs date and time will be presented in format ddMMMyyyy and hh: mm.

23.7 Spelling format

The spelling format to be used is English US.

23.8 Presentation of treatment groups

This study is single arm so, we have only one treatment group i.e. Basaglar.

23.9 Presentation of visits

- Visit 1 (Week -2)
- Visit 2 (Week 0)
- Visit 3 (Week 4)
- Visit 4 (Week 8)
- Visit 5 (Week 12)
- Visit 6 (Week 16)
- Visit 7 (Week 20)
- Visit 8 (Week 24)
- Visit 9 (Week 28)

24. Appendix 2: Partial date conventions for adverse events.

The whole missing date will not be imputed for this study and only partial date imputation will be performed. Conventions pertaining to partial dates are presented in Table 24.1.

Table 24.1: Algorithm for Partial Date Imputation of Adverse Event

ADVERSE EVENT	MISSING	IMPUTATION
Start Date	Day	If AE start month = Treatment start month and AE start year = Treatment start year, then AE start day= Treatment start day Otherwise AE start day=01
	Day and Month	If AE start year = Treatment start year, then AE start day and month = Treatment start day and month Otherwise AE start day = 01 and AE start month=Jan
	Day, Month and Year	No imputation will be performed
End Date	Day	If AE end month = Date of study completion/discontinuation month and AE end year = Date of completion/discontinuation year, then AE end day = date of completion/discontinuation day Otherwise AE End day = Last day of respective month, used if this does not result in a date after the subject's trial exit date (e.g. death) in which case the trial exit date will be used
	Day and Month	If AE end year = Date of study completion/discontinuation year, then

	AE End day and month = Date of study completion/discontinuation day and month Otherwise AE end day = Last day of respective month and AE end month = Last month of the year, used if this does not result in a date after the subject's trial exit date (e.g. death) in which case the trial exit date will be used
Day, Month and Year	No imputation will be performed