SYNOPSIS

Name of Sponsor/Company:	Biocon Limited
Name of Finished Product:	Insulin Tregopil (IN-105) Tablets
Name of Active Ingredient:	Methoxy triethylene glycol propionyl–insulin.
Title of Study:	An Open Label, Multi-center, Randomized, Parallel Group Phase II/III Clinical Study to Evaluate the Efficacy and Safety of Insulin Tregopil (IN-105) Compared with Insulin Aspart in the Treatment of Patients with Type 2 Diabetes Mellitus on Stable Dose of Metformin and Insulin Glargine.
Protocol No:	TREGO-DM2-03-I-01
Study centers:	The study will be conducted at approximately 40 centers in India.
Study duration: The study duration will be approximately 37 weeks for Part I and for Part II of the study.	**Phase:** II/III

Part I

Primary Objective

To compare the efficacy of 2 doses of Insulin Tregopil versus Insulin Aspart (IAsp) in Type 2 Diabetes Mellitus (T2DM) patients who are on stable dose of metformin and insulin glargine.

Secondary Objective

To compare the safety of 2 doses of Insulin Tregopil versus IAsp in T2DM patients who are on stable dose of metformin and insulin glargine.

Part II

Primary Objective

To compare the efficacy of Insulin Tregopil versus IAsp in T2DM patients who are on stable dose of metformin and insulin glargine.

Secondary Objective

To compare the safety of Insulin Tregopil versus IAsp in T2DM patients who are on stable dose of metformin and insulin glargine.

Exploratory Objective

To evaluate the additional glycemic variables and cardiovascular outcomes of Insulin Tregopil and IAsp in T2DM patients who are on stable dose of metformin and insulin glargine.

Methodology: The study will be conducted in 2 parts, Part I and Part II. Part I of the study is a Phase II multi-center, randomized, open label clinical study to evaluate the efficacy and safety of Insulin Tregopil (2 dose levels: 30 mg, 45 mg) compared with IAsp in the treatment of T2DM patients. Part II of the study is the Phase III, multi-center, randomized, open label clinical study to evaluate the efficacy and safety of Insulin Tregopil compared with IAsp in the treatment of T2DM patients. For Part I and Part II, the study duration will be approximately 37 weeks (3 weeks Screening, 8 weeks Run-in, 24 weeks Treatment, 2 weeks Safety follow-up). An Independent Data and Safety Monitoring Board (DSMB) will evaluate the data from Part I of the study. Part II of the study will be initiated after approval from the office of Drug Controller General of India and DSMB recommendation based on review of data from Part I of the study. Additionally, evaluation of data by DSMB will be performed during Part II of the study. Further details of the DSMB meetings including frequency of meetings for evaluation of data will be provided in the Statistical Analysis Plan (SAP)/DSMB charter.

In both Part I and Part II of the study, T2DM patients with glycated hemoglobin (HbA1c) 7.5 to 10% (both inclusive), on stable dose of metformin ± oral antidiabetic drugs (OADs) ± basal insulin who are eligible for insulin glargine administration as per investigator discretion and who satisfy the selection criteria will be enrolled. The eligible patients will go through a **Run-in period** of 8 weeks. At the time of enrollment into the Run-in period, all OADs except stable dose of metformin will be discontinued; insulin glargine will be administered subcutaneously. The Run-in period will have an initial 4 weeks of insulin glargine **dose titration**

period and subsequent 4 weeks of **dose stabilization period**. The patients who are already on a basal insulin will be switched over to/continued on insulin glargine and those who are insulin naïve will be started on insulin glargine. Initiation and titration of insulin glargine dose will be instructed to the patient by investigator/designee as per the titration algorithm and/or as per the investigator judgement wherein the deviation in dose from the recommended titration algorithm must be documented and explained. The titration will be monitored by a centralized titration review team and such deviations will be evaluated by the titration review team to conclude if the explanation is agreeable or a protocol deviation needs to be reported. Additional 1 week (i.e., up to 5 weeks) of titration is permitted, however, the total duration of Run-in period should not be extended beyond 8 weeks.

At the end of 8 weeks Run-in period, patients will enter the **treatment period** of 24 weeks and will be allocated (randomization by minimization method) to 3 treatment arms (Part I) or randomized to 2 treatment arms (Part II); if found eligible for randomization according to the following randomization criteria: HbA1c $\geq 7\%$ and $\leq 9\%$, fasting plasma glucose (FPG) ≤ 140 mg/dL, 2-hour post-prandial glucose (PPG) ≥ 180 mg/dL after standardized test meal evaluated at central laboratory, and acceptable compliance as concluded by the investigator discretion, and based on the specified compliance criteria. The blood sample for randomization criteria assessment will be drawn at the Day -7 visit. Any new information received during the Run-in period indicating ineligibility of the patient based on selection criteria will result in exclusion of the patient from randomization into the treatment period. Randomization will ensure an equal distribution of study patients across the treatment arms of the study.

In both Part I and Part II of the study, the patient allocation into the treatment arms will be stratified by: Baseline HbA1c at randomization: 7 to 8% or > 8%; OAD/basal Insulin use at Screening: (metformin alone; metformin + other OADs; metformin ± OADs + basal insulin); Baseline body mass index (BMI) at randomization: ≤ 25 kg/m^2 and > 25 kg/m^2; Gender: Male/Female; Metformin dose: ≥ 1500 mg/day; < 1500 mg/day.

Part I of the study will have 3 treatment arms: Insulin Tregopil 30 mg, Insulin Tregopil 45 mg, and IAsp arms. Patients will be allocated (by minimization method) in 1:1:1 ratio into the 3 treatment arms. The first 5 patients in the Insulin Tregopil 45 mg arm in Part I of the study will be observed for any safety concerns like severe hypoglycemia for approximately up to 24 hours after administration of first dose before continuing with allocation of patients in this arm.

Part II of the study will have 2 treatment arms: Insulin Tregopil arm (starting dose of 30 mg with titration up to a maximum dose of 45 mg or starting dose of 45 mg; determined by Part I data evaluation) and IAsp arm.

In the Insulin Tregopil arms, the respective doses (30 mg, 45 mg) of Insulin Tregopil will be administered orally 10 ± 2 minutes prior to each major meal (breakfast, lunch and dinner) starting at the randomization visit .However, at Baseline (V9) visit, the first dose of the study drug/comparator drug will be administered after completion of STM (i.e., after collection of last PD blood samples at 240 minutes). In the IAsp arm, specific doses of IAsp will be administered subcutaneously, within 5 minutes prior to each major meal starting at the randomization visit.However, at Baseline (V9) visit, the first dose of the study drug/comparator drug will be administered after completion of STM (i.e., after collection of last PD blood samples at 240 minutes).

In the first 4 weeks post-randomization, titration of Insulin Tregopil and IAsp dose will be performed based on the titration criteria specified and respective dose titration algorithms. The titration will be based on meal-specific average of the self-monitored blood glucose (SMBG) levels (pre-meal and/or post-meal [as applicable] for IAsp and post-meal for Insulin Tregopil) on 2 days as per the SMBG values performed in the week leading up to the titration visit. The optimum dose regimen identified at the end of the titration period of 4 weeks will be administered for the rest of the treatment period up to 24 weeks, except in patients where investigator discretion for additional titration in the presence of persistent lack of PPG control is allowed; up to a maximum of 8 weeks after randomization. Persistent lack of PPG control is considered, if 3 values in a single week for a particular meal and/or average meal-specific SMBG values over a week or more show a 2-hour PPG > 180 mg/dL. 2-hour PPG value following a standardized test meal will be used for confirmation of lack of PPG control before allowing titration of prandial insulin between 4 and 8 weeks after randomization. The titration will be performed as per the titration algorithm, while investigator discretion is allowed; where in, the deviation in dose from the recommended titration algorithm must be documented and explained. The titration will be monitored by a centralized titration review team and such deviations will be evaluated by the titration review team to conclude if the explanation is agreeable or a protocol deviation needs to be reported.

The maximum dose of Insulin Tregopil is 45 mg prior to each of the 3 major meals of the day.

Note: after randomization, up-titration of Insulin Tregopil and IAsp is allowed for up to a maximum of 8 weeks and no titration of insulin glargine (an inherent ± 10% variation is acceptable) or metformin is allowed throughout the treatment period. Up-titration of Insulin Tregopil and IAsp is not allowed between 8 and 24 weeks of treatment period. Only down-titration for safety related reasons and re-up titration to the last higher dose based on the titration criteria, titration algorithm and the hypoglycemia criteria is allowed. Patients will be switched back to standard of care after 24 weeks of treatment period and will be followed-up for 2 weeks after the completion of treatment period during which adverse events (AEs) related to Insulin Tregopil or IAsp will be assessed.

The rescue criteria and hypoglycemia criteria will apply to patients enrolled in both Part I and Part II of the study. The data from Part I and Part II of the study will be analyzed and will be presented in the clinical study report.

Surveillance of insulin titration will be performed centrally (review of SMBG values, insulin dose change, FPG, PPG and HbA1c values) by a Titration review team. The team will daily review the information received and follow-up on significant deviations from the titration algorithm. Detailed plan on data review by titration review team and communication plan for titration advice from the titration review team to the investigator will be detailed in a separate titration review manual.

Efficacy assessments will include: HbA1c assay, 9-point SMBG; standardized test meal for PPG assessment, FPG, continuous glucose monitoring (CGM), glycated albumin, fasting insulin, C-peptide, proinsulin; Diabetes Treatment Satisfaction Questionnaire, Diabetes Treatment Satisfaction Questionnaire change and Diabetes Self-management Questionnaire; body weight.

Safety assessments will include: vital signs, physical examination, 12-lead electrocardiogram (ECG), standard clinical laboratory evaluations including hematology, clinical chemistry (including fasting lipid profile), 3-point SMBG, symptomatic hypoglycemia self-monitoring, urinalysis and review of AEs.

7-point SMBG will be performed during titration period.

Planned number of patients:	**Part I**: Approximately 90 patients will be allocated to the 3 treatment arms (Insulin Tregopil 30 mg, Insulin Tregopil 45 mg and IAsp arms) in a 1:1:1 ratio, with 30 patients in each arm. **Part II**: Approximately 268 patients will be randomized to Insulin Tregopil and IAsp arms in 1:1 ratio (approximately 134 patients in each arm). Insulin Tregopil dose (30 mg or 45 mg) in Part II will be determined based on the evaluation of Part I data.
Inclusion/exclusion criteria:	The same inclusion and exclusion criteria will be applicable for Part I and Part II of the study: **Inclusion criteria** Patients may enter the study only if they meet all of the following inclusion criteria: 1. Male and female patients between the ages of 18 to 70 years, both ages inclusive, who have provided written informed consent for participation in the study and willing to comply with study procedures. 2. Patients with an established diagnosis of T2DM and a duration of diabetes mellitus of at least 6 months at Screening based on criteria given below as per American Diabetes Association (ADA) 2017 guidelines:

	o HbA1c $\geq$ 6.5% **OR**
	o FPG $\geq$ 126 mg/dL. (fasting is defined as no caloric intake for at least 8 hours.) **OR**
	o 2-hour prandial glucose (PG) level of $\geq$ 200 mg/dL during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organisation (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. **OR**
	o In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$ 200 mg/dL.
	(If there is suspicion, the investigator can do a fasting plasma C-peptide [Levels < 0.3 nmol/L is indicative of Type 1 Diabetes Mellitus (T1DM) and would need the patient to be excluded]).
	3. Patients should be on a stable dose of metformin (at least 1500 mg daily [daily dose of at least 1000 mg is permitted if intolerant to 1500 mg dose]) for a period of at least 3 months prior to Screening.
	4. Patients eligible for initiation of or already receiving insulin glargine.
	5. Body mass index of 18.5 to 35.0 kg/m^2 (both values inclusive).
	6. Patients on stable diet and physical activity practices in the 3 months prior to Screening with stable weight, (with no more than 5 kg gain or loss), in the 3 months prior to Screening; this information will be obtained from the patient history.
	7. Hemoglobin $\geq$ 10.0 g/dL.
	8. HbA1c of 7.5 to 10.0% (both inclusive).
	9. All women of childbearing potential (i.e., pre-menopausal) should use at least 2 reliable forms of contraception during the study, one of which must be a physical barrier method and should agree to continue the contraceptive measures during the study and for at least 10 days after receiving the last dose of the investigational medicinal product (IMP)/comparator drug.
	a. Periodic abstinence (e.g., calendar method, ovulation-symptothermal, and post-ovulation methods) and withdrawal method are not acceptable methods of contraception.
	b. Post-menopausal females must have had no regular menstrual bleeding for at least 1 year prior to Screening. Follicle-stimulating hormone (FSH) test can be done for confirmation if necessary as per investigator discretion

(Plasma FSH level of > 40 IU/L is indicative of menopause).

    c. Female patients who report surgical sterilization must have had the procedure at least 6 months prior to Screening. If not, appropriate contraceptives should be used as described above.

10. All female patients of childbearing potential (irrespective of sterilization status) must have negative serum pregnancy test result at Screening.

11. Male patients must be using 2 acceptable methods of contraception one of which must be a physical barrier method, (e.g., spermicidal gel plus condom; condom plus partner is sterilized at least 6 months prior) for the entire study duration and for at least 10 days following the last IMP/comparator drug administration.

Exclusion criteria

Patients will not be allowed to enter the study for any of the following reasons:

1. History or presence of a medical condition or disease that in the investigator's opinion would place the patient at an unacceptable risk from study participation or interfere with the patient's compliance to the study procedures.

2. History of hypersensitivity or known contraindication to any of the active or inactive ingredients or excipients of Insulin Tregopil, insulin, insulin analog preparations (including IAsp), or metformin.

3. Patients known to be positive for autoimmune antibodies indicative of T1DM. e.g., Glutamate decarboxylase antibodies, anti-insulin antibodies.

4. Treatment with glucagon-like peptide 1 agonists within 12 weeks prior to Screening.

5. History of regular use (> 2 weeks of continuous therapy) of any premix or prandial insulin prior to Screening. (previous use of prandial insulin is allowed in case of hospitalization or for gestational diabetes or a severe condition; requiring intermittent use of prandial insulin for less than 2 weeks, but not during the last 6 months prior to Screening visit).

6. Ongoing treatment with OADs (eg, thiazolidinedione's) contraindicated or unapproved for combination treatment with insulin (according to applicable product information) at

Screening visit.

7. Presence of gastrointestinal (GI) disorders or conditions known to significantly alter the absorption of orally administered drugs or significantly alter upper GI or pancreatic function including but not limited to GI motility disorders like gastroesophageal reflux disease, irritable bowel syndrome, inflammatory bowel disease (Crohn's disease), malabsorption syndrome.

8. Patients on or likely to start use of drugs including but not limited to colesevelam, acarbose, pramlintide, regular use of metoclopramide, domperidone; which interfere with the absorption of oral drugs at the time of Screening or within 5 times the half-life of the drug, whichever is longer.

9. History of $\geq$ 2 episodes of severe hypoglycemia (as per ADA 2017) within the 6 months before Screening and/or presence of hypoglycemia unawareness as judged by the investigator.

10. History of > 1 episode of hyperglycemic hyperosmolar coma or hospitalization for uncontrolled diabetes (e.g., diabetic ketoacidosis), within the 6 months prior to Screening.

11. Any clinically significant abnormality in 12-lead ECG or safety laboratory tests deemed clinically relevant by the investigator at Screening.

12. Serological evidence of human immunodeficiency virus, hepatitis B (HbsAg) or anti-hepatitis C antibodies at Screening.

13. History of drug or alcohol dependence or abuse during the 1 year prior to Screening.

14. Have received another investigational drug within 90 days (or as per local regulations, if any) prior to Screening or if the Screening visit is within 5 half-lives of another investigational drug (whichever is longer).

15. Previous participation in this study (participation is defined as enrolment in the Run-in period).

16. Patients with the following secondary complications of diabetes:

   o Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy (by the investigator, site ophthalmologist or an optometrist; as per standard site practice) within 6 months prior to Screening.

   o Renal dysfunction indicated by modification of diet in renal disease, estimated glomerular filtration rate < 45 mL/min/1.73 m^2 and/or diabetic nephropathy and/or clinical nephrotic syndrome at Screening.

    o   History or presence of severe form of neuropathy or signs and symptoms of severe cardiac autonomic neuropathy.

    o   Patients with non-traumatic amputation (at any time) or clinically significant vascular procedure as a complication of diabetes within 1 year prior to Screening.

    o   History of diabetic foot ulcer or non-healing diabetic ulcers in the 1 year prior to Screening.

17. Any elective surgery requiring hospitalization planned during the study period.

18. Clinically significant major organ disease at the time of Screening includes but not limited to:

    o   Uncontrolled (despite treatment) or untreated severe hypertension defined as systolic blood pressure above or equal to 180 mmHg or diastolic blood pressure above or equal to 100 mmHg (Stage 2 as per American Heart Association classification of hypertension)

    o   Uncontrolled hyperlipidemia (total cholesterol > 400mg/dL or very high serum triglycerides [≥ 500 mg/dL] levels as per American Association of Clinical Endocrinologists classification)

    o   Uncontrolled hyperthyroidism or hypothyroidism as per investigator's assessment (investigator may conduct thyroid function test, if required for assessment).

    o   Impaired hepatic function (alanine aminotransferase or aspartate aminotransferase value > 2 times the upper limit of the reference range or serum bilirubin > 1.5 times the upper limit of the reference range).

19. Clinically significant cardiovascular and/or cerebrovascular disease within 12 months before Screening including, but not limited to unstable angina, myocardial infarction, Class III or Class IV congestive heart failure according to the New York Heart Association criteria, valvular heart disease, cardiac arrhythmia requiring treatment, pulmonary hypertension, cardiac surgery, coronary angioplasty, stroke or transient ischemic attack.

20. Patients who needed in the last 12 months or may require during the study period, systemic (including oral, intravenous, intramuscular) glucocorticoid therapy for more than 2 consecutive weeks.

21. History of cancer within the past 5 years prior to Screening, except successfully treated non-melanoma skin cancer or cervical carcinoma in situ.

22. Patients who have donated blood or plasma within 12 weeks prior to Screening (450 mL blood or equivalent).

23. Patients having hematological disorders (including but not limited to sickle cell disease, acquired and inherited hemolytic anemias, severe iron deficiency anemia) which can affect the HbA1c assessment.

24. Patients who take acetaminophen (paracetamol) containing medications on a regular basis and are unable or unwilling to substitute with a medication not containing acetaminophen (paracetamol) the day before placement of the sensor and throughout each 7-day CGM sensor periods.

25. Patients, who in the opinion of the investigator, may not be able to understand and/or comply with the study procedures including answering the study questionnaires, maintaining a stable diet and exercise pattern (e.g., tendency to go on prolonged fast), frequent time zone travels etc., will be excluded from the study.

Additional post Run-in inclusion criteria for Part I and Part II (Randomization criteria):

- FPG of ≤ 140 mg/dL;
- 2-hour PG of ≥ 180 mg/dL after standardized test meal;
- HbA1c $\geq 7\%$ and $\leq 9\%$.

Note: All the above assessments will be performed at the central laboratory. One retest for the above values performed at central laboratory may be permitted with the last observation considered confirmatory.

- Acceptable compliance will be evaluated by the investigator as per the specified criteria below:
  - $\geq 80\%$ compliance with insulin glargine administration (dose and timing) during Run-in.

  - $\geq 10/14$ time points of the SMBG measurements during Run-in period (each of the SMBG measurements includes 14 total time points i.e., 2 days of the 7-point SMBG that will be performed on any 2 days of the week leading to the titration visit).

Any new information received during the Run-in period indicating ineligibility of the patient will result in exclusion of the patient at treatment period entry/randomization.

Test product, dose and mode of administration:	Investigational medicinal product (study drug): Insulin Tregopil (IN-105) Formulation: 15 mg tablet

	Dose 1: Dose 1 is the dose for 30 mg Insulin Tregopil arm. Dose starts at 30 mg thrice daily (TID) oral; (2 tablets of 15 mg each administered 10 ± 2 minutes prior to the 3 major meals of the day) and titration determined by the investigator as per the titration algorithm and titration criteria specified in the protocol.
	Dose 2: Dose 2 is the dose for 45 mg Insulin Tregopil arm. Dose starts at 45 mg TID (3 tablets of 15 mg each administered 10 ± 2 minutes prior to the 3 major meals of the day) and titration determined by the investigator as per the titration algorithm and titration criteria specified in the protocol.
	Mode of Administration: Oral; intact tablet to be swallowed with water.
Comparator product, dose, and mode of administration:	**Comparator**: Insulin Aspart 100 U/mL; prior to the 3 major meals of the day (within 5 minutes prior to each meal). Dose will start at 4 U/meal and titration is determined by the investigator as per titration algorithm and titration criteria specified in the protocol. Mode of Administration: Subcutaneous injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region.
Supportive drugs:	• Insulin glargine 100 U/mL; once daily; dose determined by the investigator as per titration algorithm and specified titration criteria Mode of Administration: Subcutaneous injection Dose preferably administered in the evening; at the same time every day. • Metformin (Extended release/immediate release tablets) to be continued at the stable dose regimen; once daily or twice daily or as applicable.

Criteria for evaluation:

Part I

Primary Endpoint:

Change from Baseline in HbA1c at 24 weeks.

Secondary Endpoint:

Number of severe or clinically significant hypoglycemia events during 24 weeks of treatment period.

Part II

Primary Endpoint:

Change from Baseline in HbA1c at 24 weeks.

Secondary Endpoints:

- Change from Baseline in HbA1c at 12 weeks.

- Proportion of patients achieving HbA1c < 7% at Week 12, and Week 24; without reported clinically significant or severe hypoglycemic events between end of Week 8 and Week 24 (i.e., after the titration period of 8 weeks for prandial insulin [Insulin Tregopil/IAsp]).

- Frequency of hypoglycemia events during the 24 week treatment period.

- Change from Baseline in weight at Week 24.

- Change in lipid profile (triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol) from Baseline over 24 weeks.

- Change from Baseline in the mean 60 minutes, 90 minutes and 120 minutes PPG excursion assessed

from standardized test meal at Week 12 and Week 24.

- Change from Baseline in the mean PPG excursion (overall mean and meal-specific [breakfast, lunch and dinner] mean) at 60 minutes and 120 minutes assessed from 9-point SMBG at Week 8, 12, 16, and 24.

- Incidence and severity of AEs based on laboratory and clinical safety parameters over 24 weeks.

- Immunogenicity: incidence and change from Baseline in the relative levels of anti-drug antibody over 24 weeks.

- Area under the glucose curve (AUC/time) below 70 mg/dL derived from CGM at Baseline and Week 24.

Exploratory Endpoints:

- Proportion of treatment-emergent major cardiovascular AEs (cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction).

- Change in glycated albumin, levels over 24 weeks

- Change in fasting insulin, C-peptide and proinsulin levels in Insulin Tregopil arm over 24 weeks.

- Patient reported outcomes, by Diabetes Treatment Satisfaction Questionnaire change score; change from Baseline over 24 weeks.

- Change in patient reported outcomes of monitoring of primary diet and physical exercise pattern from Baseline over 24 weeks by Diabetes Self-Management questionnaire.

- Area under the glucose curve (AUC)/time above 180 mg/dL (over 180 minutes post-meal for 3 major meals of the day) derived from CGM at Baseline and Week 24.

- Percentage of time with glucose in the following ranges

  - ≤ 70 mg/dL
  - > 180 mg/dL (over 180 minutes post-meal for 3 major meals of the day).

- Exploratory measures of glycemic control and variability derived from CGM at Baseline and Week 24.

Statistical methods:

Sample size determination

Part I of the study is an exploratory study and no statistical rationale is defined for the estimation of sample size. The minimum number of 30 patients in each of Insulin Tregopil 45 mg, Insulin Tregopil 30 mg and IAsp treatment arms are deemed adequate for the assessment of safety and efficacy.

The primary objective of Part II of the study is to compare the efficacy of Insulin Tregopil versus IAsp in T2DM patients who are on stable dose of metformin and insulin glargine. This will be done by evaluating if Insulin Tregopil is non-inferior to IAsp in terms of glycemic control effect as assessed by mean change from Baseline in HbA1c after 24 weeks of treatment using a non-inferiority margin of 0.4%. Sample size in Part II of the study is determined based on this primary objective.

Using a one-sided confidence interval (CI) with a confidence level of 97.5%, a non-inferiority margin of 0.4%, a true difference of 0, and based on previous clinical studies and literature a standard deviation of 1% in change in HbA1c after 24 weeks of treatment, a total of 114 patients per treatment arm would give 85% power to conclude non-inferiority when comparing Insulin Tregopil versus IAsp. In order to account for an expected rate of patients discontinuing from study drug/comparator drug of 15% (based on previous clinical studies), and further taking the (conservative) assumption that these patients are excluded from the Per Protocol analysis set, 134 patients should be randomized into each of IAsp and Insulin Tregopil treatment arms (a total of 268 patients).

Analysis methods

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation, 95% confidence interval (CI), median, minimum, and maximum. Categorical variables will be summarized using proportions (counts and percentages). All statistical hypothesis tests will be performed at 5% level of significance (two-sided test). All statistical analysis will be performed using SAS® version 9.4 (or higher version) for Windows (SAS Institute Inc., USA).

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study medication (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding Baseline value.

Data on patient disposition (number of patients screened, number of screen failures with reasons, number of patients enrolled, number of Run-in failures with reasons, number of patients randomized, number of patients completed, number of patients discontinued and reason for discontinuation) will be presented using counts and percentages. Number of patients enrolled in each study center will be summarized as counts and percentages.

Demographic and Baseline evaluations for the intent-to-treat analysis set will be presented for Insulin Tregopil and IAsp arms.

Detailed statistical methodology for the analysis of efficacy and safety data, statistical hypothesis and handling of missing data, data presentation for Part I and Part II data will be described in SAP and will be finalized before database lock.

Efficacy

The primary endpoint is change from Baseline in HbA1c at 24 weeks.

Change from Baseline in HbA1c at 24 weeks of treatments will be analyzed using mixed model for repeated measures (MMRM) where all available post-baseline HbA1c measurements obtained up to EoT will be entered as the dependent variables; visit and treatment are included as fixed factors, with Baseline HbA1c and stratification factor variables as covariates. Furthermore, the interaction terms of visit by treatment, visit by stratification factors and visit by Baseline HbA1c will be included in the model. An unstructured covariance matrix for HbA1c measurements within the same patient will be employed. Regarding missing data, this analysis approach relies on the assumption that data are missing at random. The estimated differences between each Insulin Tregopil and IAsp at Week 24 and corresponding two-sided p-value and 95% CI will be presented. Possible effects of other covariates may also be investigated. Details of such analyses will be described in the SAP.

The model will be fitted to all the data simultaneously (all treatment arms) and from this model the relevant treatment differences will be estimated.

In Part I of the study, efficacy data will be evaluated and compared for Insulin Tregopil 45 mg versus IAsp and Insulin Tregopil 30 mg versus IAsp using descriptive statistics. Additionally, Part I primary efficacy endpoint data will be evaluated and compared for Insulin Tregopil 45 mg versus IAsp and Insulin Tregopil 30 mg versus IAsp using the same statistical analysis methods which are planned for Part II study data without testing any hypothesis.

In Part II of the study, efficacy data will be evaluated for Insulin Tregopil versus IAsp using Non-inferiority test hypothesis.

Non-inferiority will be considered confirmed if the upper bound of the 2-sided 95% CI is below or equal to 0.4%.

Non-inferiority test hypothesis:

H_0: D > 0.4% against H_A: D ≤ 0.4%

where D is the difference in mean change in HbA1c (Baseline to Week 24) between the 2 treatment arms

Non-inferiority of Insulin Tregopil against IAsp will be tested.

After non-inferiority is established, superiority of Insulin Tregopil against IAsp may be tested. Superiority for change in HbA1c will be claimed if the upper limit of the two-sided 95% CI for the estimated difference in mean change in HbA1c is below 0%.

When establishing non-inferiority for change in HbA1c, the analysis will be based on the Intent-to-treat (ITT) and supplemented by an analysis with the Per protocol analysis set as supportive evidence. The ITT will be

used in the analysis when concluding superiority.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be tabulated in incidence tables by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be summarized by SOC, PT, and treatment arms. Treatment-emergent AEs will be further summarized by maximum severity and relationship to study medication. Prior and concomitant medications will be summarized by treatment.

Number of hypoglycemic events during 24 weeks of treatment will be summarized by treatment. Details of various analyses and summary data presentations for hypoglycemic data will be described in the SAP.

Other routine safety assessments such as vital signs, 12-lead ECG and safety laboratory tests will be summarized by treatment arms using statistics for continuous or categorical data, as appropriate.