CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

A prospective, multi-center, Phase 1b/2a study to assess the safety and tolerability of different doses of AG019 administered alone or in association with teplizumab in patients with clinical recent-onset Type 1 Diabetes Mellitus (T1D).

Sponsor Study Code: AG019-T1D-101

Sponsor	Precigen ActoBio T1D, LLC 20374 Seneca Meadows Parkway Germantown, MD 20876 USA
Product/Compound/Device	AG019
Phase of the study	Phase 1b/2a
EudraCT number	2017-002871-24
Author	XXX Senior Biostatistician
Company	XXX
Address	XXX
Telephone number	
Version	Final
Date	28-05-2021

SIGNATURES

Sponsor Study Code: AG019-T1D-101

Author

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Signature: _____ Date/time: _____
Add time to all dates if on the same day as unblinding.

Reviewing Statistician

Name, highest academic level, job title:	XXX
Company	XXX

Signature: _____ Date/time: _____

Sponsor Approval

Name, job title:	XXX
Company	Precigen ActoBio T1D, LLC

Signature: _____ Date/time: _____

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ABBREVIATIONS

AE	Adverse Event
AG019	Genetically modified *Lactococcus lactis* strain sAGX0407
ALT	Alaninne Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFU	Colony Forming Units
CGM	Continous Glucose Monitor
CMV	Cytomegalovirus
CRO	Contract Research Organization
CRF	Case Report Form
CRP	C-Reactive Protein
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
DSMB-SAP	Data Safety Monitoring Board Statistical Analysis Plan
EBV	Eppstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGRF	Estimated Glomerular Filtration Rate
GAD65	Glutamic Acid Decarboxylase 65
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoproteins
hIL-10	Human Interleukin 10
HIV	Human Immunodeficiency Viruses
hPINS	Human Proinsulin
IA-2	Insulinoma-Associated Protein 2
IAP	Interim Analysis Plan

ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDAA1c	Insulin dose adjusted HbA_{1C}
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IV	Intravenous
ITT	Intention to Treat
LDH	Lactate dehydrogenase
LDL	Low Density Lipoproteins
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MMTT	Mixed Meal Tolerance Test
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PD-ITT	Pharmacodynamic Intention To Treat
PD-PP	Pharmacodynamic Per Protocol
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RDW	RBC Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
TD1	Type 1 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
VLDL	Very Low Density Lipoproteins
WBC	White Blood Cell
WHO	World Health Organization
ZnT8	Zinc Transporter 8

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CSP) Version 9, dated June 10, 2020. This includes all analysis to be performed by XXX. The Pharmacokinetic (PK) analysis, the analysis regarding the Mixed Meal Tolerance Test (MMTT), the analysis of immune markers and the mechanistic assessments that will be performed by other Contract Research Organizations (CROs) are not included.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of different doses of encapsulated AG019, containing genetically modified *Lactococcus lactis* (*L. lactis*) producing human proinsulin (hPINS) and human interleukin-10 (hIL-10) (sAGX0407), alone as well as in association with teplizumab.

2.2 Secondary Objectives

The secondary objectives of this study are:

- to obtain pharmacodynamics (PD) data of AG019 alone as well as AG019 in association with teplizumab,
- to determine the potential presence of sAGX0407 or its secreted proteins in systemic circulation (safety – systemic exposure) and the presence of *L. lactis* bacteria in fecal excretion (local exposure): pharmacokinetic profile

3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint will be assessed by analysis of the incidence of treatment-emergent adverse events (TEAEs) collected up to the 6-month follow-up visit. A TEAE is defined as any adverse event (AE) not present prior to the initiation of the treatment(s) or any AE already present that worsens in either intensity or frequency following exposure to the treatment(s).

3.2 Secondary Endpoints

The PD activity of the study drug(s) is assessed by measurement of biomarkers in blood and serum samples. Relevant parameters are assessed, including immune markers for effect, relevant T1D parameters and relevant cytokines. These will be presented by another CRO and thus will not be a part of the statistical analysis described in this SAP. This SAP will only discuss hemoglobin A1c (HbA1c), insulin use and insulin dose adjusted HbA1c as PD variables as these will be analysed by XXX.

Samples intended for mechanistic assessments are collected from all repeat dose patients in AG019 Cohorts 2 and 4, and from all patients in the combination cohorts. All collected samples intended for mechanistic assessments are planned to be analyzed by a central lab and will not be a part of the statistical analysis in this SAP.

Following parameters are assessed for analysis of systemic and local exposure to *L. lactis* (PK profile):

- Presence of live *L. lactis* clinical strain bacteria in whole blood
- Measurable serum levels of human interleukin 10 (hIL-10) and human proinsulin (hPINS)
- Presence of *L. lactis* clinical strain bacteria in fecal excretion

The PK profile will be presented by Precigen Actobio so PK will not be a part of this SAP.

Safety information collected at all other time points (all Adverse Events (AEs), laboratory variables, vital signs, physical examination, electrocardiogram (ECG), viral status, hypoglycemic events, hyperglycemic events, study drug accountability and concomitant medication) will be assessed as secondary endpoints and analysed by XXX.

4 OVERALL STUDY DESIGN

4.1 Overview of Study Design

This Phase 1b/2a, multi-center study is conducted in patients with clinical recent-onset Type 1 Diabetes Mellitus (T1D).

AG019 is the genetically modified *L. lactis*, strain sAGX0407, containing the gene sequences coding for hPINS and hIL-10, and comprising an environmental containment system, formulated for oral administration as gastro-resistant hard capsules.

In addition to the scheduled 19 clinic visits, all patients were asked to keep a diary for collection of information relating to the study drug intake, concomitant medication intake, occurrence of AEs including hypoglycemic and hyperglycemic events, and insulin use. A detailed schedule on the measurements for each visit can be found in the Appendix A to the CSP. Information on when the measurements were planned to be collected can also be found under each subsection in this SAP.

Eight (8) single dose patients and a maximum of 48 repeat dose patients were allowed to be enrolled in clinical sites in the US and Belgium. AG019 was administered twice daily for 8 weeks at either a low dose (2 capsules/d) or at a high dose (6 capsules/d). This study consists of 2 phases and 6 cohorts. All repeat dose patients in all cohorts described below will be followed up for a total of 12 months (8 weeks of treatment plus 10 months of post-treatment follow-up).

4.1.1 Phase 1b

This open-label part of the study will investigate the safety and tolerability of different doses of AG019, in 2 age groups (18-42 years of age and 12-17 years of age, respectively), administered as single or repeat doses. Patients were enrolled in 4 sequential cohorts (AG019 cohorts):

- **AG019 Cohort 1**: 2 capsules per day, patients 18-42 years
- **AG019 Cohort 2**: 6 capsules per day, patients 18-42 years
- **AG019 Cohort 3**: 2 capsules per day, patients 12-17 years
- **AG019 Cohort 4**: 6 capsules per day, patients 12-17 years

Single dose patients

In every AG019 cohort, 2 single dose patients were enrolled in a first stage. Each of these patients were treated for 1 day with AG019 (2 or 6 capsules of XXX Colony Forming Units [CFU], depending on the cohort), and were followed up for a total of 4 days (treatment day [Day 1] plus 3 additional days), after which they had completed their study participation (Day 4).

Repeat dose patients

A minimum of 4 repeat dose patients were enrolled per AG019 cohort. In addition, both single dose patients in each AG019 cohort were offered the option of being re-enrolled as repeat dose patients in the same AG19 cohort. Therefore, if both single dose patients agree to be re-enrolled as repeat dose patients, the maximum number of repeat dose patients per cohort were 6. All repeat dose patients were planned to be treated for 8 weeks with AG019 and followed up for a total of 12 months (8 weeks of treatment plus 10 months of post-treatment follow-up).

4.1.2 Phase 2a

The Phase 2a double-blind portion of the study will investigate the safety and tolerability of AG019, in association with intravenous (IV) teplizumab in 2 cohorts ("combination cohorts") of 12 patients. Each patient is planned to be administered 6 capsules daily of AG019 (or placebo) for 8 weeks, in association with daily IV infusions of teplizumab (or placebo) for the first 12 days of the 8-week treatment period.

- **Combination Cohort 1**: 12 patients (18-40 years) received AG019 (6 capsules per day, 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions
- **Combination Cohort 2**: 12 patients (12-17 years) received AG019 (6 capsules per day, 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions

Within each of these combination cohorts, the first 2 enrolled patients were treated with active treatment (AG019 plus teplizumab) in an open label fashion. Patients 3-12 were randomized (4:1) to receive double active treatment or double placebo in a double-blind fashion.

4.2 Determination of Sample Size

In total, 8 single dose patients and up to 48 repeat dose patients were planned to be enrolled.

This is a preliminary study designed to provide information to be used in the design of subsequent studies. This study is descriptive in nature and is not designed to provide analytical results regarding efficacy. As such, the sample size is not based on statistical considerations, rather it is believed that at least 4 patients per dose level in the AG019 cohorts and 12 patients

in the combination cohorts will provide sufficient data to evaluate preliminary safety and activity of the Investigational Medicinal Products (IMP) as administered in the protocol.

Patients who discontinued after entry into the treatment phase were allowed to be replaced if approved by the Sponsor.

5 DATA SETS TO BE ANALYZED

The following analysis sets will be used for the statistical analysis and presentation of data:

- **The Safety (SAF) Analysis Set.** The safety population will include all patients who received at least one dose of AG019. Only patients with clear documentation that no study medication was received may be excluded from analysis. Patients will be analyzed according to dose received. This population will be used for all data summaries.

- **The Pharmacodynamic Intention To Treat (PD-ITT) Analysis Set.** All patients in the repeat dose and combination cohorts who received at least one dose of AG019 will be included in the PD-ITT analysis set.

- **The Pharmacodynamic Per Protocol (PD-PP) Analysis Set.** All data from patients in the repeat dose and combination cohorts who received at least 75% of the scheduled doses of AG019* and at least one dose of teplizumab in the combination cohorts and had no major protocol deviations affecting the main PD endpoints at the time point of data collection** will be included in the PD-PP analysis set.

* XXXXXXXXXXXXXXXXX

** XXXXXXXXXXXXXXXXX

All patients to be included in the PD-ITT and PD-PP Analysis sets will be determined before data base lock. The Safety Set is considered the primary analysis dataset, and will be used for safety presentations and all other data summaries (except for PD summaries). All summaries will be performed according to dose received. Baseline presentations will be based on the safety set.

6 STATISTICAL AND ANALYTICAL PLANS

The planned tables and listings are presented in Section 7.

6.1 Changes in the Planned Analyses

There has been no changes to the planned analyses.

6.2 Blind Review

Details regarding a blind review of data will be specified in the Pre-Analysis Review Form.

6.3 Hypotheses and Statistical Methods

6.3.1 Definitions

Baseline — Visit 1 is defined as the baseline visit, however if a measurement is retaken at Visit 2 before dosing this will be used as the baseline value instead of the Visit 1 value. This concerns laboratory measurements, vital signs, physical examination and concomitant medication (including insuline use). For fasting glucose baseline is defined as the average of the -10 minute and 0 minute values at screening (Visit 1).

Difference from baseline — The difference from baseline is defined as the difference from the baseline according to the definition above.

Relative day — The relative day of an event is derived as:

Relative day = (Start date) - (Date of first administration of IMP) + 1

For events occurring or starting before the date of first administration of IMP, the relative day is derived as:

Relative day = (Start date) - (Date of first administration of IMP)

In this way, there will be no Day 0. Day 1 is the same day as the day of first administration of IMP, and Day -1 is the day before.

TEAE — A TEAE is defined as any adverse event (AE) not present prior to the initiation of the treatment(s) or any AE already present that worsens in either intensity or frequency following exposure to the treatment(s).

6.3.2 Summary Statistics

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term descriptive statistics refers to number of patients (n), mean, median, standard deviation (SD), standard error of the mean (SEM), minimum and maximum for continuous data and counts and percentages for categorical data.

Summary statistics will be presented per cohort (based on age group and number of capsules), treatment group and assessment time and/or visit, as applicable. The groups will be divided into single dose for 2 and 6 capsules, repeat dose for 2 and 6 capsules, Active and Placebo. See Table 1 for details.

Table 1

Cohort	Treatment	Number of AG019 capsules per day	Total Number of teplizumab infusions	Age Group
AG019 Cohort 1	AG019, single dose	2	NA	Adults
AG019 Cohort 1	AG019, repeat dose	2	NA	Adults
AG019 Cohort 2	AG019, single dose	6	NA	Adults
AG019 Cohort 2	AG019, repeat dose	6	NA	Adults
AG019 Cohort 3	AG019, single dose	2	NA	Adolescents
AG019 Cohort 3	AG019, repeat dose	2	NA	Adolescents
AG019 Cohort 4	AG019, single dose	6	NA	Adolescents
AG019 Cohort 4	AG019, repeat dose	6	NA	Adolescents
Combination Cohort 1	AG019, repeat dose + teplizumab infusion	6	12	Adults
Combination Cohort 1	Placebo capsules, repeat dose + Placebo infusion	6	12	Adults
Combination Cohort 2	AG019, repeat dose + teplizumab infusion	6	12	Adolescents
Combination Cohort 2	Placebo capsules, repeat dose + Placebo infusion	6	12	Adolescents

NA: not applicable

6.3.3 Patient/Subject Data Listings

Data collected in the Case Report Forms (CRFs) will generally be listed in Appendix 16.2 (see section 7.2). CRF check questions [e.g. Lab samples taken (Yes/No)] and reminders will not always be listed.

Listings will be sorted by cohort, treatment group and patient number and parameter and visit/time point as applicable.

In CRF modules where a date is recorded, the date and the relative day will be included in the corresponding listing. In modules where both a start date and stop date are recorded, the duration will be given.

6.3.4 Demographic and Other Baseline Characteristics

Demographic data and baseline characteristics will include:

- age
- sex
- ethnicity
- weight and body mass index (BMI)
- insulin use (%) and numbers of units per kilo body weight,
- baseline HbA1c, and insulin dose adjusted according to baseline HbA1c
- presence of Glutamic Acid Decarboxylase 65 (GAD65) antibodies, Insulinoma-Associated Protein 2 (IA-2) antibodies, zinc transporter 8 (ZnT8) antibodies and insulin antibodies
- Infectious diseases: Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), human immunodeficiency viruses (HIV), Hepatitis B (HBV) and Hepatitis C (HCV)
- time from diagnosis to study treatment start
- time from insulin start to treatment start
- tobacco, alcohol and illicit drug consumption

Subject disposition, demographic data and other baseline data will be presented using summary statistics.

Some data as laboratory measurements, vital signs and physical examination are measured at baseline, but also at other visits. Baseline data for these parameters will be presented together with the rest of the data in by-visit displays. Physical examination included visual inspection of skin, examination of eyes, ears and throat, auscultation of heart, lungs and abdomen, and percussion/palpation of abdomen.

The medical history comprises a general medical history (including history of alcohol abuse, illicit drug abuse and smoking history), relevant T1D related medical history (including date of diabetes diagnosis, relevant glycaemia levels, autoantibody positivity, current insulin use and start date of insulin therapy as applicable) and medication history.

6.3.5 Pharmacodynamic Assessments

Throughout the study, following metabolic outcome assessments were performed:

- Hemoglobin A1c ($HbA1_C$) at Visit 1 and Visit 15-19
- Insulin dose adjusted HbA_{1C} (IDAA1c): insulin dose adjusted measurement of glycemic control calculated as:
  HbA1c (%) + [4 x insulin dose (IU/Kg/24h)]. The last collected value of insulin dose will be used for Visit 1-13 and the average for the 3 days before each visit will be used for Visit 14-19

Summary statistics, graphs and listings will be given for the PD variables.

In addition summary statistics for insulin dose per body weight (IU/kg) will be shown per visit. For Visit 14-19 the average use the 3 days before the visit will be used.

6.3.6 Compliance to Treatment

Compliance to AG019 and teplizumab will be calculated, separately.

All patients in the repeat dose cohorts, and all patients in the combination cohorts who are randomized to study treatment, were planned to be treated for 8 weeks (56 days) with either 2 or 6 capsules (low or high dose) of AG019.

All patients in the combination cohorts were planned to be treated for 12 days with teplizumab or teplizumab placebo (daily IV infusions for at least 30 minutes) in addition to their AG019/placebo treatment.

Each patient was instructed to return all used and unused study drug at each visit during the active treatment period and at the end of the treatment phase. A count of the used and unused capsules was performed to assess compliance. Teplizumab (or corresponding placebo) accountability and compliance were verified at every follow-up visit by the site staff.

AG019 compliance will be calculated as the percentage of total doses received / total planned doses that were actually taken x 100. For single dose patients the planned total doses were 2 or 6 capsules. For patients in the repeat cohorts dosed with 2 capsules/day the total planned amount was 112 capsules. For patients in the repeat cohorts dosed with 6 capsules/day and patients in the combination cohorts (which were also dosed with 6 capsules/day) the total planned amount was 336 capsules.

Teplizumab compliance will be calculated as the percentage of days teplizumab infusion was given of the planned 12 days. Incomplete infusions will be calculated as given for that day.

Compliance to AG019 and teplizumab will be tabulated with summary statistics for the safety set. All individual data will be listed.

6.3.7 Concomitant Medications

All concomitant medications/therapies (including insulin medication) will be classified according to ATC level 3 group text and World Health Organization (WHO) Drug Dictionary preferred name. The medications will be divided into two timing categories based on start date and end date: Prior and Concomitant Medications:

- Prior Medications: start date and end date before first day of IMP
- Concomitant Medications:
    - Start date before first day of IMP and end date after or on same day as first day of IMP or no end date, i.e. ongoing after first day of IMP; or
    - Start date after or on same day as first day of IMP

If the date for a concomitant medication is completely missing, it will be assumed that the medication was started before treatment and classified as Prior Medication. If the year and/or month are available, medication start in relation to the first day of IMP will be evaluated as far as possible (e.g., if only the year when the medication was started is available and ongoing is checked, the medication will be classified as a Concomitant Medication). If the medication was started in the same month as the first day of IMP, the medication will be classified as a

Concomitant Medication. Relative day will not be calculated for medications with incomplete dates.

The concomitant medications will be presented in a summary table according to timing in relation to IMP (i.e., Prior and Concomitant). Each subject will only be counted once for each medication and timing category, on a preferred name level.

One list for each timing category (Prior and Concomitant) will be presented.

6.3.8 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system.

The severity of adverse events will be given in grades 1 to 5 per National Cancer Institute common terminology criteria for adverse events (CTCAE) version 4.0.

All AEs were categorized by the Investigator with respect to their possible relationship to the IMP. The relationship of the AE to AG019, as well as the relationship of the AE to teplizumab, will be assessed separately by the investigator to be not related, unlikely, possible, probable or definite. The categorization:

- reasonably related defined as possible, probable or definite versus
- not reasonably related defined as not related or unlikely will be given in summaries of all adverse events.

If a subject has more than one event with the same preferred term (PT), then the worst severity and the worst relationship will be used.

A TEAE is defined as any adverse event (AE) not present prior to the initiation of the treatment(s) or any AE already present that worsens in either intensity or frequency following exposure to the treatment(s). Hence, events with an onset time at or after the time of treatment start are treatment emergent. Events present at baseline that worsen during the study in either intensity of frequency are also treatment emergent, whereas events present at baseline that become less severe during the study are not. Events that recur during the study are treatment emergent if they recur after complete or partial recovery of the initial event, i.e. should the event first become less severe and then return to its initial severity, it will be considered as a TEAE. AEs reported on the same day as treatment start or after treatment start will be considered TEAEs, as investigators are instructed only to report TEAEs after treatment start.

A Serious Adverse Event (SAE) is defined as any AE occurring at any dose regardless of relationship to IMP that results in any of the following outcomes:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

If the start date of an AE is missing, it will be assumed that the AE started after the first administration of IMP. If the start date of an AE is partially missing, and it has started the same year and/or month as the IMP it will be assumed that the AE started after the first administration of IMP. If an AE occurred on the same day as dosing but the onset time is missing the AE will be assumed to be a TEAE.

The infusion of teplizumab was considered withheld if the answer to the CRF question 'Was the Teplizumab infusion given?" was 'No, infusion not started' and/or if the answer on the AE page on 'Action Taken With Study Treatment Teplizumab' was 'Drug interrupted' or 'Drug withdrawn'.

Study treatment of AG019 was considered discontinued if the answer to the CRF question "Action Taken with Study Treatment AG019" was "Drug interrupted" or "Drug withdrawn".

A summary table per cohort will present number of TEAEs, number of unique TEAEs (counted once within each subject at the preferred term level) and number of subjects with at least one event for TEAEs, SAEs, related TEAEs, TEAEs leading to discontinuation of IMP/withdrawal and more.

Tables with

- All AEs by System Organ Class (SOC) and PT,
- All TEAEs by SOC and PT, in total and for the AG019 treatment period only,
- All TEAEs by SOC and PT according to severity, in total and for the AG019 treatment period only,
- All TEAEs by SOC and PT according to relatedness, in total and for the AG019 treatment period only,
- All serious TEAEs by SOC and PT,

will be given. If there are no events an empty table will be produced.

All AEs will be listed. In addition all TEAEs leading to AG019 treatment discontinuation and study infusion withholding will be listed.

6.3.9 Other Safety Assessments

Vital Signs

For repeat dose patients, weight, sitting blood pressure, heart rate, respiratory rate and body temperature will be measured at Visit 1, 2, 5, 8, 13-19. Height is measured at Visit 1. For single dose patients vital signs will be measured at screening, treatment and post treatment.

For all vital signs parameters summary statistics will be produced for observed values. In addition, the difference from baseline to each visit at which they were assessed will be derived and presented.

Shift tables showing the number of subjects who changed from normal, abnormal not clinical significant or abnormal clinical significant at baseline to normal, abnormal not clinical significant or abnormal clinical significant at each post-baseline time of assessment will be presented.

All vital signs will be listed.

Clinical Laboratory Measurements

From screening to the last visit lab parameters will be collected, see CSP Appendix A for details.

Parameters to be analysed will include:

- Hematology: complete blood count: Red Blood Cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), RBC distribution width (RDW), white blood cell (WBC) count, differential count, platelet count
- Serum Chemistry: blood glucose, sodium, potassium, chloride, calcium, CO_2/bicarbonate
- Liver function tests: alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), lactate dehydrogenase (LDH), total protein, albumin, total bilirubin
- Pregnancy tests for women of childbearing potential: serum (at screening), urine (at other visits)
- Coagulation tests: international normalized ratio (INR)
- Inflammatory: C-reactive protein (CRP)

Following additional blood parameters will be analysed at screening, and if no concerns are identified, these parameters will not require analysis at follow-up visits:

- Kidney function tests: uric acid, urea/blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR)
- Cardiovascular tests: total cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL - optional)
- Thyroid stimulating hormone (TSH)

In addition to the above lab assessments to be analysed by the site's local lab, EBV/CMV/HCV/HBV/HIV monitoring assessments will be done. These measurements were performed at screening for all patients and at Visit 13-16, Visit 19 for repeat dose patients. Potential reactivation will be assessed at regular intervals by polymerase chain reaction (PCR) for viral load.

For hematology, clinical chemistry, liver function, coagulation parameters and CRP summary statistics will be produced for observed values. In addition, the difference from baseline to each visit at which they were assessed will be derived and presented.

Shift tables showing the number of subjects who changed from normal, abnormal not clinical significant or abnormal clinical significant at baseline to normal, abnormal not clinical significant or abnormal clinical significant at each post-baseline time of assessment will be presented.

Figures showing mean and median values over time per chohort will be shown for CRP, AST and lymphocytes.

Number of patients with positive/negative serology at baseline and positive/negative for PCR per visit will be tabulated.

All laboratory parameters will be listed. Abnormal values will be flagged in listings.

In addition, all study patients (except for the single dose patients) will receive a XXX continuous glucose monitor (CGM) device for the entire duration of their study participation. The data generated by the device will be downloaded at every site visit. The devices will store data for up to 30 days. The device measures glucose every 5 minutes, thus every measurement will be said to have a duration of 5 minutes when the calculation of total duration is performed. The first measurement is said to measure the glucose value 5 minutes before the actual measurement. For the CGM data collected at each visit:

- The total CGM recording time,
- Time in range (the time greater than or equal to 71 mg/dl and less than or equal to 179 mg/dl),
- Time above range (the time above 179 mg/dl),
- Time in the low range (the time below 71 mg/dl),
- Time in the very low range (the time below 50 mg/dl) and
- Time with missing values

will be summarized in hours/minutes and percentages of the total CGM recording time, per cohort.

Physical Examination

The physical examination included visual inspection of skin, examination of eyes, ears and throat, auscultation of heart, lungs and abdomen, and percussion/palpation of abdomen. The results will be recorded as

- Normal,
- Abnormal Not Clinically Significant or
- Abnormal Clinically Significant.

For repeat dose patients the physical examination will be performed at Visit 1, 2, 5, 8, 13-19. For single dose patients the physical examination will be performed at screening, treatment and post treatment.

The frequencies (and percentage) of normal, abnormal but not clinically significant or abnormal and clinically significant will be tabulated.

Physical Examination data will be listed.

ECG

The investigator will perform a 12-lead ECG. The results will be recorded as

- Normal,
- Abnormal Not Clinically Significant or
- Abnormal Clinically Significant.

For single dose patients ECG status will be collected at screening (Visit 1) and at post treatment only if there is a suspicion of cardiac problems. For repeat dose patients ECG status will be collected at Visit 1, Visit 15, Visit 19 and in addition at Visit 17 if there is a suspicion of cardiac problems.

The frequencies (and percentage) of normal, abnormal but not clinically significant or abnormal and clinically significant will be tabulated.

ECG data will be listed.

Hypoglycemic events

Hypoglycemic events will be documented in the patient diary. Events of hypoglycemia will be classified as outlined below.

- hypoglycemia Level 1: A glucose alert value of 3.9 mmol/l (70 mg/dl) or less for at least 20 minutes
- hypoglycemia Level 2: A glucose level of <3.0 mmol/l (<54 mg/dl), sufficiently low to indicate serious, clinically important hypoglycemia.
- hypoglycemia Level 3: Severe hypoglycemia, as defined by the American Diabetes Association, denoting severe cognitive impairment requiring external assistance for recovery.

For the purposes of this study, hypoglycemia events classified as level 1 will not be recorded separately on the hypoglycemia event electronic case report form (eCRF), unless the investigator feels that the event is medically important. Hypoglycemia events level 2 and 3 will be recorded separately on the hypoglycemia event eCRF. The evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk. In addition, all hypoglycemia events meeting the definition of SAE should be recorded as serious adverse events in the eCRF.

Time of the events will be divided in the following time periods:

- Pre-treatment: all events until the day before treatment start
- During treatment: all events reported on the day of treatment start (Day 1) and up to the last treatment day
- Post-treatment: all events reporter after the last treatment day

The number of hypoglycemic events and patients with hypoglycemic events will be summarized per cohort, treatment, level and time period.

All hypoglycemic events recorded in the eCRF will be listed. Relative day to treatment start will be included in the listing.

Hyperglycemic events

Major hyperglycemic events will be defined and graded as follows:

- Grade 4 = coma or life-threatening event or event resulting in hospitalization.
- Grade 5 = death.

For this study diabetic ketoacidosis should be reported as grade 4 hyperglycemia (a single adverse event) resulting in hospitalization and/or life threatening consequences.

Hyperglycemic events will be collected and presented as SAEs with no separate tabulation. See section 6.3.9 for futher details on presentation.

6.4 Level of Significance, Multiple Comparisons and Multiplicity

The primary objective of this study is to assess safety and tolerability of AG019. The study is descriptive in nature and is not designed to provide analytical results regarding efficacy.

6.5 Adjustment for Covariates

Not applicable as the output will contain no statistical analyses. Summary tables will show changes from baseline.

6.6 Handling of Dropouts and Missing Data

The data will be analysed as is except for missing dates for concomittant medication and adverse event, see those sections.

6.7 Multicentre Studies

Since this is only a small study primarily focused on safety no site or country effect will be studied.

6.8 Examination of Subgroups

No examination of subgroups is planned.

6.9 Interim Analysis

Preliminary results (interim analysis 1) for the open-label part of the study and a second interim analysis (described in the Interim Analysis Plan [IAP]) has been performed previously.

The primary analysis will be performed when all patients have passed the Day 180 visit. This interim analysis will contain the same TFLs that will be produced for the final output, if possible.

All decisions on data for blinded subjects will be taken before breaking the blind for the third interim analysis. Since this is a study of descriptive nature, with no statistical tests, the influence of the interim analyses should be considered negligible.

6.10 Data Monitoring

A Data Safety Monitoring Board (DSMB) has reviewed the eCRF-reported safety related data for all enrolled patients at predefined time points.

7 LIST OF OUTPUT

7.1 Tables to be Produced for the Clinical Study Report (Section 14 according to ICH E3)

(Table numbers refer to section numbers in ICH E3)

14.1 DEMOGRAPHIC DATA

(Baseline presentations will be based on the safety set if not otherwise stated below)

- Subject Disposition in Analysis Sets and Reason for Exclusion (all included subjects)
- Subject Discontinuation (all included subjects)
- Screening Failures including Reasons for Failure
- Demographics (age, sex and ethnicity)

- Background Characteristics (% of patients on insulin, HBA1c, insuline adjusted HBA1c, time from diagnosis to treatment start, EBC, CMV, HIV, HBV, HCV, GAD65 antibodies, IA-2 antibodies, ZnT8 antibodies and insulin antibodies)
- Weight, BMI and use of tobacco, alcohol and illicit drugs
- Baseline insulin use (dose in IU/kg and time from insulin start to treatment start)

14.2 EFFICACY DATA

Pharmacodynamic Assessments:

Summary statistics for absolute values and change from baseline for (PD Analysis Set):

- HbA1c
- Insuline dose adjusted HbA1c

Summary statistics for insulin use per kg body weight per visit (PD Analysis Set)

Pharmacodynamic Assessments - Figures:

- Average HbA1c
- Individual HbA1c values (spaghetti plots)
- Average insulin dose adjusted HbA1c
- Individual insulin dose adjusted HbA1c (spaghetti plots)

14.3 SAFETY DATA

(Safety presentations will be based on the safety set unless otherwise stated below)

14.3.1.x Summary of All Adverse Events for single dose AG019 patients

14.3.1.x Summary of All Adverse Events for repeat dose AG019 patients

14.3.1.x Summary of All Adverse Events for combination cohort patients

14.3.1.x All Adverse Events by System Organ Class and Preferred Term

14.3.1.x Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

14.3.1.x Treatment-Emergent Adverse Events by System Organ Class and Preferred Term during AG019 treament period

14.3.1.x Treatment-Emergent Adverse Events by Severity, System Organ Class and Preferred Term

14.3.1.x Treatment-Emergent Adverse Events by Severity, System Organ Class and Preferred Term during AG019 treatment period

14.3.1.x Treatment-Emergent Adverse Events by Relationship to AG019, System Organ Class and Preferred Term

14.3.1.x Treatment-Emergent Adverse Events by Relationship to AG019, System Organ Class and Preferred Term during AG019 treatment period

14.3.1.x Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

14.3.1.x Treatment-Emergent Adverse Events Leading to Premature AG019 Treatment Discontinuation by System Organ Class and Preferred Term

14.3.4.x Laboratory Measurements:

Summary Statistics by Visit with Difference from Baseline (Hematology & INR, Clinical Chemistry, Liver Function & CRP and HbA1c)

Shift Tables (Hematology & INR, Clinical Chemistry, Liver Function & CRP)

Figures of mean and median CRP, AST and Lymphocytes over time

Number of patients with positive/negative serology at baseline and positive/negative for PCR per visit

Summary of CGM Recording Time

14.3.5 Compliance to treatment with AG019

Compliance to treatment with teplizumab

14.3.6.x Vital Signs:

Summary Statistics with Difference from Baseline

Shift Tables

14.3.7.x Physical Examination per visit and treatment

14.3.8.x ECG per visit and treatment

14.3.9.x Summary of Hypoglycemic Events

14.3.10.x Concomitant Medication and Therapy (including insulin medication)

- Prior Medications and Therapies
- Concomitant Medications and Therapies

7.2 Listings of Individual Patient Data and Other Information to be Produced for the Clinical Study Report (Sections 16.1 and 16.2 in ICH E3)

(Listing numbers refer to the relevant appendix number in ICH E3. CRF check questions/reminders will not be listed.)

16.2.1.x Discontinued Patients, Reason for Discontinuation

Visit Dates and AG019 Treatment End Date

16.2.2 Protocol Deviations

16.2.3.x Patients Excluded from the Pharmacodynamic Analysis

(Evaluability, Reason for Evaluability Classification)

Treatment Allocation and Evaluability for All Subjects

16.2.4.x Demographics and Other Background Characteristics

Medical History

History of T1D (diagnosis and insulin use)

Smoking, Alcohol and Illicit Drug Use

Inclusion Criteria Not Met and Exclusion Criteria Met

16.2.5.x Compliance to treatment with AG019

Compliance to treatment with teplizumab

16.2.6.x Pharmacodynamic Measurements:

- HbA1c
- Insulin dose adjusted HbA1c

16.2.7.x Adverse Events

Adverse Events for patients with infusion withholding

16.2.8.x Listing of Individual Laboratory Measurements

16.2.9.x Vital Signs

16.2.10.x Physical Examination

16.2.11.x ECG

16.2.12.x Concomitant Medication and Therapy (including insulin medication)

- Prior Medications and Therapies
- Concomitant Medications and Therapies

16.2.13.x Hypoglycemic Events