# Clinical Study Protocol

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| Protocol Title: | 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). |
| Investigational Drug: | AG019 |
| Protocol Number: | AG019-T1D-101 |
| EudraCT Number:<br>IND number: | 2017-002871-24<br>18000 |
| Sponsor: | Precigen ActoBio T1D, LLC<br>20374 Seneca Meadows Parkway<br>Germantown, MD 20876<br>USA |
| Sponsor Signatory: | Name and Title:<br><br>_____<br>Signature |
| Protocol Date: | Final 9.0 11-Jun-2020 |

**GCP STATEMENT**

This trial will be conducted in compliance with this protocol, Good Clinical Practices and applicable regulatory requirements.

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## List of Abbreviations

| | |
|---|---|
| ADA | American Diabetes Association |
| AE | adverse event |
| AG019 | genetically modified *Lactococcus lactis* strain sAGX0407 |
| ALT | alaninne aminotransferase |
| ALP | alkaline phosphatase |
| APC | antigen presenting cell |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BCG | Bacillus Calmette-Guérin |
| BID | bis in die (twice daily) |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| CA | competent authority |
| CBC | complete blood count |
| CCR6 | Chemokine receptor type 6 |
| CD | cluster of differentiation |
| CFR | Code of Federal Regulations |
| CFU | colony forming units |
| CGM | continous glucose monitor |
| CMV | cytomegalovirus |
| $CO_2$ | carbon dioxide |
| CRA | clinical research associate |
| (e)CRF | (electronic) Case Report Form |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CRS | cytokine release syndrome |
| CS | clinically significant |
| CTCAE | common terminology criteria for adverse events |
| DC | dendritic cell |
| DP | drug product |
| DS | drug substance |
| DSMB | Data Safety Monitoring Board |
| EBV | Eppstein-Barr Virus |
| ECG | electrocardiogram |
| ELISA | enzyme-linked immunosorbent assay |
| eGFR | estimated glomerular filtration rate |
| ePRO | electronic patient reported outcomes |
| EU | European Union |
| FDA | Food and Drug Administration |
| Fc | crystallizable fragment |
| FcR | Fc receptor |
| Foxp3 | Forkhead box p3 |

| | |
|---|---|
| FPG | fasting plasma glucose |
| GAD65 | glutamic acid decarboxylase 65 |
| GALT | gut-associated lymphoid tissue |
| GCP | Good Clinical Practices |
| GI | gastrointestinal |
| GM | genetically modified |
| Hb | hemoglobin |
| HBV | Hepatitis B virus |
| Hct | hematocrit |
| HCV | Hepatitis C virus |
| HDL | high density lipoproteins |
| hIL-10 | human interleukin-10 |
| HIV | human immunodeficiency virus |
| hPINS | human proinsulin |
| HPMC | hydroxypropylmethylcellulose |
| i.e. | id est |
| IA-2 | insulinoma-associated protein 2 |
| IAA | insulin autoantibody |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IFN | interferon |
| IgG | immunoglobulin G |
| IL | interleukin |
| IMP | investigational medicinal product |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IV | intravenous |
| kcal | kilocalories |
| *L. lactis* | Lactococcus lactis |
| LDH | lactate dehydrogenase |
| LDL | low density lipoproteins |
| mM | milliMolar |
| mAb | monoclonal antibody |
| MCC | microcrystalline cellulose |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA | medical dictionary for regulatory activities |
| MHC | major histocompatibility complex |
| MM | Medical Monitor |
| MMTT | mixed meal tolerance test |

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|---|---|
| MoA | mode of action |
| NCI | Natoional Cancer Institute |
| NCS | non-clinically significant |
| NOD | nonobese diabetic |
| NSAID | non-steroidal anti-inflammatory drugs |
| OKT3 | Orthoclone Kung T3 |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PMN | polymorphonuclear neutrophils |
| qPCR | quantitative real-time polymerase chain reaction |
| RBC | red blood cell |
| RDW | red blood cell distribution width |
| REB | research ethics board |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| sAGX0407 | *Lactococcus lactis* strain sAGX0407, genetically engineered to produce human proinsulin and human interleukin-10 |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SEM | Standard error of the mean |
| SUSAR | suspected unexpected serious adverse reaction |
| T1D | type 1 diabetes mellitus |
| TB | tuberculosis |
| TCR | T cell receptor |
| TEAE | treatment-emergent adverse event |
| Teff (cell) | effector T (cell) |
| TGF | transforming growth factor |
| TID | ter in die (three times daily) |
| Treg (cell) | regulatory T (cell) |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |
| US | United States |
| VLDL | very low density lipoproteins |
| WBC | white blood cell |
| WHO | World Health Orgnization |
| ZnT8 | zinc transporter 8 |

# 1. INTRODUCTION AND STUDY RATIONALE

## 1.1. Background

Approximately 10-15 million people worldwide suffer from T1D, the most common metabolic disorder in infancy and adolescence, affecting 167,000 children in the US alone. The SEARCH for Diabetes in Youth study estimated that, in 2009, 18,436 children in the US were newly diagnosed with T1D (Hamman et al., 2014). Recent data shows that the prevalence of T1D in children in the US increased by 21.1% between 2001 and 2009 (Hamman et al., 2014). It is reported that global incidence of T1D is increasing by 3% every year (Egro, 2013).

T1D is an autoimmune disease that results from a progressive T cell mediated destruction of the insulin-producing β-cells in the islets of Langerhans in the pancreas, in genetically susceptible individuals (Knip, 2002). The absolute loss of β-cells, and therefore insulin production, results in increased glucose levels in urine and blood (i.e., glycosuria and hyperglycemia). This leads to chronic hyperglycemia which instigates micro- and macrovascular complications (van Belle et al., 2011).

Patients with T1D require lifelong treatment with insulin. Untreated or poorly controlled T1D can lead to blindness, kidney failure, nerve damage, and cardiovascular complications such as coronary heart disease, stroke, and accelerated atherosclerosis (American Diabetes Association, 2014). Moreover, long term management requires a multidisciplinary approach that includes physicians, nurses, dieticians, and other specialists. T1D-associated healthcare costs in the US reach $14 billion annually (Atkinson et al., 2014).

Immune intervention for recent-onset T1D aims to prevent or reverse the disease by blocking autoimmunity, thereby preserving or restoring β-cell mass and function and decreasing the likelihood of both hypoglycemia and the long-term complications associated with T1D.

Antigens may behave as immunogens that provoke an adaptive immune response or as tolerogens that induce a state of specific immunological unresponsiveness (immune tolerance) to subsequent challenging doses of the antigen. Several factors determine the immunogenic versus tolerogenic capacity of an antigen, including its molecular form, the nature of antigen presenting cells (APCs), the dose, the route of administration and local response environment (Anderton et al., 1999).

The gut-associated lymphoid tissue (GALT) is the largest immune organ in the body and is the primary route by which individuals are exposed to antigens. Tolerance induction is the default immune pathway in the gut. Oral tolerance is the active process by which the immune system does not respond to an orally administered antigen. One of the major mechanisms of oral tolerance is the induction of antigen-specific regulatory T (Treg) cells, a process that is related to the gut dendritic cells (DCs) and linked to both transforming growth factor (TGF)-β and retinoic acid (Commins, 2015).

Treg cells have the capacity to induce or re-install tolerance to autoantigens while minimizing detrimental effects on host defense. Treg cell expansion can be achieved using cytokines. Activating or expanding antigen-specific Treg cells may achieve the same therapeutic effect as broad spectrum immunosuppression without the associated toxicity. In an autoimmune disease such as T1D, antigen-specific restoration of tolerance should be targeted (Cabrera et al., 2012).

A number of studies in T1D animal models have demonstrated a pathogenic and/or beneficial role for these cytokines as well as their therapeutic potential in T1D (Nepom et al., 2013).

The effect of IL-10 on T1D has been studied in animal models. One study has shown that systemic overexpression of IL-10 in nonobese diabetic (NOD) mice, using a viral vector, significantly ameliorated T1D in a dose dependent manner (Goudy et al., 2003). The IL-10 therapy dramatically increased the percentage of $CD4^+CD25^+$ Treg cells. This study demonstrated the potential for immunomodulatory gene therapy to prevent autoimmune diseases, including T1D, and implicates IL-10 as a molecule capable of increasing the percentages of Treg cells *in vivo*.

AG019 consists of the biologically contained food-grade lactic acid bacteria *L. lactis*, strain sAGX0407, genetically engineered for the *in situ* expression and secretion of hPINS and hIL-10. Through oral administration of AG019, the GM *L. lactis* sAGX0407 bacteria will be introduced orally into the patient's GI tract (distal ileum and entire colon), where they will reside for a limited period of time. During their residency in the GI tract, the engineered bacteria will produce and deliver therapeutic concentrations of hIL-10 and hPINS locally, without systemic exposure, with the aim of inducing long term tolerance to β-cell antigens.

AG019 will be administered in association with a treatment with teplizumab, a humanized anti-CD3 mAb. This mAb primarily targets the CD3/ T cell receptor (TCR) complex, a molecule complex associated with antigen recognition, which is found on the cell membrane of mature T lymphocytes and which is associated with T cell activation.

*Non-clinical Studies*

Proof-of-concept studies have demonstrated that intestinal co-delivery of hPINS and hIL-10 using GM *L. lactis*, in association with a short term, low dose treatment with a surrogate hamster anti-mouse CD3 mAb, reverses T1D in NOD mice via induction of forkhead box P3 $(Foxp3)^+$ Treg cells (Takiishi et al., 2012; Takiishi et al., 2017).

The non-clinical studies have focused on determining the Mode of Action (MoA), establishing PD data, obtaining PK data, investigating the toxicology and safety pharmacology, and evaluating the safety profile of AG019 in association with teplizumab.

More detailed information about these non-clinical studies is contained in the Investigator's Brochure for AG019.

*Effects in humans*

To date, AG019 alone as well as AG019 in association with teplizumab have not been studied in humans.

Teplizumab has been studied extensively in more than 800 patients with recent-onset T1D. These studies have enabled the identification of a safe dose regimen. Furthermore, this teplizumab treatment regimen preserved insulin production and reduced the use of exogenous insulin in some patients with new-onset T1D. (Herold et al., 2005; Herold et al., 2009; Sherry et al., 2011; Hagopian et al., 2013; Herold et al., 2013; Tooley et al., 2016).

## 1.2.Rationale

Currently, no disease curing or modifying treatments are available for T1D. There is a high unmet need to develop effective treatments for T1D patients.

T1D is a cell-mediated autoimmune disorder resulting in the absolute destruction of the pancreatic insulin-producing β-cells. The disease is immune-mediated and thought to be caused by a combination of genetic and environmental factors that ultimately leads to loss of insulin secreting β-cells in pancreatic islets and high levels of blood glucose. High blood glucose levels and autoimmunity cause acute complications, such as ketoacidosis, as well as a wide variety of late complications. Although current insulin products achieve satisfactory glycemic control in the majority of patients, barriers such as reaching glycemic goals, fear of hypoglycemia, and the complexity and demands of day-to-day management (insulin dose adjustment, self-monitoring of blood) have an enormous impact on patient quality of life.

Although patients with T1D have a life-long dependency on injections of exogenous insulin to meet metabolic demands, this cannot mimic the physiologically regulated hormone response of a normal β-cell population. Insulin supplementation does not reverse the β-cell destructive process and is by itself not without life-threatening risks. Insufficient insulin levels can put the patient in a hyperglycemic state, which can ultimately result in diabetic ketoacidosis, causing nausea, vomiting, dry mouth, shortness of breath, and a fruity breath smell. On the other hand, insulin overdose can cause dangerous hypoglycemia where blurred vision, sudden mood changes, nervousness, pale skin, headache, shaking, and a loss of consciousness can occur. In addition, insulin replacement is an intensive therapy requiring continuous monitoring of blood glucose levels, adapting insulin injections accordingly and following a strict diet.

Nonclinical studies performed to date by IA have confirmed that intestinal delivery of hIL-10 and hPINS by GM *L. lactis*, in association with a short-term treatment with systemic anti-CD3 mAb, reverted diabetes in NOD mice and increased frequencies of local Treg cells, which not only accumulated in the pancreatic islets, but also suppressed immune response in an autoantigen-specific way. Initial blood glucose concentrations and insulin autoantibody (IAA) positivity were predictors of stable reversal of hyperglycemia (Takiishi et al., 2012; Takiishi et al., 2017). Cured mice remained responsive to disease-unrelated antigens; which argues against excessive immunosuppression. Treatment success of the co-administration was significantly superior to monotherapy of either *L. lactis* sAGX0407 or anti-CD3 mAb alone. Though the exact mechanisms are not yet fully understood, studies suggest that the anti-CD3 mAb specifically depletes effector T (Teff) cells, and also induces the migration of chemokine receptor type 6 $(CCR6)^+$ T cells from the peripheral circulation and the secondary lymphoid organs to the GI tract, where they secrete IL-10 (Waldron-Lynch et al., 2012). This results in an accumulation of tolerance promoting IL-10 secreting $CD4^+CD25^{high}CCR6^+Foxp3$ Treg cells in the GI mucosal tissues, which is an attractive target for antigen-specific modulation through topical delivery of antigen (hPINS) and the tolerance inducing cytokine (hIL-10) secreted by *L. lactis* sAGX0407. These phenomena appear to be very effective in installing stable and long term antigen specific tolerance.

Given the positive results obtained in the NOD mouse model, the Sponsor believes that co-delivery of a Treg cell enhancer and an antigen implicated in β-cell autoimmunity will be able to reverse T1D in humans, and that the effectiveness will be increased upon association with anti-CD3 mAb.

# 2. OBJECTIVES

## 2.1. Primary Objective

The primary objective of this study is to assess the safety and tolerability of different doses of AG019 alone as well as AG019 in association with teplizumab.

## 2.2. Secondary Objectives

The secondary objectives of this study are:

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

# 3. STUDY DESIGN

## 3.1. General information

This Phase 1b/2a, multi-center study will be conducted in patients with clinical recent-onset T1D.

A maximum of 8 single dose patients and a maximum of 48 evaluable repeat dose patients will be enrolled in clinical sites in the US and Belgium.

This study will consist of 2 phases:

- Phase 1b: this open label part of the study will investigate the safety and tolerability of 2 different doses of AG019, in 2 age groups (18-40 years of age, further referred to as adults, and 12-17 years of age, further referred to as pediatrics, respectively), administered as single or repeat doses. Patients will be enrolled in 4 sequential cohorts (AG019 cohorts).
- Phase 2a: this randomized, double blind part of the study will investigate the safety and tolerability of AG019, in association with teplizumab, in 2 age groups (18-40 years of age and 12-17 years of age respectively), in comparison with placebo. Patients will be enrolled in 2 cohorts (combination cohorts).

In all AG019 cohorts (see Section 5.2), 2 single dose patients will be enrolled prior to the enrollment of the repeat dose patients, and patients will be enrolled sequentially into 2 descending age groups (adult cohorts, 18-40y, and pediatric cohorts, 12-17y). The single dose patients will be followed up for a total of 4 days, after which they will have completed their participation in the study.

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). After the 12-month follow-up visit the patients will have completed their participation in the study.

The treating Investigator and MM will review the eCRF-reported safety related data (including clinical data, local lab results and safety related data transcribed from the patient's diary into the eCRF) at defined study time points. The specific role and responsibilities of the MM are outlined in Section 11.4.

A DSMB will be established and will review the eCRF-reported safety related data for all enrolled patients at specified time points (including safety related data transcribed from the patient's diary into the eCRF). The specific role and responsibilities of the DSMB are outlined in Section 11.4 and in the DSMB charter.

In addition to the scheduled clinic visits, all patients will be asked to keep a diary for collection of information relating to the study drug intake, concomitant medication intake, occurrence of adverse events including hypoglycemic and hyperglycemic events, and insulin use.

During the study, all patients will receive appropriate diabetic therapy according to current ADA or equivalent guidelines (Section 5.1.3).

## 3.2.Phase 1b portion

The **Phase 1b open-label portion** of the study will enroll 4 sequential AG019 cohorts evaluating the safety of AG019 administered orally for 8 weeks. In each of these 4 cohorts, enrollment of up to 6 repeat dose patients[4] will be preceded by enrollment of 2 single dose patients as outlined below.

- **AG019 Cohort 1**: 2 capsules per day, patients 18-40y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients
- **AG019 Cohort 2**: 6 capsules per day, patients 18-40y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients
- **AG019 Cohort 3**: 2 capsules per day, patients 12-17y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients
- **AG019 Cohort 4**: 6 capsules per day, patients 12-17y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients

Within each of these cohorts, patients will be enrolled as follows:

- Treatment of single dose patient 1
  - ➢ Data review after the Day 4 follow-up visit (treating Investigator and MM)

[4] 4 repeat dose patients will be enrolled per AG019 cohort. In addition, both single dose patients in each AG019 cohort will be offered the option of being re-enrolled as repeat dose patients in the same AG019 cohort, provided that no safety concerns have been identified during their participation as a single dose patient. Therefore, if both single dose patients agree to be re-enrolled as repeat dose patients, the maximum number of repeat dose patients will be 6.

- Treatment of single dose patient 2
  - Data review after the Day 4 follow-up visit (treating Investigator and MM)
- Treatment of repeat dose patient 1
  - Data review after the Day 7 follow-up visit (treating Investigator and MM)
- Treatment of repeat dose patient 2
  - Data review after the Day 7 follow-up visit (treating Investigator and MM)
- Treatment of the remaining repeat dose patients
  - Data review after the Day 7 follow-up visit of the last patient (DSMB – review of all available data from all patients enrolled into all cohorts)

Once all repeat dose patients in a cohort have had their Day 7 follow-up visit, the DSMB will review all available data from all patients enrolled into all cohorts. If no safety concerns are identified, the DSMB will formulate a recommendation to the sponsor on opening the next cohort(s) for treatment.

## 3.3.Phase 2a portion

The **Phase 2a double-blind portion** of the study will evaluate 2 cohorts of patients administered AG019 daily for 8 weeks[5], in association with daily IV infusions of teplizumab for the first 12 days of the 8-week treatment period (combination cohorts).

- **Combination Cohort 1**: 12 patients (18-40y) to receive AG019 (6 capsules per day[5], 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions
- **Combination Cohort 2**: 12 patients (12-17y) to receive AG019 (6 capsules per day[5], 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 will be treated with active treatment (AG019 plus teplizumab) in an open label fashion. Patients 3-12 will be randomized (4:1) to receive active treatment or placebo in a double-blind fashion. Therefore enrollment will be done as follows:

- Treatment of patient 1: Treatment with AG019 plus teplizumab
  - Data review of all data collected up to the Day 12 follow up visit (the last day of teplizumab infusion) (treating Investigator and MM)
- Treatment of patient 2: Treatment with AG019 plus teplizumab
  - Data review of all data collected up to the Day 12 follow up visit (the last day of teplizumab infusion) (DSMB – review of all available data from all patients enrolled into all cohorts)
- Treatment of patients 3-12: randomization (4:1) to double Active Treatment or double Placebo.

[5] The dose of AG019 to be administered in the Phase 2a portion of the study is not yet known and will be determined by the results of the Phase 1b portion of the study. If the AG019 cohorts reveal safety concerns associated with the 6-capsule treatment, the DSMB will recommend lowering the AG019 dose in all ongoing AG019 and combination cohorts.

The overall enrollment plan is outlined in Figure 1.

## 3.4.Rationale for the study design

The ActoBiotics® platform, consisting of GM *L. lactis* bacteria, has been used to deliver therapeutic proteins and peptides, including bioactive cytokines and antigens, to mucosal tissues in several preclinical and clinical studies (Steidler et al., 2000; Steidler et al., 2003; Braat et al., 2006; Rottiers et al., 2009; Coulie, 2013; Limaye et al., 2013; Coulie, 2014; Robert et al., 2014).

Through oral administration of AG019, the GM *L. lactis* sAGX0407 bacteria will be introduced into the patient's GI tract (distal ileum and entire colon), where they will reside for a limited period of time. The residence time of the bacteria is transient and determined by the intestinal transit rate. During their residency in the GI tract, the engineered bacteria will produce and deliver therapeutic concentrations of hIL-10 and hPINS locally, without systemic exposure, with the aim of inducing long term tolerance to β-cell antigens.

The Sponsor has already demonstrated in nonclinical and clinical studies that the ActoBiotics® platform has an excellent safety profile. XXXX

XXX

XXX

More details about the nonclinical studies are described in the AG019 Investigator Brochure.

AG019 has not been tested in human patients to date, neither as standalone treatment nor in combination with teplizumab. Therefore the Sponsor has designed the study in such a way that the safety of AG019 alone as well as in combination with teplizumab can be investigated while keeping potential risks for the patients to a minimum. The following measures have been taken to allow for minimal risks for the patients in this study:

- The safety of AG019 alone will first be evaluated before opening the combination cohorts.
- A dose escalation was built into the AG019 cohorts, allowing to evaluate the safety profile of low dose AG019 before evaluating the safety of a higher dose of AG019
- In each AG019 cohort, 2 single dose patients will be enrolled in a staggered way, and their data will be reviewed, before opening treatment of the repeat dose patients.
- A significant portion of recent-onset T1D patients are children. It is therefore important to include this population already in the early stages of development. Measures have been taken, to enable the Sponsor to thoroughly investigate the safety of AG019 alone as well as in association with teplizumab in adults, before opening the corresponding pediatric AG019 and combination cohorts for treatment.
- A DSMB and medical monitor will be heavily involved in each review and decision step, as outlined in the enrollment plan, before proceeding to the next cohort
- An extensive set of study stopping criteria and dose adjustment/stopping criteria has been generated.

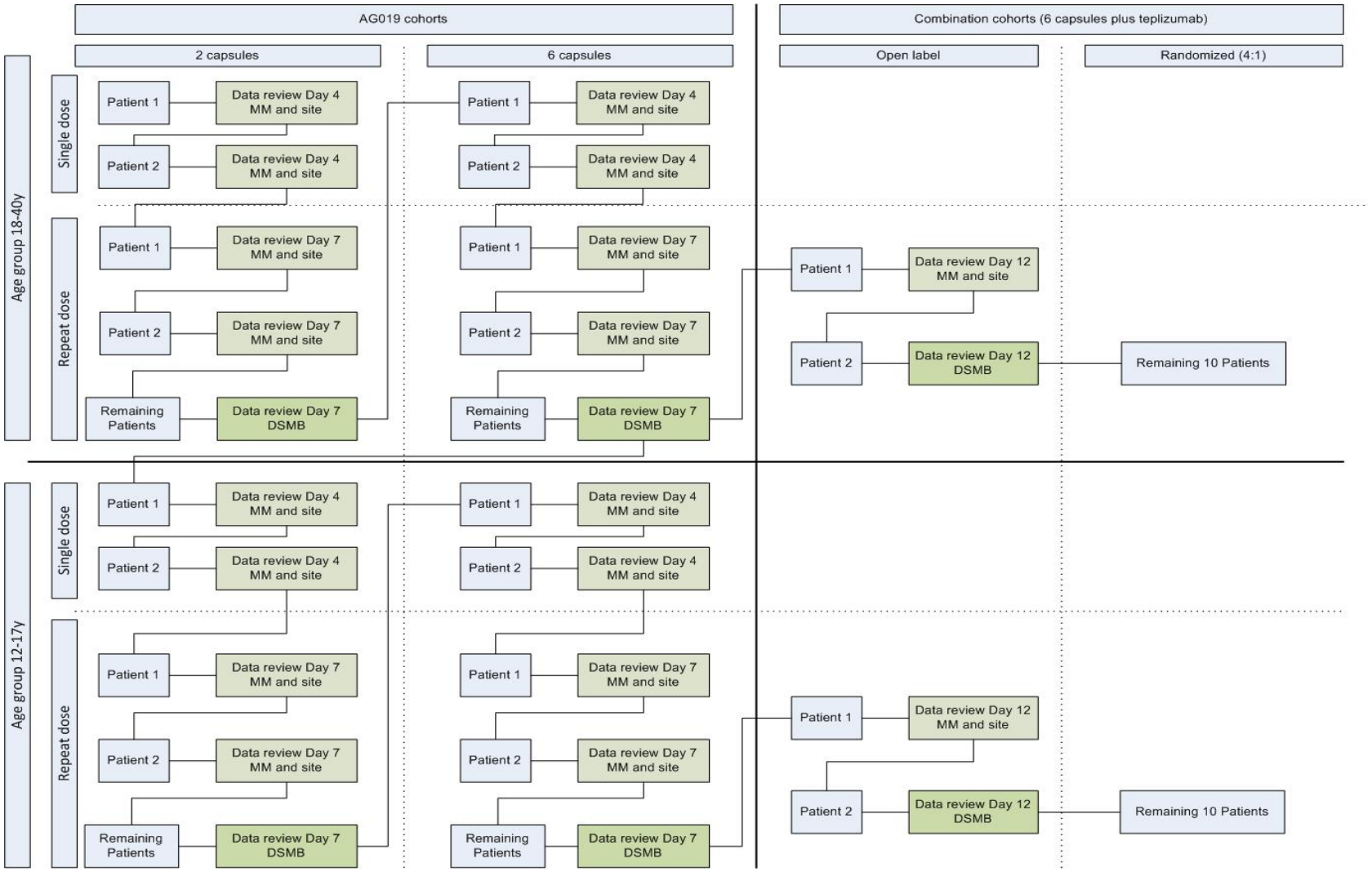


**Figure 1:** Overall enrollment plan.

# 4. STUDY POPULATION

The study population will consist of adults and children who have clinical recent-onset diagnosis of type 1 diabetes mellitus.

Screening for eligible patients will be performed within 28 days prior to the first administration of study drug.

## 4.1. Sample Size

A maximum of 48 patients will be enrolled in clinical sites in US and Belgium.

In total, 8 single dose patients and up to 48 repeat dose patients[6] will be enrolled.

Patients who discontinue after entry into the treatment phase may be replaced if approved by the Sponsor**.** Details about the different cohorts are outlined in Section 5.2.

## 4.2. Inclusion Criteria

The below tables provide an overview of all inclusion and exclusion criteria which are required to be met for:

- AG019 cohorts: column 'AC'
- Combination cohorts: column 'CC'

[6] 4 repeat dose patients will be enrolled per AG019 cohort. In addition, both single dose patients in each AG019 cohort will be offered the option of being re-enrolled as repeat dose patients, provided that no safety concerns have been identified during their participation as a single dose patient. Therefore, if both single dose patients agree to be re-enrolled as repeat dose patients, the maximum number of repeat dose patients per AG019 cohort will be 6.

| Inclusion Criteria | AC | CC |
|---|---|---|
| Male or non-pregnant, non-lactating females, 18-40 (both inclusive) years of age or ≥ 12-17 (both inclusive) years of age[7]:<br>• Females of child bearing potential must have a negative serum pregnancy test at the screening visit, and, if heterosexually active, must<br>  • use a hormonal (oral, implantable or injectable) method of birth control which remains the same in both nature and dose throughout the study; *or*<br>  • have documentation of placement of an intrauterine device or intrauterine system; *or*<br>  • use a barrier method of contraception (i.e.; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository).<br>• Females unable to bear children must have documentation of such in the case report form (i.e., tubal ligation, hysterectomy, or post-menopausal [defined as a minimum of one year since the last menstrual period]).<br>• Males must agree to not conceive a child during their participation in the study and must agree to use a barrier method of birth control throughout the study (i.e.; condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository), or must have documentation of sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). | X | X |
| Diagnosis of diabetes according to the ADA recommended criteria:<br>• FPG concentration (after 8 or more hours of no caloric intake) ≥126 mg/dL*, *or*<br>• Plasma glucose concentration ≥200 mg/dL 2 hours after ingesting a 75-g oral glucose load in the morning after an overnight fast of at least 8 hours*, *or*<br>• Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, non-fasting) plasma glucose concentration ≥200 mg/dL<br>*In absence of unequivocal hyperglycemia, result to be confirmed by repeat testing | X | X |
| Evidence of auto-antibodies to at least 1 of the following β-cell autoantigens: insulin°, IA-2, GAD65, ZnT8<br>If evidence of autoantibody positivity is documented in the patient's medical file, the assessment does not need to be repeated as part of eligibility verification<br>°Insulin autoantibody positivity should be assessed within 10 days following initiation of exogenous insulin treatment. | X | X |
| Stimulated C-peptide measured during 4h Mixed Meal tolerance Test (MMTT) > 0.2 nmol/L *(note: this inclusion criterion does not apply to single dose patients)* | X | X |
| The first administration of AG019 should occur no later than 150 days post diagnosis. | X | X |
| Body weight ≥ 33kg | X | X |
| Willing and medically able to postpone live vaccine immunizations for at least 8 weeks after randomization | | X |

[7] Age-dependent enrolment in each cohort needs to be considered when evaluating this inclusion criterion.

| Inclusion Criteria | AC | CC |
|---|---|---|
| Ability and willingness of patient to participate fully in all aspects of this clinical study | X | X |
| Written informed consent obtained and documented (patient, parent, guardian as applicable) | X | X |
| Willingness to use a continuous glucose monitoring device and willingness to comply with the protocol defined glucose monitoring *(note: this inclusion criterion does not apply to single dose patients)* | X | X |
| • Total bilirubin ≤1.0 x upper limit of normal (ULN)<br>• Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤1.5 x ULN<br>• ≥1,000 lymphocytes/µL<br>• ≥1,000 polymorphonuclear neutrophils (PMN)/µL<br>• ≥100,000 platelets/µL<br>• Hgb ≥10 g/dL<br>• Serum Creatinin ≤1.5 x ULN<br>• eGFR ≥60 mL/min/1.73m²<br>• INR ≤0.1 above upper limit of normal<br>• Absence of clinically significant age appropriate abnormalities on all other lab values, except for abnormalities directly attributable to T1D. | X | X |

## 4.3.Exclusion Criteria

The below table provides an overview of all exclusion criteria which are required to be met for:

- AG019 cohorts: column 'AC'
- Combination cohorts: column 'CC'

| Exclusion criteria | AC | CC |
|---|---|---|
| Previous history of serious cytokine release syndrome to teplizumab or other humanized anti-CD3 monoclonal antibodies with no or minimal capacity to bind Fc receptors. | | X |
| Current use of any systemic antibiotics, except for the following: XXX | X | X |
| Use of immunosuppressive or immunomodulatory therapies, including systemic steroids within 1 month prior to randomization | X | X |
| Participation in another investigational drug trial within 12 weeks prior to the first study drug intake and during participation in this study | X | X |
| History of recurrent infections, other autoimmune diseases, cardiac disease, malignancy, or any other (chronic) medical condition which, in the investigator's opinion, could compromise participant safety | X | X |

| Exclusion criteria | AC | CC |
|---|---|---|
| Documented history of human immunodeficiency virus (HIV), Hepatitis Virus Type C (HCV), Hepatitis Virus Type B (HBV) infection | X | X |
| Evidence of active infection with Epstein-Barr Virus (EBV) or cytomegalovirus (CMV) | X | X |
| Positive result of SARS-Cov2 PCR test at screening or within 3 days before randomization | | X |
| Untreated hypothyroidism or active Graves' disease | | X |
| Evidence of any active infection with the exception of superficial skin infections | | X |
| Vaccination with live virus or organism within 8 weeks prior to randomization (vaccination with killed virus within 2 weeks prior to randomization should be avoided as vaccine immunity may be compromised; however it is not exclusionary) | | X |
| Evidence of active or latent tuberculosis (TB). All patients must be evaluated for TB; including history of TB or possible previous contact with TB. Appropriate screening tests (e.g. TST, TSPOT, QuantiFeron, or other appropriate tests) should be performed in all patients unless vaccinated with BCG. | X | X |
| Administration of anti-CD3 antibody in past year | X | X |
| Current therapy with any other anti-diabetic agents other than insulin (MDI, CSII or analogue). Current or planned therapy with experimental (i.e., unapproved) insulin. Patients on therapy for type 2 diabetes (e.g. metformin) should stop their therapy in order to be eligible for study participation. | X | X |
| Use of medications known to influence glucose tolerance | X | X |
| Daily use of systemic non-steroidal anti-inflammatory agents | X | X |
| Compromised GI mucosal integrity or motility, not attributable to T1D (i.e., recent diarrhea, gluten sensitive enteropathy, inflammatory bowel disease, irritable bowel syndrome), or current use of medications known to influence GI motility | X | X |
| Inability to swallow size 1 capsules. If needed, this may be verified by asking the patients to swallow one placebo capsule with water. | X | X |
| Alcohol or illicit drug consumption, which in the opinion of the investigator, may interfere with the patient's ability to comply with the study procedures | X | X |
| Active psychiatric problems, which in the opinion of the investigator, may interfere with the patient's ability to comply with study procedures | X | X |

## 4.4.Controlling Enrolment

Due to the design of the study, the enrolment plan, the regular MM/DSMB review and the fact that this is a multicentre study, controlling enrolment will be a critical factor for the success of this trial. Enrolment will be controlled by using the interactive web response system (Interactive Response Technology, IRT) in both Phase 1b and Phase 2a portions of this trial. All patients will require

registration in IRT. Details on the use of the IRT system, for registration of patients or for randomization of patients, will be outlined in the IRT manual.

## 4.5.Removal of Patients

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason. The Investigator and Sponsor also have the right to withdraw patients from the study. Patients may be removed from the study for the following reasons:

- Adverse reactions
- Clinical sepsis regardless of the cause
- At the request of the Investigator, MM, DSMB or Sponsor, whether for administrative or other reasons
- Protocol violation or unreliable behavior
- Termination of the study by the Sponsor

The date of and the reason for discontinuation will be recorded in the electronic case report form (eCRF).

Patients who withdraw from the study after receiving the first dose of IMP for reasons other than safety or tolerability may be replaced:

- Patients who withdraw before the Day 180 follow-up visit (primary end point) may be replaced upon consultation with the coordinating investigator and sponsor
- Patients who withdraw after the Day 180 follow-up visit will not be replaced

If a patient discontinues, all end of study visit procedures should be conducted.

If a patient is removed from the study, the date of the last dose of IMP and all observations collected up to the time of termination will be recorded on the eCRF along with the reason for termination. Scheduled safety evaluations and follow-up examinations (see Visit Schedule, Appendix A) will be conducted, if possible.

When a patient fails to return for scheduled assessments, the following efforts should at a minimum be made to contact him/her to determine a reason for the failure to return: 3 phone attempts, including the date and time, should be documented in the patient's source documents. If there is no response to the phone calls, a certified letter should be sent to the patient. After these efforts have been exhausted, a patient should be identified as lost to follow-up in the eCRF.

Patients enrolled into the Combination Cohorts who are excluded prior to receiving the first dose of IMP (teplizumab and AG019 or corresponding placebos) due to any of the criteria mentioned in Section 11.4.3.5 will be replaced. Replacement of patients will be done through the IRT. Details of this procedure are outlined in the IRT manual.

### 4.6.Special considerations

As this is a First In Human study, no participating patient is allowed to donate any sperm or egg cells during their participation in the study and for 12 months thereafter.

# 5. STUDY TREATMENT

## 5.1.Treatments

### 5.1.1AG019

Single dose patients will be treated with (2 or 6 capsules of) AG019.

All patients in the repeat dose cohorts, and all patients in the combination cohorts who are randomized to study treatment, will be treated for 8 weeks with AG019 with one of the doses listed in Table 2:

**Table 2:** AG019 dosing regimens for repeat dose patients

| Dose | Number of capsules | Total daily dose | Treatment duration |
|---|---|---|---|
| Low dose AG019 | 2 (1 morning, 1 evening) | XXX | 8 weeks |
| High dose AG019 | 6 (3 morning, 3 evening) | XXX | 8 weeks |

The total treatment duration for repeat dose patients is 8 weeks or 56 days. Patients will be required to take AG019 for 56 days, even if the Day 56 follow-up visit is not scheduled on Day 56 (there is a 2-day visit window on the Day 56 follow-up visit).

- If the Day 56 follow-up visit is scheduled on Day 54 or Day 55, patients will take their remaining AG019 home again and will continue to take AG019 until the evening dose on Day 56. The patients will then take their remaining AG019 back to the site on Day 90 for final accountability
- If the Day 56 follow-up visit is scheduled on Day 57 or Day 58, patients should be instructed to take AG019 until the evening dose on Day 56.

The daily dose of AG019 to be used in the Phase 2a portion of the study (combination cohorts) is not yet known and will be determined by the results of the Phase 1b portion of the study (AG019 cohorts). Based upon the data obtained in the nonclinical studies, the Sponsor anticipates that a 6-capsule regimen will be administered in the combination cohorts. Following rules will apply:

- If the DSMB concludes that no safety concerns are associated with the high dose of AG019 (6 capsules per day) in the Phase 1b portion of the study (AG019 cohorts), the patients enrolled

in the Phase 2a portion of the study (combination cohorts) will take the high dose of AG019 for 8 weeks.

- If the DSMB concludes that safety concerns are associated with the high dose of AG019 (6 capsules per day) in the Phase 1b portion of the study (AG019 cohorts) and that no safety concerns are associated with the low dose of AG019 (2 capsules per day), the DSMB will recommend lowering the AG019 dose in all ongoing and planned (AG019 and) combination cohorts .

If, at any time during the study, safety concerns associated with the high dose of AG019 are identified, the DSMB will recommend lowering the daily dose of AG019 in all ongoing and planned AG019 cohorts, as well as in all ongoing and planned combination cohorts.

XXX

### 5.1.2Teplizumab

All patients in the combination cohorts who are randomized to study treatment, as well as the first 2 patients in the combination cohorts who are treated in open label, will be treated for 12 days with teplizumab (daily IV infusions) according to the below schedule, in addition to their AG019 treatment:

XXX

XXX

The parameters used to calculate the daily dosing of study drug will be based on the height and weight at Day 1. The total cumulative average dose will be 9034 µg/m² or approximately ~17 mg for each patient. This total dose is the same as that used in previous trials in a 14 day regimen (Sherry et al., 2011; Hagopian et al., 2013; Herold et al., 2013; Herold et al., 2013) with the change that the protocol

has been shortened XXX

### 5.1.3T1D therapy during the study

During the study, all patients will receive appropriate diabetic therapy according to current ADA or equivalent guidelines. Treatment with commercially available insulin (multiple dose insulin injection therapy, continuous subcutaneous insulin infusion therapy or analogue therapies) is allowed. Treatment with other forms of commercially available insulin therapy, or treatment with experimental insulin, is not allowed during this study.

In accordance with ADA recommendations, preprandial glucose level target should be 4.4-7.2 mmol/L (80-130 mg/dL) and peak post prandial (1-2h after meal) glucose level target should be <10 mmol/L (<180 mg/dL).

### 5.1.4Other concomitant therapy

Any concomitant therapy used by the patient at any time following ICF signature must be recorded in the eCRF through the end of the short term follow-up must be recorded on the eCRF. In addition, for any SAEs that require medication for treatment, those medications must be recorded on the concomitant medications page. The medication name, dosage, frequency, route of administration, start and stop dates, and indication for use must be recorded. The medical monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies are administered. The MM will subsequently advise on actions to be taken, if any.

Prohibited therapy during the entire treatment period includes any antibiotic treatment known to affect the viability of *L. lactis* sAGX0407 (see Appendix B), β-cell stimulants, immunosuppressive or immunomodulatory therapies, including systemic steroids, other investigational drug(s), vaccination with live virus or organism, anti-CD3 antibody, any anti-diabetic agents other than insulin, medications known to influence glucose tolerance and daily use of non-steroidal anti-inflammatory agents.

For patients enrolled in the combination cohorts, premedication with ibuprofen or similar non-steroidal anti-inflammatory drugs (NSAID) and with an antihistamine is recommended and may be useful in patients who develop rashes during teplizumab administration.

As paracetamol may induce false positive signals of hyperglycemia by the continuous glucose monitoring devices, its use for reasons other than the reasons mentioned in the previous paragraph should be avoided as much as possible throughout the study.

## 5.2.Description of the cohorts

The enrollment plan is presented in Figure 1 and is described below.

### 5.2.1AG019 Cohorts

A total of 8 single dose patients and up to 24 repeat dose patients[8] will be enrolled sequentially into the following AG019 cohorts:

- **AG019 Cohort 1**: 2 capsules per day, patients 18-40y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients[8]
- **AG019 Cohort 2**: 6 capsules per day, patients 18-40y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients[8]
- **AG019 Cohort 3**: 2 capsules per day, patients 12-17y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients[8]
- **AG019 Cohort 4**: 6 capsules per day, patients 12-17y
  - Single dose: 2 patients
  - Repeat dose: up to 6 patients[8]

A total of 2 single dose patients and up to 6 repeat dose patients[8] will be enrolled in each open label safety cohort, designed to investigate the safety profile of AG019 administered alone.

*Single dose patients*

In a first stage, 2 single dose patients will be enrolled in a staggered way. Each of these patients will be treated for 1 day with AG019 (number of capsules of AG019 will correspond to the cohort these patients have been enrolled into). These patients will be followed up for a total of 4 days (Treatment day [Day 1] plus 3 additional days), after which they will have completed their study participation (Day 4).

After study completion of each single dose patient, the treating Investigator and MM will review the collected data, and if no safety concerns are identified, treatment of the next patient (i.e., the second single dose patient or the first repeat dose patient) can begin.

Each single dose patient will be offered the option of being re-enrolled as repeat dose patient, provided that no safety concerns have been identified during their participation as a single dose patient. A wash-

[8] 4 repeat dose patients will be enrolled per AG019 cohort. In addition, both single dose patients in each AG019 cohort will be offered the option of being re-enrolled as repeat dose patients, provided that no safety concerns have been identified during their participation as a single dose patient. Therefore, if both single dose patients agree to be re-enrolled as repeat dose patients, the maximum number of repeat dose patients per cohort will be 6.

out period of 7 days will be required before the single-dose patients can be re-enrolled as repeat dose patients, to ensure that no AG019 bacteria are present in their GI tract at the time of re-enrollment. In addition, these patients cannot be enrolled as staggered patients into the repeat dose group.

If a single dose patient wishes to be re-enrolled as repeat dose patient, all inclusion and exclusion criteria applicable to repeat dose patients should be met (including those criteria that do not apply to single dose patients).

*Repeat dose patients*

A minimum of 4 repeat dose patients will be enrolled per AG019 cohort. In addition, both single dose patients in each AG019 cohort will be offered the option of being re-enrolled as repeat dose patients in the same AG19 cohort, provided that no safety concerns have been identified during their participation as a single dose patient. Therefore, if both single dose patients agree to be re-enrolled as repeat dose patients, the maximum number of repeat dose patients will be 6.

Each of these repeat dose patients will be treated daily for 8 weeks with AG019. The first 2 repeat dose patients will be enrolled in a staggered way.

- After treatment of the first patient, the data collected up to the Day 7 follow-up visit will be reviewed by the treating Investigator and MM, and if no concerns are identified, the second patient will be treated.
- After the Day 7 follow-up visit of this second patient, the collected data will be reviewed by the treating Investigator and MM, and if no concerns are identified, the remaining patients will be treated.

Once all repeat dose patients in a cohort have had their Day 7 follow-up visit, the DSMB will review all available data from all enrolled patients in all cohorts. If no safety concerns are identified, the DSMB will formulate a recommendation to the sponsor on opening the next cohort(s) for treatment, according to the enrollment schedule outlined in Figure 1. Detailed guidelines on the recommendations to be formulated by the DSMB will be described in the DSMB Charter. A brief summary of these guidelines is included in Section 11.4.2.

All Repeat dose patients in all AG019 cohorts will be followed up for a total of 12 months (8 weeks of treatment plus 10 months of post-treatment follow-up). After the 12-month follow-up visit (Day 360) the patients will have completed their participation in the study.

### 5.2.2Combination Cohorts

The **Phase 2a double-blind portion** of the study will evaluate 2 cohorts ("combination cohorts") of 12 patients. Each patient will be administered 6 capsules daily [9] of AG019 (or placebo) for 8 weeks, in association with daily IV infusions of teplizumab for the first 12 days of the 8-week treatment period.

[9] The dose of AG019 to be administered in the Phase 2a portion of the study is not yet known and will be determined by the results of the Phase 1b portion of the study. If the AG019 cohorts reveal safety concerns associated with the 6-capsule treatment, the DSMB will recommend lowering the AG019 dose in all AG019 and combination cohorts.

- **Combination Cohort 1**: 12 patients 18-40y to receive AG019 (6 capsules per day[9], 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions
- **Combination Cohort 2**: 12 patients 12-17y to receive AG019 (6 capsules per day[9], 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 will be treated with active treatment (AG019 plus teplizumab) in an open label fashion. Patients 3-12 will be randomized (4:1) to receive (double) active treatment or (double) placebo in a double-blind fashion. Therefore enrollment will be done as follows:

- Treatment of patient 1: Treatment with AG019 plus teplizumab
  - Data review of all data collected up to the Day 12 follow up visit (the last day of teplizumab infusion) (treating Investigator and MM)
- Treatment of patient 2: Treatment with AG019 plus teplizumab
  - Data review of all data collected up to the Day 12 follow up visit (the last day of teplizumab infusion) (DSMB – review of all available data from all patients in all cohorts)
- Treatment of patients 3-12: randomization (4:1) to double active treatment or double placebo.

All patients in all Combination cohorts will be followed up for a total of 12 months (8 weeks of treatment plus 10 months of post-treatment follow-up). After the 12-month follow-up visit (Day 360) the patients will have completed their participation in the study.

## 5.3.Identity of Investigational Medicinal Product

### 5.3.1AG019

The clinical formulation of AG019 DS consists of live GM *L. lactis* bacteria, genetically modified to secrete hIL-10 and hPINS. The bulk DS is a slightly yellow, lyophilized powder.

The oral IMP consists of solid, XXX capsules filled with AG019 DS and XXX.

XXX.

XXX

### 5.3.2Teplizumab

The formulation of teplizumab consists of:

XXX

XXX

## 5.4.Labelling, Packaging and Storage

XXX

## 5.5.Investigational Medicinal Product Administration

XXX

Detailed instructions for dose preparation and dispensing to patients will be provided to the clinical site by the Sponsor or its designee.

Total bilirubin, AST, ALT, LDH, Complete Blood Count (CBC), and INR will be evaluated to verify the need to withhold teplizumab (or placebo) infusion prior to each (potential) teplizumab administration, as described in Appendix A. The drug infusion withholding criteria presented in Section 11.4.3.5 should be evaluated.

## 5.6.Placebo/Comparator

XXX

AG019 placebo and teplizumab placebo will be packaged identically to their active counterparts and will be matched for size, color and taste (as applicable), to prevent possible breaches in the blinding.

Administration of placebo will be identical to administration of its respective active treatment.

## 5.7.Study Drug Accountability

The Investigator or his/her designee is responsible for ensuring adequate accountability of all used and unused study drug (AG019, teplizumab and their corresponding placebos). This includes acknowledgement of receipt of each shipment of study drug (quantity and condition), patient dispensing records and returned or destroyed study drug. Dispensing records will document quantities received. Quantities dispensed to patients will be documented, including lot number, date dispensed, patient identification number, patient initials and the initials of the person dispensing the study drug.

Throughout the course of the study, the Sponsor or its designee will perform study drug accountability and provide instructions for adequate study drug disposal. Study drug accountability records must be readily available for audit by the Sponsor or its designee and for inspection by regulatory authorities at any time.

The Investigator will not allow study drug to be given to any patient not included in the study or any unauthorized person.

It is the responsibility of the site personnel to maintain adequate study drug dispensing records.

AG019 (or corresponding placebo) compliance will be reviewed by the study staff at every follow-up visit during the active treatment period. Each patient will be 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 will be performed to assess compliance.

Teplizumab (or corresponding placebo) accountability and compliance will be verified at every follow-up visit by the site staff. Adequate documentation of receipt, dispensing and return will be maintained by the site staff.

## 5.8.Return and destruction of study drug

All patients are required to return all empty medication blisters, partially used blisters and unused blisters to the study site upon completion of treatment or in case of withdrawal. If a patient is lost to follow-up during the treatment phase, the site should make every reasonable effort to obtain the used, partially used and unused blisters.

Unused AG019 capsules will be destroyed by a dedicated drug destruction facility. Local destruction by the site is not allowed unless mandated by the site's local procedures. If unused, used and partially used study drug is destroyed on site, this can only be done after IMP accountability has been performed by the Sponsor or its designee.

Materials used for teplizumab infusions, as well as empty teplizumab vials, can be destroyed locally by the sites. All materials and vials are to be treated as hazardous medical waste per the site's Standard Operating Procedures.

Unused teplizumab vials will be destroyed by a dedicated drug destruction facility. Local destruction by the site is not allowed unless mandated by the site's local procedures. If unused, used and partially used study drug is destroyed on site, this can only be done after IMP accountability has been performed by the Sponsor or its designee.

## 5.9.Method of Assigning Patients to Treatment

In the AG019 cohorts, all patients (single dose and repeat dose) will be treated with AG019. Registration of every patient will be required through the IRT (see Section 4.4).

In the combination cohorts, the first 2 patients will be treated with AG019 + teplizumab. The remaining 10 patients in each combination cohort will be randomized (4:1) to study drug or placebo. Patients randomized to receive study drug will be treated with AG019 + teplizumab, patients randomized to receive placebo will be treated with AG019-placebo and teplizumab-placebo. Randomization will be done through the IRT.

During the screening and treatment phase, every study visit for every patient will need to be registered in the IRT. Details about the functionality and use of the IRT are found in the IRT manual.

## 5.10.Blinding

For the randomized patients in the combination cohorts, blinding will be accomplished by arranging for AG019 and placebo components as well as teplizumab and placebo components to have identical packaging. IMP will be delivered in a blinded fashion, as outlined in the Pharmacy Manual. All study personnel at the site, the patient and the Sponsor (except for the clinical supply manager) will be blinded to treatment allocation in the randomized portion of the combination cohorts for the first 6 months of the study. Once all patients in all combination cohorts have completed their 6-month follow-up visit (Day 180), unblinding will be done and all data will be analyzed and reported. After completion of the full 12 months follow-up all additional data will be analyzed and reported separately.

The identity of IMP assigned to patient numbers or to individual boxes of IMP can be accessed through IRT. When it is medically indicated, the Investigator may contact the MM and Sponsor to discuss the possibility of breaking the blind for a patient. A patient's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the patient (i.e., medical emergency). In the absence of a medical emergency, breaking the code should not be considered.

For emergency blind-break procedures, contact the MM or his/her designee at the contact numbers provided in the Study Manual. The reason and date/time of the unblinding and the name of the individual who broke the blind must be appropriately documented in the patient's medical record or source documents and in the eCRF.

# 6. ASSESSMENTS

At predefined time points, all participating patients will undergo a series of assessments in order to evaluate the safety and tolerability of AG019 alone as well as the safety and tolerability of AG019 co-administered with teplizumab. Additional assessments will be done in order to evaluate the pharmacodynamics activity and the pharmacokinetic profile of AG019 alone as well as the safety and tolerability of AG019 co-administered with teplizumab.

XXX

## 6.1. General assessments

General assessments for this study will include:

- **Informed Consent**: Before study procedures are performed, patients will be informed about the study and required to sign and date the IRB/IEC approved ICF. For patients <18 years of age, assent of the patient will be obtained, as well as consent from the parents and/or legally acceptable representative. Details about informed consent procedure are listed in Section 11.3.
- **Inclusion/exclusion criteria**: As part of the screening visit, all inclusion and exclusion criteria listed in Section 4 will be verified.
- **Medical History and demographic data**:
    - 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
    - Demographic data will include age, ethnicity and year of birth
- **Physical examination** including visual inspection of skin, examination of eyes, ears and throat, auscultation of heart, lungs and abdomen, and percussion/palpation of abdomen. Other assessments may be performed at the discretion of the investigator. Clinically significant abnormalities will be recorded in the eCRF.
- **Vital signs** including height (collected at screening only), weight, sitting blood pressure, heart rate, respiratory rate and body temperature.

- **12-lead electrocardiogram (ECG)**: To monitor the heart function of the study participants, the investigator will perform a 12-lead ECG and will determine whether the result of this test is normal or not. Abnormal test results will be recorded as adverse events.
- **Placement of a continuous glucose monitoring (CGM) device:** Once all in/exclusion criteria are verified, the investigator will train the patient on the placement of the CGM device during the baseline visit. The CGM device will be placed, so the patient will know how to do this at home. The placement of the CGM, as well as the first CGM reading, will be done prior to administration of the first dose of study drug(s). The Sponsor will supply the CGM devices.
- **Tuberculosis test:** As part of the eligibility verification, all patients will undergo a test to determine whether the patient shows signs of active or latent tuberculosis. The decision on the type of test to be used is left to the discretion of the investigator, and could include e.g. TST, TSPOT, QuantiFeron or other appropriate tests.
- **Concomitant medications**: At every visit, the investigator will obtain information about concomitant medications the patient is taking (including dose, frequency, route of administration, start and stop dates)

## 6.2.Safety Assessments

Safety will be assessed by collecting and recording Adverse Events (AEs) and laboratory assessments and the presence of *L. lactis* sAGX0407 in whole blood.

The study will utilize local laboratories for safety assessments. The clinical laboratory will indicate laboratory values out of normal ranges. The Investigator must assess all abnormal clinical laboratory results for clinical significance in a timely fashion. A notation of 'clinically significant' (CS) or 'non-clinically significant' (NCS) with initials and date will be documented on the respective laboratory report next to any abnormal value. An abnormal clinical laboratory value will be considered and documented as an AE, if in the opinion of the Investigator, it is clinically significant. The Investigator will follow proper adverse event reporting procedures.

For details on the data to be collected for adverse events, please refer to Section 8.

XXX

## 6.3.Laboratory Assessments

### 6.3.1General considerations

Throughout the study, blood samples will be collected at regular intervals, as described in the Visit schedule

XXX

XXX

### 6.3.2Local lab assessments

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), AST, ALT, lactate dehydrogenase (LDH), total protein, albumin, total bilirubin
- Pregnancy tests for women of childbearing potential: serum (at screening), urine (at other visits – the Sponsor can provide urine dip sticks if needed)
- Coagulation tests: 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)

Total bilirubin, AST, ALT, LDH, Complete Blood Count (CBC), and INR will be evaluated to verify the need to withhold teplizumab (or placebo) infusion before each (potential) teplizumab administration, as described in the Visit Schedule The drug infusion withholding criteria presented in Section 11.4.3.5 should be evaluated.

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. Potential reactivation will be assessed at regular intervals by viral serologies (IgG/IgM) and/or polymerase chain reaction (PCR) for viral load.

As part of the eligibility verification, the presence of one or more autoantibodies against beta cell antigens will be verified. If documentation of autoantibody positivity is found in the patient's medical file, the assessment does not have to be repeated at screening.

As part of the eligibility verification, all new patients will be tested for SARS-Cov2 at screening and within 3 days before the start of teplizumab/placebo infusions.

### 6.3.3Central lab assessments

#### 6.3.3.1Pharmacokinetic Assessments

Following parameters will be assessed for analysis of systemic and local exposure to *L. lactis*:

- Presence of live *L. lactis* clinical strain bacteria in whole blood,XXX
- Measurable serum levels of hIL-10 and hPINS, XXX
- Presence of *L. lactis* clinical strain bacteria in fecal excretion, XXX

Throughout the study, blood and feces samples will be collected at regular intervals for analysis by the central laboratory, as described in the Visit schedule.

- Blood sample collection for PK analysis, collected form all repeat dose patients in all AG019 cohorts and the combination cohorts
- Feces sample collection for PK analysis, collected from all repeat dose patients in AG019 Cohorts 2 and 4, and from all patients in the combination cohorts

Blood and feces samples for PK assessments will be analyzed by a central lab.

Details on sample collection, labeling, storage, shipment and analysis are described in the central lab manual.

The Site will train the patients on how to collect feces samples. All stool samples will be collected and labeled with patient number, and date and time of sample collection.

#### 6.3.3.2Mechanistic Assessments

The pharmacodynamic activity of the IMP will be assessed by measurement of biomarkers in blood and serum samples. Relevant parameters will be assessed, including immune markers for effect, relevant T1D parameters and relevant cytokines.

Throughout the study, blood samples will be collected at regular intervals for analysis by the central laboratory, as described in the Visit schedule. Samples intended for mechanistic assessments will be collected from all repeat dose patients in AG019 Cohorts 2 and 4, and from all patients in the combination cohorts

All collected samples will be analyzed by a central lab. Details on sample collection, labeling, storage, shipment and analysis are described in the central lab manual.

### 6.3.3.3Metabolic outcome assessments

Throughout the study, following metabolic outcome assessments will be performed at regular intervals as described in the Visit schedule. Blood samples collected as part of these assessments will be analysed by a central lab:

- Insulin dose adjusted $HbA_{1C}$ (IDAA1c = HbA1c (%) + [4 x insulin dose (U/Kg/24h)]): insulin dose adjusted measurement of glycemic control
- 4h mixed meal tolerance test (MMTT): measure of C-peptide levels, C-peptide area under the curve (AUC) and blood glucose levels after mixed meal stimulation

Details on collection, processing, storage and shipment will be provided in the central lab manual.

#### 6.3.3.3.1Mixed Meal Tolerance Test

The MMTT is a liquid meal that is ingested in the fasting state with timed measurements. Also this test is meant to assess the potential participant's insulin production capability. This assessment will be conducted within 21 days of randomization (except for the single dose patients) and at predefined follow-up visits as outlined in the visit schedule. In order for the results to be meaningful, it is important for the participant to follow certain dietary and lifestyle guidelines in the days preceding the test. A high carbohydrate diet must be followed for the three days leading up to the test.

The test should be rescheduled if the participant has a blood glucose (measured on his/her home meter) less than 70 mg/dL (3.85 mmol/L) or greater than 200 mg/dL (11.1 mmol/L).

The participant is required to fast starting the night before the test, and is instructed to consume only water for at least ten hours preceding the test. Long-acting insulin or Basal rates (insulin pump users) will continue as normal. The use of rapid-acting insulin is acceptable up to 2 hours before the MMTT and the use of short-acting insulin up to 6 hours before the MMTT to correct hyperglycemia.

Mixed Meal Dose: The test meal (Boost High Protein) is given at a dose of 6 mL per kilogram body weight. Maximum dose is 360 mL. Boost High Protein is supplied in 8 fluid ounce containers. The Sponsor will supply the test meals.

The MMTT takes approximately four hours to complete, and must be scheduled in the morning (i.e. must be started before 10 AM). It is important to carefully review the eligibility criteria with the participant before starting the test, since if certain criteria have been violated the test will need to be rescheduled for another date.

Procedure: Mixed Meal Dose

Step 1. Ensure the patient is currently fasting

Step 2. Prepping Participant for MMTT

a. The MMTT must begin between 7:00 - 10:00 a.m. for proper interpretation.
b. Obtain the weight of the participant and calculate Boost High Protein meal size = 6 mL/kg, up to 360 mL, 1lb = 0.45 kg

c. The MMTT test uses a standard oral mixed meal formula (Boost High Protein) composed of liquid sucrose, soy protein, casein, and soy oil. The test meal is given at a dose of 6 kcal/kg body weight, at 1 kcal/mL to a maximum of 360 kcal.
d. The participant should remain sitting or resting in bed quietly throughout the test.
*Note: The participant can engage in quiet, non-strenuous activities such as reading, playing cards, watching TV and may walk to the bathroom between blood draws if necessary (but should otherwise remain in resting position until the test is completed).*
*It is recommended that participants not be asked to answer questions for the purpose of completing case report forms during the MMTT.*
e. Place an IV line into an antecubital vein, using an intracatheter/butterfly needle (usually 20 or 22 gauge depending upon the size of the participant). *Note: The intracatheter may be kept patent between samples with a slow saline drip or heparinized saline solution (as per the guidelines of your institution) in a 20 mL syringe, injecting about 2-3 mL after each blood draw.*
f. Before the procedure, fill several 3 mL syringes with luer-lock tips with 1 mL normal saline solution to flush the adapter after each blood draw. This is only necessary if the blood sampling is more than 3 minutes apart.

Step 3. Obtain baseline samples:

a. The first sample should be taken at least 10 minutes after establishing the line(s) and when participant is calm and relaxed (if possible, depending on age) - this is the "-10 minute" sample
b. The second sample should be taken just prior to drinking the Boost High Protein - this is the "0 minute" sample
c. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost High Protein must be completely consumed within five (5) minutes.
d. Obtain post-meal blood samples.
e. Samples are taken at 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes
f. A timer should be turned on at 0 min
g. The actual start time for each blood draw should be recorded in the patient's source documents and on the Requisition form
h. Upon completion of the test, the participant should have a snack, for example peanut butter or cheese crackers, coffee, milk or ginger ale.

## 6.4.Other assessments

### 6.4.1Electronic Patient Reported Outcomes (ePRO)

All patients (except for the single dose patients) will be asked to keep an electronic diary. The diaries will contain following information:

- Safety related information (all experienced adverse events and serious adverse events, including signs of clinical sepsis and known risks associated with the use of anti-CD3 mAb or with T1D glycemic control)
- Occurrence of hypoglycemic events including all relevant information for standard classification (these will be captured separately from other safety related information)
- Deviations from planned study drug intake (e.g. missed doses or incorrect doses taken)
- Changes in concomitant medication intake
- Insulin requirements: Daily

The electronic diaries will be kept from the day of signing the informed consent until the patient is withdrawn or completes the study.

A site research coordinator will train the patients on how to complete the electronic diary.

The research coordinator will review these diaries at every follow-up visit to verify that they have been completed properly and consistently. If needed, the patients will be re-trained on the completion of the diary. All relevant data reported in the diaries will be translated into the eCRF by the research coordinator.

### 6.4.2Continuous Glucose Monitoring (CGM)

All study patients (except for the single dose patients) will receive a XXX CGM device for the entire duration of their study participation. The investigator will train the patients on how to place the CGM device and will provide written instructions to the patient. The data generated by the device will be downloaded at every site visit. The devices will store data for up to 30 days.

# 7. STUDY PROCEDURES

## 7.1.Visit Schedule

The schedule of assessments, evaluations and laboratory studies is presented in XX. A summary of procedures to be performed per visit is given below.

## 7.2.Single Dose Patients

### 7.2.1Screening Visit (Day -28 – Day 0)

Following screening observations and procedures will be completed within 28 days prior to randomization:

- Signed and dated ICF
- Assessment against inclusion and exclusion criteria
- Medical history

- Demographic Data
- Physical Exam
- Vital signs
- 12-lead ECG
- Serum pregnancy test (in females of childbearing potential)
- Blood sampling for local lab (hematology, chemistry, specific screening blood analysis and autoantibodies testing)
- Infectious diseases (EBV, CMV, HIV, HCV, HBV)
- Tuberculosis test
- Drugs of abuse test
- Record concomitant medications
- Record adverse events
- Register patient in IRT
    - Registration in IRT should be done as soon as eligibility is confirmed and ICF is signed. Ideally this should be done before the Day 1 visit (start of treatment visit).

### 7.2.2Treatment Visit (Day 1)

Prior to the first intake of AG019, following observations and procedures will be completed:

- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Record Adverse events
- Record concomitant medications
- Administer morning dose of AG019

For Single Dose patients, it is recommended to schedule the Day 1 visit on a Monday, Tuesday or Friday, to avoid having to schedule the Day 4 visit (end of study visit) on a weekend day.

### 7.2.3End of Study visit (Day 4)

Following observations and procedures will be completed:

- Physical exam
- Vital signs
- 12-lead ECG (only if there is suspicion of cardiac problems)
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab
- Record Adverse events
- Record concomitant medications
- IMP accountability

## 7.3.Repeat Dose Patients

### 7.3.1Screening Visit (Day -28 – Day 0)

Following screening observations and procedures will be completed within 28 days prior to randomization:

- Signed and dated ICF
- Assessment against inclusion and exclusion criteria
- Medical history
- Demographic Data
- Physical Exam
- Vital signs
- 12-lead ECG
- Serum pregnancy test (in females of childbearing potential)
- Blood sampling for local lab (hematology, full chemistry, specific screening blood analysis, infectious disease, autoantibodies)
- SARS-Cov2 PCR test (only applicable for patients in the combination cohorts)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Blood sample for central lab PK
- Feces collection for central lab PK[10] (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Tuberculosis test
- Mixed Meal Tolerance Test (MMTT) for C-peptide and glucose assessments
- Drugs of abuse test
- Record concomitant medications
- Record adverse events
- ePRO preparation / explanation
- Assessment of insulin use and hypoglycemic events
- Register patient in IRT
    - Registration in IRT should be done as soon as eligibility is confirmed and ICF is signed to allow for timely shipment of study drug. Ideally this should be done at least 1 week before the Day 1 visit (start of treatment visit).

### 7.3.2Baseline Visit (Day 1 – start of active treatment)

Prior to the first administration of IMP, following observations and procedures will be completed:

[10] Sites should make every reasonable effort to collect feces during the screening visit. If feces cannot be collected during the screening visit, patients will be asked to collect feces between the Screening visit and the Day 1 visit, according to the instructions provided by the site and the collection materials provided by the central lab.

- SARS-Cov2 PCR test (only applicable for patients in the combination cohorts, to be taken within 3 days before the first teplizumab/placebo infusion)
- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Record concomitant medications
- Record adverse events
- Placement of CGM device, training of patient on how to place the CGM device at home
- ePRO review including insulin use and hypoglycemic events
- Blood sampling for local lab (hematology, full chemistry, INR)
- Evaluation of drug infusion withholding criteria (only for Combination Cohorts)
- Administer first dose of AG019/placebo (for combination cohorts, randomized treatment should be respected)
- First teplizumab/placebo (randomized treatment should be respected)

For patients enrolled in the Repeat Dose AG019 cohorts, it is recommended to schedule the Day 1 visit on a Friday, to avoid having to schedule follow-up visits on weekend days.

For patients enrolled in the Combination cohorts, it is recommended to schedule the Day 1 visit on a Monday, to avoid study drug infusions in 2 consecutive weekends.

### 7.3.3Visits during active treatment phase

#### 7.3.3.1For all patients in AG019 cohorts and Combination Cohorts

##### 7.3.3.1.1Day 4 follow-up visit

Following observations and procedures will be completed:

- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, full chemistry, INR)
- Record concomitant medications
- Record adverse events
- Study drug accountability
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- Evaluation of drug infusion withholding criteria (only for Combination Cohorts)
- Teplizumab/placebo (randomized treatment should be respected) infusion

##### 7.3.3.1.2Day 7 follow-up visit

Following observations and procedures will be completed:

- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, full chemistry, INR)
- Record concomitant medications
- Record adverse events
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- Evaluation of drug infusion withholding criteria (only for Combination Cohorts)
- Teplizumab/placebo (randomized treatment should be respected) infusion
- Study drug accountability

#### 7.3.3.1.3Day 12 follow-up visit

Following observations and procedures will be completed:

- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, full chemistry, INR)
- Record concomitant medications
- Record adverse events
- Infectious disease monitoring (PCR)
- Blood sample for central lab PK
- Blood sample for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- Evaluation of drug infusion withholding criteria (only for Combination Cohorts)
- Teplizumab/placebo (randomized treatment should be respected) infusion including blood sample for safety labs and evaluation of drug infusion withholding criteria (only for Combination Cohorts)
- Study drug accountability

#### 7.3.3.1.4Day 28 follow-up visit

Following observations and procedures will be completed:

- Register visit in IRT
- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Record concomitant medications
- Record adverse events
- Infectious disease monitoring (PCR)
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- AG019/placebo dispensing (for combination cohorts, randomized treatment should be respected)
- AG019 drug accountability

#### 7.3.3.1.5Day 56 follow-up visit (End of Treatment)

Following observations and procedures will be completed:

- Physical Exam
- Vital Signs
- 12-lead ECG
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Blood sample for central lab PK
- Feces collection for central lab PK (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Record concomitant medications
- Record adverse events
- Infectious disease monitoring (PCR)
- AG019 drug accountability
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download

### 7.3.3.2Additional visits for patients in Combination Cohorts

For patients in the Combination cohorts, additional follow-up visits for teplizumab infusions will take place on Day 2, Day 3, Day 5, Day 6, Day 8, Day 9, Day 10 and Day 11. During each of these visits, following observations and procedures will be completed:

- Register visit in IRT
- Record concomitant medications
- Record adverse events
- Teplizumab infusion including blood sample for safety labs and evaluation of teplizumab infusion withholding criteria

### 7.3.3.3Additional feces sampling (at home) on Days 58, 60, 62 and 64 (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)

After the Day 56 follow-up visit, patients in AG019 Cohorts 2 and 4 and in the combination cohorts will be asked to collect additional feces samples every other day until Day 64. The samples will be collected and kept in the patient's freezer, and will be handed over to the site personnel during the next follow-up visit. Sites can arrange for a courier to pick up the collected samples from the patient's home after Day 64, if the patient does not want to store the feces samples in his/her freezer until the next site visit (Day 90).

Details on collection, labelling and storage of the samples will be explained verbally and in writing to the patients.

A 2-day visit window is allowed for the Day 56 visit. The first feces sample will be collected in the hospital on the Day 56 follow-up visit, regardless on which day this visit takes place. If it is not possible to collect a feces sample at the site, the sample collection equipment will be given to the patient and a sample will be collected at home, ideally on the same day. Subsequent samples will be collected every 2 days following this visit, as described in the below table.

| EOT visit date | First sample | Second sample | Third sample | Fourth sample | Fifth sample |
|---|---|---|---|---|---|
| D54 | D54 | D56 | D58 | D60 | D62 |
| D55 | D55 | D57 | D59 | D61 | D63 |
| D56 | D56 | D58 | D60 | D62 | D64 |
| D57 | D57 | D59 | D61 | D63 | D65 |
| D58 | D58 | D60 | D62 | D64 | D66 |

### 7.3.4Visits after the active treatment phase

#### 7.3.4.1Day 90 follow-up visit

Following observations and procedures will be completed:

- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Infectious disease monitoring (PCR)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Blood sample for central lab PK
- Mixed Meal Tolerance Test (MMTT)
- Record concomitant medications
- Record adverse events
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download

#### 7.3.4.2Day 180 follow-up visit

Following observations and procedures will be completed:

- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Mixed Meal Tolerance Test (MMTT)
- Record concomitant medications
- Record adverse events
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- 12-lead ECG (only if there is suspicion of cardiac problems)

#### 7.3.4.3Day 270 follow-up visit

Following observations and procedures will be completed:

- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)

- Blood sampling for local lab (hematology, chemistry)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Record concomitant medications
- Record adverse events
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download

#### 7.3.4.4Day 360 follow-up visit (End of Study)

Following observations and procedures will be completed:

- Physical Exam
- Vital Signs
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Infectious disease monitoring (PCR)
- Blood sampling for mechanistic assessments (only for repeat dose patients in AG019 Cohorts 2 and 4 and for patients in the combination cohorts)
- Blood sampling for central lab (HbA1c)
- Mixed Meal Tolerance Test (MMTT)
- Record concomitant medications
- Record adverse events
- ePRO review including insulin use and hypoglycemic events
- CGM readings/download
- 12-lead ECG

## 7.4.Unscheduled visits

If a patient returns for an unscheduled visit, following observations and procedures will be completed at a minimum:

- Register visit in IRT
- Physical Exam
- Vital Signs
- 12-lead ECG (only if there is suspicion of cardiac problems)
- Urine pregnancy test (in women of childbearing potential)
- Blood sampling for local lab (hematology, chemistry)
- Infectious disease monitoring (PCR)
- Record concomitant medications
- Record adverse events

If a patient returns for an unscheduled visit and this visit results in study discontinuation for any reason, the procedures outlined in the End of Study visit (Section 7.3.4.4) should be conducted.

# 8. ADVERSE EVENT REPORTING

Throughout the study, AEs will be recorded in the source documents and transcribed onto the appropriate pages of the eCRF regardless of whether the AEs are considered treatment related. All AEs with onset dates from signature of the ICF through study exit will be recorded as an AE on the eCRF. All SAEs with onset dates from signature of the ICF through study exit must be recorded following the guidelines in Sections 8.4, 8.6, 8.7, 8.8 and 8.9. Any AE that occurs at any time after completion of the study, which the investigator considers to be related to study drug, must be reported.

Conditions existing prior to screening will be recorded as part of the patient's medical history. To avoid confusion, the AE should be recorded in standard medical terminology. The Investigator is responsible for assessing the relationship of AEs to the AG019 as well as to teplizumab (Section 8.3).

## 8.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered an investigational product or in whom an investigational product is to be administered, and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to this investigational product. This includes an event that emerges during treatment having been absent pre-treatment or an event that worsens relative to the pre-treatment state ("treatment-emergent adverse event" [TEAE]). Recurrent symptoms of a chronic pre-existing condition are not considered AEs unless they occur in a worse or unexpected pattern during study drug administration.

## 8.2. Assessing Severity of Adverse Events

The severity of adverse events will be designated as mild, moderate, severe, life threatening, or fatal per National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.0. If not specifically addressed in NCI CTCAE version 4.0, use the table below:

| | |
|---|---|
| Mild – Grade 1 | Transient or mild discomfort; requiring no limitation of activity; no therapy |
| Moderate – Grade 2 | Mild-moderate impact on activity; requiring some assistance and medical intervention |

| | |
|---|---|
| Severe – Grade 3 | Marked impact on activity; requiring some assistance and medical intervention |
| Life Threatening – Grade 4 | Complete disability; requiring significant assistance and medical intervention and/or hospitalization |
| Death – Grade 5 | Adverse event with fatal outcome |

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 8.2.1Grading of Hypoglycemic and Hyperglycemic Events

For this study of participants with type 1 diabetes, the NCI-CTCAE will not be used to grade hypoglycemia and hyperglycemia. Please refer to the grading criteria for hypoglycemic and hyperglycemic events below.

In line with the Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes (International Hypoglycaemia Study, 2017), 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.

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 (DKA) should be reported as grade 4 hyperglycemia (a single adverse event) resulting in hospitalization and/or life threatening consequences.

## 8.3.Assessing Relationship to Study Treatment

All AEs will be 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, as follows:

- Not related: No relationship between the AE and the administration of IMP, judged clearly and incontrovertibly due to extraneous causes (disease, environment etc.).
- Unlikely: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.
- Possible: The AE might be due to the administration of IMP. An alternative explanation such as concomitant medication(s), concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.
- Probable: The AE might be due to the administration of IMP. An alternative explanation such as concomitant medication(s), concomitant disease(s) is less likely. The time relationship is suggestive, i.e., it is confirmed by de-challenge.
- Definite: There is no uncertainty in relationship to the administration of IMP. The AE cannot be reasonably explained by an alternative explanation such as concomitant medication(s), concomitant disease(s). The time relationship is very suggestive, i.e. it is confirmed by de-challenge and re-challenge.

“Not related and Unlikely related” correspond to “no reasonable possibility”. “Possible, probable and definite” correspond to “reasonable possibility”.

## 8.4.Recording of Adverse Events

All AEs encountered during the clinical study will be recorded in detail in the source documents and documented in the eCRF, from signature of the ICF through study exit. All AEs that meet the seriousness criteria (Section 8.6) should also be recorded on the SAE Report Form. All SAEs must be reported to the sponsor or delegated organization within the timeline stated in Section 8.7.

The recording of AEs will be based on data obtained from the following sources:

- Medical and surgical history
- Physical examinations including vital signs
- Clinical laboratory test results
- Information provided by the patient, either during the follow-up visits or in the patient’s diary

All clinical events, including both observed (such as any reaction at sites of application) and volunteered problems, complaints, or symptoms, are to be recorded. The need to capture this information is not dependent upon whether the clinical event is associated with the use of any IMP.

If at any time during the study a patient develops symptoms suggesting clinically significant bacteremia that can be attributed to *L. lactis* sAGX0407 (as determined by three consecutive positive blood cultures), study treatment will be discontinued.

A disposition plan for the management of clinical sepsis is provided in Appendix B.

For the purposes of this study, hypoglycemia events classified as level 1 as defined in Section 8.2.1 will not be recorded separately on the hypoglycemia event eCRF, unless the investigator feels that the event is medically important. Hypoglycemia events level 2 and 3 as defined in Section 8.2.1 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 as mentioned in Section 8.6, should be recorded as serious adverse events in the eCRF.

Major hyperglycemic events as defined in Section 8.2.1 will be recorded as serious adverse events. In addition, all hyperglycemia events meeting the definition of SAE as mentioned in Section 8.6, should be recorded as serious adverse events. Any other hyperglycemic event (defined as blood glucose >140mg/dL for at least 20 minutes) will not be recorded as adverse event, unless the investigator considers the event to be medically important.

## 8.5.Adverse Event Follow-up Period

All patients with AEs will be followed until the event resolves, stabilizes, becomes chronic, the patient completes the study or the patient is lost to follow-up.

## 8.6.Serious Adverse Event Definition

In addition to classifying the AE as mild, moderate, severe, life-threatening or fatal, the Investigator should determine whether or not an AE is an SAE. The Investigator shall make an accurate and adequate report on any SAE to the Sponsor or its designee and to any IRB/IEC that has reviewed and is continuing to review the study regarding any SAEs (see Sections 8.7 and 8.9).

An 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, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following situations will be considered important medical events and must be reported as SAEs:

1. Grade 4 or higher lymphopenia for 7 or more days occurring in the first 30 days after the start of the teplizumab infusion.

2. Grade 3 or higher lymphopenia occurring anytime later than the first 30 days after the start of the teplizumab infusion.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event causing the prolongation is an SAE. Planned hospitalizations are not considered SAEs.

"Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at an emergency department.

Pregnancy in a study participant, or in the female partner of a male participant, occurring after signature of the ICF are considered immediately reportable events using specific reporting forms and must be reported within 1 calendar day after the Investigator has gained knowledge of them. The patient (if female) will discontinue IMP. Details of the outcome of the pregnancy (e.g. full term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported no longer than one month after the expected due date. Any abnormal outcome in the neonate will be followed-up.

## 8.7.Reporting of Serious Adverse Events

For any SAEs, regardless of causal relationship, the Investigator must inform the Sponsor's pharmacovigilance vendor (XXX), the contract research organization (CRO) Project manager or Lead clinical research associate (CRA) as well as the Sponsor's representatives mentioned on the Contact Details page of this protocol within 1 calendar day of becoming aware of the event by mailing the completed SAE Report Form and any other pertinent SAE information to XXX as indicated on the SAE Report Form. Follow-up information collected for an initial report of an SAE must be reported to XXX within 1 calendar day of receipt by the Investigator.

XXX

Reports of any pregnancy in a patient, or partner of a patient, must also be emailed to the above mentioned email address within 1 calendar day (see Section 8.6).

The information to be recorded for SAEs should include the following:

- The onset of any new AE or the worsening of an observation documented from signature of the ICF
- The specific type of event in standard medical terminology
- The duration of the clinical event (start and stop dates)
- The severity of the clinical event
- Seriousness (SAE) criteria
- Relevant laboratory and examination results
- Dosing schedule of IMP(s)

- Indications and dosing schedules of concomitant medications
- Relationship of the AE to the IMP(s) as defined in Section 8.3
- Management of IMP(s) administration and other action taken to alleviate the clinical events
- Past medical and surgical history and concurrent diseases
- De-challenge/re-challenge results, if applicable
- The outcome of the clinical event
- Serious Adverse Event Recording Period

SAEs will be collected and recorded by the Investigator beginning from the signature of the ICF until the patient is withdrawn or has completed the study.

## 8.8.Serious Adverse Event Follow-up Period

All patients who experience SAEs will be followed until the events resolve, stabilize, become chronic or the patients complete the study or are lost to follow-up.

## 8.9.Regulatory Reporting of Adverse Events

If there are serious, unexpected adverse drug reactions (for Europe, SUSAR: Suspected Unexpected Serious Adverse Reaction) associated with the use of the IMP, the appropriate regulatory agency(ies) and all participating investigators will be notified by the Sponsor or its designee in accordance with the following Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A), Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (CT-3).

It is the responsibility of the investigator to promptly notify the IRB/IEC of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in the current Investigator's Brochure of AG019 or teplizumab.

## 8.10.Expected adverse events

### 8.10.1AG019

As AG019 has not been studied in humans, there are no expected adverse events associated with AG019. However, due to the general profile of the IMP, sepsis as a result of systemic exposure of AG019 could be expected. Instructions on the management of clinical sepsis attributable to AG019 are described in Appendix B.

All SAEs which are reported, for which a relationship to AG019 cannot be excluded, will be reported as SUSARs (see Section 8.9).

### 8.10.2Teplizumab

A full description of the adverse events experienced by patients in trials using teplizumab is in the Investigator's Brochure. The descriptions below highlight the most common drug related events and potential adverse events.

XXX

# 10.STATISTICAL METHODS

Statistical considerations are briefly described below.

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 frequencies and percentages for categorical data. The term "treatment group" refers to assigned dose group/dosing frequency.

After all patients in all AG019 and Combination cohorts have completed their 6-month follow-up visit unblinding will be done and all data will be analyzed and reported. After completion of the full 12 months follow-up all additional data will be analyzed and reported separately.

More details on the analysis and presentation of study results will be provided in the statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of treatment allocation codes.

## 10.1.Study Endpoints

Primary Endpoint

The primary end point 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 event not present prior to the initiation of the treatment(s) or any event already present that worsens in either intensity or frequency following exposure to the treatment(s).

Secondary Endpoints

The pharmacodynamic activity of the study drug(s) will be assessed by measurement of biomarkers in blood and serum samples. Relevant parameters will be assessed, including immune markers for effect, relevant T1D parameters and relevant cytokines. Details about the analysis of the collected PD samples will be described in the SAP.

Following parameters will be assessed for analysis of systemic and local exposure to *L. lactis*:

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

Safety information collected at all other time points will be assessed as secondary end points.

## 10.2.Sample Size Consideration

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 per dose level in the combination cohorts will provide sufficient data to evaluate preliminary safety and activity of the IMP as administered in this protocol.

## 10.3. Definitions of Study Populations for Analysis

### 10.3.1 The Safety (SAF) Analysis Set

The safety population will include all patients who receive at least one dose of study medication. Only patients with clear documentation that no study medication was received may be excluded from analysis. Patients will be analyzed according to the dose received. This population will be used for all data summaries.

### 10.3.2 The Pharmacokinetic (PK) Analysis Set

For each cohort, all patients who received the IMP as scheduled and provided sufficient samples to reliably estimate the PK parameters will be included in the PK analysis set.

More details on the PK parameters, analysis and presentation of study results will be provided in the SAP.

### 10.3.3 The Pharmacodynamic (PD) Analysis Set

For each cohort, all patients who received the IMP as scheduled and provided sufficient samples to reliably estimate the PD parameters will be included in the PD analysis set.

More details on the PD parameters, analysis and presentation of study results will be provided in the SAP.

## 10.4. Baseline Characteristics and Demographic Variables

Demographics and limited medical history will be summarized by treatment group.

## 10.5. Pharmacokinetic Analysis

Blood samples will be collected at specific time points throughout the study. These will be used to evaluate the pharmacokinetics of AG019 by treatment group and study visit.

Feces samples will be collected from repeat dose patients for pharmacokinetic analysis.

Details on collection, storage and handling of blood and feces samples will be included in the central lab manual.

## 10.6. Pharmacodynamic analysis

Blood samples will be collected at specific time points throughout the study. These will be used to evaluate immune markers for effect, relevant T1D parameters and relevant cytokines.

Details on collection, storage and handling of blood and feces samples will be included in the central lab manual.

## 10.7. Safety Analysis

Safety will be assessed based on TEAEs, physical examination findings, vital sign measurements and clinical laboratory tests.

Adverse events will be coded to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. The occurrence of treatment emergent AEs will be summarized by treatment frequency received using preferred terms, system organ classifications and severity. If a patient experiences multiple events that map to a single preferred term, the greatest severity and/or strongest investigator assessment of relation to study drug will be assigned to the preferred term for the appropriate summaries. Separate summaries of treatment emergent SAEs and treatment emergent AEs that are related to either IMP will be generated. Summaries may be repeated according to study phase. All AEs will be listed for individual patients showing both verbatim and preferred terms.

Descriptive summaries of vital signs and quantitative clinical laboratory changes will be presented by treatment received and study visit. The number and percentage of patients experiencing laboratory abnormalities and clinically relevant laboratory abnormalities will be summarized by treatment received. Cross tabulations of baseline abnormality vs. worst post treatment abnormality for selected laboratory assessments will presented by treatment received.

Abnormal physical examination findings will be presented by treatment received. The number and percentage of patients experiencing each abnormal physical examination finding will be included.

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary. These data will be listed.

The number and percentage of patients with presence of sAGX0407 bacteria will be summarized by treatment group.

## 10.8. Interim Analysis

Interim analyses will be performed according to the below schedule:

- After the last Day 180 follow-up visit of the last patient enrolled into the Phase 1b portion of the study, a preliminary analysis of the data collected up to 6 months will be performed for these patients.

- Once all patients enrolled in Combination Cohort 1, as well as the 2 patients enrolled into the open label portion of Combination Cohort 2, have completed the Day 180 follow-up visit, unblinding will be done and an interim analysis will be performed.
- After the last Day 180 follow-up visit of the last patient enrolled into Combination Cohort 2, all patients in this cohort will be unblinded and an interim analysis will be performed on all, which will include an analysis of the primary endpoint of the study.

### 10.9. Reporting of Deviations to Original SAP

All deviations from the original SAP will be reported in the clinical study report.

## 11. ETHICS

### 11.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki", ICH guidelines, in particular ICH GCP E6, and the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient.

### 11.2. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

This protocol and any accompanying material for this study provided to the patient (such as patient information sheets and informed consent form) as well as any advertising or compensation given to the patient must be reviewed and approved by an appropriate IRB/IEC before patients are included into the study. It is the responsibility of the Investigator to assure that all aspects of the institutional review are conducted in accordance with the requirements of all regulatory authorities. A signed and dated letter documenting IRB/IEC approval must be obtained prior to entering patients at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

### 11.3. Patient Information and Informed Consent

In accordance with regulatory and local IRB/IEC requirements, before study procedures are performed, patients will be informed about the study and required to sign and date the IRB/IEC approved ICF. This form will be signed and dated after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH GCP and all applicable regulatory requirement(s). No patient is to be screened or treated until an ICF, written in a language in which the patient is fluent, has been obtained. The signed ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF.

An assent form has also been developed for participants less than 18 years of age. Assent of children along with consent of the parents will be obtained prior to any study procedures.

All participants (or their legally acceptable representative) must read, sign and date a consent form prior to participation in the study, and/or undergoing any study specific procedures.

The informed consent form must be updated or revised whenever important new safety information is available, when indicated for a protocol amendment, and/or whenever any new information becomes available that may affect a participant's participation in the study.

## 11.4.Data Safety Monitoring Board and Medical Monitor

### 11.4.1Medical Monitor

A Medical Monitor (MM) will be appointed. The role of the MM will entail following duties:

- Act as central point of contact for Investigators for addressing medical study related questions
- Collaborate with the clinical sites and investigators to review the collected data of the trial patients at pre-defined intervals, to determine whether enrollment can continue
- Review of safety data, identify possible trends in reported adverse events

The MM will keep close relationships with all participating clinical sites throughout the course of the trial. The MM will collaborate with the investigators and will regularly review the collected data, to determine whether enrollment in the trial can continue.

More detailed information on the roles and responsibilities of the MM can be found in the medical monitoring plan.

### 11.4.2DSMB

An independent DSMB will be constituted before the start of the study.

The DSMB is an independent body of experts that serves in an advisory capacity to the Sponsor to ensure that clinical trial participants are not exposed to unreasonable or unnecessary risks of AG019 and/or teplizumab. On fixed time points during the Study, as outlined in the DSMB charter and in Figure 1 (overall enrollment plan), the DSMB will review the available safety data, which include, but are not limited to serious adverse events (SAEs) and adverse events (AEs) related to the study medication.

The DSMB will supervise the ethical performance of the study and review safety data arising during the study according to the procedures described in the DSMB Charter. The Charter will describe the following activities:

The DSMB will consist of at least 3 members. Members are completely independent of the investigators and have no financial, scientific, or other conflicts of interest with the trial.

In order for the DSMB to fulfill its responsibilities, the members will observe the following guidelines:

- Members are free of apparent conflicts of interest involving financial, scientific, or regulatory matters
- Members should assess trial objectives and designs in an unbiased way
- The DSMB members will review data and pertinent procedures in order to be confident that the data on which the decisions are based are accurate and complete
- All decisions of the DSMB shall be independent

The DSMB is responsible for recommending to the Sponsor any actions necessary to maintain the safety of the patients and the integrity of the trial. The DSMB will also be responsible for recommending to the Sponsor if patients should be enrolled into the next cohort. To fulfill these responsibilities, the DSMB will do the following:

- Review and approve the Data Safety Monitoring Board charter
- Monitor recruitment figures including data for patients that are lost to follow-up
- Hold six scheduled teleconferences and any ad hoc meetings as needed to review safety data
- Request additional information if required to fulfill responsibilities
- Issue recommendations to the Sponsor using secure communication
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the patients or the ethics of the trial
- Ensure the confidentiality of the trial data
- Securely maintain accurate records of deliberations and decisions

The DSMB chairperson will advise the Sponsor of the DSMB's recommendations after each meeting. Examples of DSMB recommendations include the following:

- Administrative changes to the trial if withdrawals are high
- Modification of inclusion/exclusion criteria for safety reasons
- Modification of the safety monitoring process
- Suspension of recruitment pending further safety review, if data received suggest significant net adverse effect of AG019 and/or teplizumab treatment
- Continuation of recruitment into the next cohort(s), if data received suggest no significant adverse effect of AG019

In order to make proper recommendations to the Sponsor on lowering the dose of AG019, and/or on opening cohorts for recruitment, the DSMB will review all available safety data from all patients enrolled up to that point.

### 11.4.3Study/Treatment Stopping Criteria

#### 11.4.3.1Criteria for premature study termination

If clinical sepsis occurs in a patient, and it is exclusively attributable to AG019 bacteria alone (confirmed by positive plating and PCR), the study will be terminated. Details about the evaluation and management of clinical sepsis of any kind (attributable to AG019 or not) are outlined in Appendix B.

#### 11.4.3.2Criteria for suspension of enrollment

Enrollment (defined as initiation of treatment in a new patient) in all ongoing and planned study cohorts may be temporarily suspended if one of the following occurs:

- XXX

In the event that these criteria are met, the DSMB will be notified in writing within 24 hours. The notification will include detailed information of the event(s) and finding(s) that have led to meeting the criteria for enrollment suspension. The DSMB will determine whether enrollment needs to be suspended until a safety review has been performed, and will notify the Sponsor of their decision in writing.

- If the DSMB concludes upon initial notification that enrollment should be suspended until a more detailed safety review has been performed, the Sponsor will inform the Institutional Review Boards/Ethics Committees/Research Ethics Board (IRB/EC/REB), FDA and other applicable regulatory authorities and all participating sites within 24 hours of the DSMB's decision and will schedule an ad-hoc DSMB meeting to review the relevant safety information. The safety review will include a comprehensive evaluation of the safety experience from this trial. A report of the safety review will be provided to the FDA, other applicable regulatory authorities, Institutional Review Boards/Ethics Committees/Research Ethics Boards (IRB/EC/REB) and all participating sites. Enrollment will not resume until a satisfactory report of the safety review has been provided by the DSMB.
- If the DSMB concludes that enrollment should not be suspended, the Sponsor may schedule an ad-hoc DSMB meeting to review the relevant safety information upon request of the DSMB.

*XXX

#### 11.4.3.3Criteria for adjusting AG019 treatment

If clinically significant safety concerns relating to AG019 are identified in ≥ 20% of all patients treated with the high dose of AG019, the DSMB will recommend lowering the AG019 dose in all AG019 and Combination cohorts.

#### 11.4.3.4Criteria for discontinuation of AG019 treatment in a single patient

If at any time during the study a patient develops symptoms suggesting clinically significant sepsis for any reason (as determined by 1 positive blood culture), study treatment (both AG019 and teplizumab as applicable) will be discontinued. In addition, the guidelines for management of clinical sepsis as outlined in Appendix B should be followed.

In addition, withdrawal of informed consent will result in discontinuation of AG019 treatment.

Pregnancy in a study participant, or in the female partner of a male participant, occurring after signature of the ICF must be reported within 1 calendar day after the Investigator has gained knowledge of them. The patient (if female) will discontinue IMP. Details of the outcome of the pregnancy (e.g. full term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported no longer than one month after the expected due date. Any abnormal outcome in the neonate will be followed up.

### 11.4.3.5 Teplizumab Withholding in an Individual Patient During the 12-Day Treatment Period

Total bilirubin, AST, ALT, LDH, Complete Blood Count (CBC), and INR will be evaluated to verify the need to withhold teplizumab (or placebo) infusion before each (potential) teplizumab administration, as described in the Visit Schedule (Appendix A).

#### 11.4.3.5.1 Temporary interruption of teplizumab infusions

If any of the following lab abnormalities is observed (normal range per local lab reference ranges), the test may be repeated on the same day. If the repeated test result normalizes, that day's dose may be given. If the value is still in the indicated range or worsens, or if the test cannot be repeated on the same day, that day's dose should be withheld.

- XXX

If the above event(s) resolve(s) within 2 days, study drug dosing may be resumed according to the original schedule. The treatment course will not be extended beyond 12 days.

If the above events do not resolve after 2 consecutive days of interruption, the Medical Monitor must be consulted regarding continuation of study drug dosing.

#### 11.4.3.5.2Permanent discontinuation of teplizumab infusions

The following situations, laboratory abnormalities, or adverse events will lead to permanent discontinuation of infusions *during the treatment course*: (Note: Day 1 is the first day of infusion)

XXX

#### 11.4.3.6Further Evaluation after Withholding Teplizumab Infusions

The following are minimal assessments to be performed for those participants in whom an infusion is withheld (as described above):

- XXX

## 11.5.Financial Disclosure by Principal Investigators

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR §54 is adhered to. A "covered" clinical trial is any study of a drug or device in humans submitted in a marketing application

or reclassification petition patient to this part that the applicant or the FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety. This requires that investigators and all sub investigators (inclusive of family members) provide documentation of their financial interest or arrangement with the Sponsor or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the Investigator and any Sub Investigator. The Investigator and Sub-Investigator agree to notify the Sponsor of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol defined activities.

# 12.STUDY MANAGEMENT AND ADMINISTRATION

## 12.1.Curriculum vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each investigator and sub-investigator will be provided to the sponsor prior to the beginning of the clinical trial.

## 12.2.Protocol Modifications

The Sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval and CA approval as applicable prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study patients.

## 12.3.Data Quality Control and Quality Assurance

The study will be monitored and managed in accordance with ICH GCP E6.

Study data will be entered in the eCRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Queries will be generated and any discrepancies will be resolved.

## 12.4.Monitoring

The Sponsor or its designee will perform on-site monitoring visits periodically during the study. At these visits the monitor will review study documents to ensure adherence to the study protocol and regulatory requirements, and to review eCRF entries against source documents. Findings from the visit will be discussed with the investigator.

## 12.5. Audit and Inspection

The Investigator will agree to receive periodic quality assurance audits conducted by the Sponsor's clinical quality assurance personnel or its designee. In addition, the Investigator will agree to inspections by regulatory agencies to the extent permitted by law. Auditors and inspectors will have direct access to all relevant study documentation.

## 12.6. Source Documents

The Investigator must allow regulatory agencies, individuals delegated by the IRB/IEC or the Sponsor or its designee to have access to all the original documentation of the study, including the ICFs signed by the patients enrolled into the study and the relevant patient medical files. The individuals who are given access to the documentation must take every reasonable precaution to keep the identity of the patients and the proprietary information of the Sponsor as confidential information in accordance with relevant applicable legislation.

## 12.7. Electronic Data Capture

Electronic Case Report Forms (eCRFs) will be supplied by the Sponsor or its designee and should be handled in accordance with the provided instructions. All eCRFs should be filled out completely by authorized study personnel.

The Investigator should ensure the accuracy, completeness and timeliness of the data recorded on the eCRF. Data recorded on the eCRF will be consistent with source documents. Any discrepancies must be explained or resolved.

Completed eCRFs will be reviewed by the Sponsor's monitoring staff or its designee. An eCRF will be completed for each patient enrolled in the study.

## 12.8. Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators and the regulatory authority(ies) of the reason(s) for termination or suspension. The IRB/IEC also will be promptly informed by the Sponsor or Investigator and provided with the reason(s) for the termination or suspension, as specified by the applicable regulatory requirement(s).

## 12.9. Study Report

The results of the study will be presented in an integrated clinical study report according to GCP and ICH-E3 guidance. The Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Principal Investigator will submit to the Sponsor a copy of the report issued to the IRB/IEC.

## 12.10.Finance, Insurance and Publication

Insurance coverage will be handled to local requirements.

Finance, insurance and publication rights are addressed in the Investigator/Institution and/or CRO agreements as applicable.

## 12.11.Archiving and Data Retention

The Investigator shall retain adequate records for the study including copies of each patient's eCRFs, medical records, laboratory reports, ICF(s), IMP accountability records, safety reports, information regarding patients who were withdrawn and any other pertinent data. The Investigator must retain all records for at least 20 years after completion or discontinuation of the trial or at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements. The sponsor will notify the investigator when the records no longer need to be kept.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping records, custody must be transferred to a person who will accept the responsibility. The Sponsor will be notified in writing of the name and address of the new custodian as soon as possible.

## 12.12.Confidentiality

The Investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The patient's identification code and the patient's initials should be recorded on any form submitted to the Sponsor, Sponsor's designee, or IRB/IEC, unless it is forbidden to identify the patient by initials. Where it is forbidden to indicate the patient's initials, only the patient's identification code and the patient's year of birth should be recorded.

The Investigator must keep a screening log showing codes, names and addresses for all patients screened and for all patients enrolled into the trial.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except with prior written consent from the Sponsor). The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

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