SYNOPSIS

Name of the Sponsor/Company: Precigen ActoBio T1D, LLC	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
Name of Finished Product: AG019		
Name of Active Ingredient: *Lactococcus lactis* sAGX0407		

STUDY CODE:

AG019-T1D-101

EUDRACT/Clinicaltrials.gov IDENTIFIER/IND NUMBER:

2017-002871-24 / NCT03751007/18000

TITLE OF STUDY:

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).

NATIONAL COORDINATING INVESTIGATORS:

- Chantal Mathieu (Belgium)
- Kevan Herold (United States, USA)

STUDY CENTERS:

A total of 3 study centers in Belgium and 13 in the USA included patients.

PUBLICATION (REFERENCE):

No publications have been made in journals yet, but the results of the primary analysis were presented at the Federation of Clinical Immunology Societies Annual Meeting on 10-Jun-2021 and at the European Association for the Study of Diabetes (EASD) Annual Meeting on 01-Oct-2021.

The abstract for EASD is publically available in https://www.abstractsonline.com/pp8/#!/9330/presentation/670.

Links to both presentation websites are on the Precigen website: https://investors.precigen.com/search?query=AG019&f%5B0%5D=type%3Anir_event&op=Search

STUDY PERIOD (YEARS):

Date of first enrolment/first patient first visit: 24 October 2018

Date of last completed/last patient last visit: 13 October 2021

PHASE OF DEVELOPMENT:

1b/2a

BACKGROUND AND RATIONALE:

T1D is a cell-mediated autoimmune disorder resulting in the absolute destruction of the pancreatic insulin-producing β-cells, requiring life-long use of exogeneous insulin administration in an effort to maintain near-normal energy metabolism. Resulting high blood glucose levels cause acute complications, such as ketoacidosis, as well as a wide variety of late complications including neuropathy, nephropathy, retinopathy, and cardiovascular disease. Despite innovative new insulin technologies and therapies, the glycemic targets are not achieved in high proportions of T1D patients. The complexity and demands of day-to-day

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management of T1D, i.e. the need to reach glycemic goals and the fear of hypoglycemia, have an enormous impact on patient's quality of life. Insulin replacement is an intensive therapy requiring continuous monitoring of blood glucose levels, adapting insulin injections accordingly and following a strict diet, to dynamically match the kinetics of glucose absorption and insulin activation. Moreover, 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 neuroglycopenic symptoms can progress in severity from blurred vision, mood changes, nervousness, pale skin, headache, and shaking, to loss of consciousness cardiac arrhythmia, and death. Preservation of residual β-cell function in T1D patients is known to improve glycemic control, and to reduce risks of all diabetes complications, including hypoglycemia risk, and longer-term microvascular and macrovascular complications (Sørensen et al, 2013; Steffes et al, 2003).

AG019 is an oral capsule formulation consisting of the environmentally contained food-grade lactic acid bacterium *Lactococcus lactis* (*L. lactis*), strain sAGX0407, genetically engineered for *in situ* expression and secretion of human proinsulin (hPINS) and human interleukin 10 (hIL-10). Through oral administration of AG019, the genetically modified (GM) *L. lactis* sAGX0407 bacteria will be introduced orally into the patient's gastro-intestinal (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 hPINS and hIL-10 locally at the gut-associated lymphoid tissue, without systemic exposure, with the aim of inducing long term tolerance to β-cell antigens.

Nonclinical studies performed to-date by the Sponsor have confirmed that genetically modified (GM) L. lactis sAGX0407, secreting hPINS and hIL-10, alone or in association with a short-term treatment with systemic anti-cluster of differentiation (CD)3 monoclonal antibody (mAb), reverted recent-onset diabetes in nonobese diabetic (NOD) mice. Therapeutic success (defined as the return to stable normoglycemia and no need for insulin supplementation) was accompanied by preservation of functional β-cell mass and a reduction in severe insulitis, and was correlated with lower starting glycemia, and the presence of insulin autoantibodies (IAAs). The mode of action is via an increased frequency of functional proinsulin (PINS)-specific Foxp3+ Treg cells, trafficking to and accumulating in the (inflamed) target tissue, in this case the pancreatic draining lymph nodes and pancreatic islets. The increase in insulin-reactive Foxp3+ Treg cells is accompanied by a reduction of islet-specific glucose-6-phosphatase-related protein (IGRP)+CD8+ autoreactive T-cells, however without inducing a generalized immunosuppression in these animals. Even though the nonclinical efficacy studies suggest that the therapeutic potential of the combination therapy - *L. lactis* expressing hPINS and hIL-10, in combination with anti-CD3 - may be more pronounced as compared to *L. lactis* monotherapy, differences in onset (more rapid versus more gradual) and severity (more severe versus milder) of disease in NOD mice as compared to humans supports the need of a more drastic immunological intervention in mice, whereas a more broad and cautious therapeutic approach could be used in humans. It can be anticipated that the more aggressive onset and development of diabetes in NOD mice might require the anti-CD3 mediated partial "freeze" of the pathogenic effector T-cells, to create a therapeutic window which allows *L. lactis*, expressing hPINS and hIL-10, to install antigen-specific immune tolerance before the critical mass of functional β-cells has been destroyed.

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Following the positive results obtained in the NOD mouse model, AG019 has been studied in a Phase 1b/2a (first in human [FIH]) clinical study (AG019-T1D-101 [IND 18000 / EudraCT 2017-002871-24 / NCT03751007) in adult and adolescent patients with recent-onset T1D.

OBJECTIVES:

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

The secondary objectives were:

- to obtain pharmacodynamics (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): pharmacokinetics (PK) profile.

METHODOLOGY:

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

A maximum of 8 single dose patients and a maximum of 48 evaluable repeat dose patients were planned to be enrolled in clinical sites in the USA and Belgium.

This study consisted of 2 phases:

- Phase 1b: this open label part of the study investigated the safety and tolerability of 2 different doses of AG019, in 2 age groups (18-40 years and 12-17 years), administered as single or repeat doses. Patients were enrolled in 4 sequential cohorts (AG019 monotherapy cohorts).
- Phase 2a: this randomized, double-blind part of the study investigated the safety and tolerability of AG019, in association with teplizumab, in 2 age groups (18-40 years and 12-17 years), in comparison with placebo (randomization ratio 4:1). Patients were enrolled in 2 cohorts (AG019/teplizumab combination cohorts).

Phase 1b portion

AG019 was orally administered in 4 sequential AG019 monotherapy cohorts:

- **Adult, Low dose**: patients 18-40 years, 1 capsule twice daily (BID)
- **Adult, High dose**: patients 18-40 years, 3 capsules BID
- **Adolescent, Low dose**: patients 12-17 years, 1 capsule BID
- **Adolescent, High dose**: patients 12-17 years, 3 capsules BID

Within each of these cohorts, 2 single dose patients and up to 6 repeat dose patients were enrolled according to the below schedule:

- Treatment of single dose patient 1 (Data review after the Day 4 follow-up visit)
- Treatment of single dose patient 2 (Data review after the Day 4 follow-up visit)
- Treatment of repeat dose patient 1 (Data review after the Day 7 follow-up visit)

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- Treatment of repeat dose patient 2 (Data review after the Day 7 follow-up visit)
- Treatment of the remaining repeat dose patients (Data review after the Day 7 follow-up visit of the last patient (Data Safety Monitoring Board [DSMB] – review of all available data from all patients in all cohorts)

Single dose patients

In every AG019 monotherapy cohort, 2 single dose patients were enrolled in the first stage. Each of these patients was treated for 1 day with AG019 (1 or 3 capsules BID depending on the cohort, 1 x 10^{11} colony forming units [CFU] per capsule) and were followed up for a total of 4 days (treatment day [Day 1] plus 3 additional days), after which they completed their study participation (Day 4) (see Figure 1 and Table 1).

After study completion of each of the single dose patients, the treating Investigator and Medical Monitor (MM) reviewed the collected data, and if no safety concerns were identified, treatment of the next patient began.

Repeat dose patients

A minimum of 4 repeat dose patients were enrolled per AG019 monotherapy cohort. In addition, both single dose patients in each AG019 monotherapy cohort were offered the option of being re-enrolled as repeat dose patients in the same AG19 monotherapy cohort, provided that no safety concerns were 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 was 6 (see Figure 1 and Table 2).

All repeat dose patients were treated for 8 weeks with AG019 and were followed up for a total of 12 months (8 weeks of treatment plus 10 months of post treatment follow-up). The first 2 repeat dose patients were enrolled in a staggered way:

- After enrollment of the first patient, the data collected up to the Day 7 follow-up visit were reviewed by the treating Investigator and MM, and if no concerns were identified, the second patient was treated.
- After the Day 7 follow-up visit of the second patient, the collected data were reviewed by the treating Investigator and MM, and if no concerns were identified, the remaining patients were treated.

Once all repeat dose patients in a cohort had their Day 7 follow-up visit, the DSMB reviewed all available data from all enrolled patients in all cohorts. If no safety concerns were identified, the DSMB formulated a recommendation to the Sponsor on opening the next cohort(s) for treatment, according to the enrollment schedule outlined in Figure 1.

Phase 2a portion

Two cohorts ("AG019/teplizumab combination cohorts") of 12 patients were assessed. Each patient was administered 3 capsules BID[1] of AG019 (or placebo) for 8 weeks, in association with daily intravenous (IV) infusions of teplizumab (or placebo) for the first 12 days of the 8-week treatment period (see Table 2).

[1] The dose of AG019 administered in the Phase 2a portion of the study was determined by the results of the Phase 1b portion of the study.

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- **Adult AG019/teplizumab combination cohort**: 12 patients (18-40 years) to receive AG019 (3 capsules BID, 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions
- **Adolescent AG019/teplizumab combination cohort**: 12 patients (12-17 years) to receive AG019 (3 capsules BID, 8 weeks) plus teplizumab (daily infusions, 12 days), or matching placebo capsules and placebo infusions

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

- Treatment of patient 1: Treatment with AG019 plus teplizumab (Review of all data collected up to the Day 12 follow-up visit, the last day of teplizumab infusion, by the investigator and MM)
- Treatment of patient 2: Treatment with AG019 plus teplizumab (Review of all data collected up to the Day 12 follow-up visit, the last day of teplizumab infusion, as well as all other data collected in all cohorts up to this point, by the DSMB)
- Treatment of patients 3-12: randomization (4:1) to double active treatment or double placebo.

All patients in the AG019/teplizumab combination cohorts were followed up for a total of 12 months (8 weeks of treatment plus 10 months of post treatment follow-up).

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NUMBER OF PATIENTS (planned and analyzed):

AG019 monotherapy cohorts:

	Adult, Low dose		Adult, High dose		Adolescent, Low dose		Adolescent, High dose	
	SD	RD**	SD	RD**	SD	RD**	SD	RD**
No. planned:	2	6	2	6	2	6	2	6
No. screened:	2	5	2	5	2	4	2	5
Screening failures	0	0	0	0	0	0	0	0
Included and treated:	2	5	2	5	2	4	2	5
Safety analysis set:	2	5	2	5	2	4	2	5
PD-ITT: PD-PP:	0 0	5 5	0 0	5 4	0 0	4 4	0 0	5 4
No. completed the study:	2	5	2	4	2	4	2	4

AG019/teplizumab combination cohorts:

	Adult, Combination		Adolescent, Combination*	
	Placebo	Active	Placebo	Active
No. planned:	2	10	2	10
No. screened:	2	10	1	5
Screening failures	0	0	0	0
Included and treated:	2	10	1	5
Safety analysis set:	2	10	1	5
PD-ITT: PD-PP:	2 2	10 10	1 1	5 4
No. completed the study:	2	10	0	4

*Enrollment was prematurely ended due to the COVID-19 pandemic as the ability to enroll patients in the last cohort had been dramatically impacted. **A minimum of 4 RD patients were planned to be enrolled but SD patients of the same cohort were offered to be re-enrolled as RD patients in the same cohort. Therefore, if both SD patients agreed to be re-enrolled as RD patients, the maximum number of RD patients per cohort was 6.PD-ITT, Pharmacodynamic Intention to Treat analysis set; PD-PP, Pharmacodynamic Per Protocol analysis set; SD, single dose; RD, repeat dose.

The study enrollment was prematurely ended due to COVID-19 pandemic. Following an assessment of the effect of the COVID-19 pandemic on the study, it was determined that the ability to enroll patients in the adolescent combination cohort had been dramatically impacted, while treatment and 12-month follow-up was completed for the other cohorts. Therefore, in consideration of the implications of a potential study extension to enroll all patients as initially planned, as well as the convincing safety data and hint for potential efficacy, Sponsor decided to end further enrollment for the Phase 2a adolescent AG019/teplizumab combination cohort of the study.

DIAGNOSIS AND CRITERIA FOR INCLUSION:

The below table provide an overview of all inclusion criteria for:

- AG019 monotherapy cohorts: column ‘AC’

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- AG019/teplizumab combination cohorts: column 'CC'

Inclusion Criteria	**AC**	**CC**

Male or non-pregnant, non-lactating females, 18-40 (both inclusive) years or 12-17 (both inclusive) years[2]
• Females of childbearing potential must have a negative serum pregnancy test at the screening visit, and, if heterosexually active, must
  • use a hormonal (oral, implantable or injectable) method of birth control which remains the same in both nature and dose throughout the study; *or*
  • have documentation of placement of an intrauterine device or intrauterine system; *or*
  • use a barrier method of contraception (i.e.; condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository).
• 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]).
• 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 American Diabetes Association (ADA)- recommended criteria: • Fasting Plasma Glucose concentration (after 8 or more hours of no caloric intake) ≥126 mg/dL*, *or* • 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* • Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, non-fasting) plasma glucose concentration ≥200 mg/dL *In absence of unequivocal hyperglycemia, result to be confirmed by repeat testing	X	X

[2] Age-dependent enrolment in each cohort was considered when evaluating this inclusion criterion. In the first protocol versions there was no upper age limit and patients above 40 years old could be included in the study. Under protocol final version 4 (amendment 3), the upper age limit of 40 years old was defined.

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Evidence of autoantibodies to at least 1 of the following β-cell autoantigens: insulin°, islet antigen-2 (IA-2), glutamic acid decarboxylase 65 (GAD65), zinc transporter 8 (ZnT8) 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 °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 ≥ 33 kg	X	X
Willing and medically able to postpone live vaccine immunizations for at least 8 weeks after randomization		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) • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤1.5 x ULN • ≥1,000 lymphocytes/μL • ≥1,000 polymorphonuclear neutrophils (PMN)/μL • ≥100,000 platelets/μL • Hemoglobin (Hb) ≥10 g/dL • Serum creatinine ≤1.5 x ULN • Estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min/1.73m² • International Normalized Ratio (INR) ≤0.1 above upper limit of normal • Absence of clinically significant age-appropriate abnormalities on all other lab values, except for abnormalities directly attributable to T1D.	X	X

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

AG019 monotherapy cohorts:

Single dose patients were treated with 1 or 3 capsules BID of AG019 for one day.

All patients in the repeat dose AG019 monotherapy cohorts, and all patients in the AG019/teplizumab combination cohorts who were randomized to study treatment, were treated for 8 weeks with AG019 with one of the doses listed below:

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Dose	Number of capsules per day	Total daily dose	Treatment duration
Low dose AG019	2 (1 morning, 1 evening)	2 x 10^{11} CFU	8 weeks
High dose AG019	6 (3 morning, 3 evening)	6 x 10^{11} CFU	8 weeks

AG019 batch numbers: 170968A, 180369A, 180370A, 19AG02B, 19AG02C, 19AG02D, 19AG03B, 19AG03C, 19AG03D, 19AG06B, 19AG07B, 19AG07C, 19AG07D and 19AG07E.

AG019/teplizumab combination cohorts:

All patients in the AG019/teplizumab combination cohorts who were randomized to study treatment, as well as the first 2 patients in the AG019/teplizumab combination cohorts who were treated open label, received intravenous (IV) infusions with teplizumab for 12 days according to the below schedule, in addition to their AG019 oral treatment:

- Day 1: 106 µg/m² Body Surface Area (BSA)
- Day 2: 425 µg/m² BSA
- Day 3-12: 850 µg/m² BSA

Teplizumab batch number: 1-FIN-2543.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo used in combination cohorts:

Each patient who was randomized to placebo treatment was administered 3 capsules BID AG019-placebo for 8 weeks, in association with daily IV infusions of teplizumab-placebo for the first 12 days of the 8-week treatment period.

Placebo (AG019) batch number: 180017A, 180968A, 19AG04B and 19AG04C.

Placebo (teplizumab): 1-FIN-3262.

DURATION OF TREATMENT:

The total treatment duration for single dose patients was 1 day.

The total treatment duration for repeat dose patients in AG019 monotherapy cohorts and AG019/teplizumab combination cohorts was 8 weeks or 56 days.

ENDPOINTS FOR EVALUATION:

Primary Endpoint

The primary endpoint was defined as the incidence of treatment-emergent adverse events (TEAEs) collected up to the 6-month follow-up visit. A TEAE was 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).

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Secondary Endpoints

- The PD activity of the study drug(s) assessed by measurement of immune markers for effect and relevant T1D parameters.
- The PK activity for analysis of systemic and local exposure to L. lactis was assessed by:
  - Presence of L. lactis AG019 bacteria in whole blood
  - Measurable plasma levels of hIL-10 and hPINS
  - Presence of L. lactis AG019 bacteria in fecal samples
- Safety data collected at all other time points.

STATISTICAL METHODS:

Descriptive statistical methods were 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 (StD), 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.

After completion of the 6-month follow-up visit of all patients in all AG019 monotherapy and AG019/teplizumab combination cohorts, unblinding was performed and all data were analyzed. After completion of the full 12 months follow-up all additional data were also analyzed.

Additional subgroup analysis by region, age, sex, ethnicity and baseline characteristics were conducted using descriptive statistical methods.

SUMMARY OF RESULTS AND CONCLUSION(S):

SAFETY RESULTS:

AG019 treatment was well tolerated and safe when administered as a single low or high dose and as a repeated low or high daily dose for 8 weeks, be it as monotherapy or in association with teplizumab infusions.

There were no serious adverse events (SAEs) and no deaths. No AG019 treatment discontinuation occurred due to a treatment emergent adverse event (TEAE).

The incidence of TEAE up to the 6-months follow-up visit (i.e., the primary endpoint) was highest in the adult placebo combination cohort (12.5 TEAE/patient) and in the adult active AG019/teplizumab combination cohort (9.1 TEAE/patient). In the AG019 monotherapy cohorts, the highest incidence of TEAE was observed in the adolescent low dose cohort (7.0 TEAE/patient), followed by the adult and adolescent high dose cohorts (3.8 TEAE/patient each).

There was no evidence of dose-related adverse events in the AG019 monotherapy cohorts, and the AG019 safety profile was similar between adults and adolescents.

The TEAEs reported were mostly of mild and sometimes of moderate severity. The vast majority of TEAEs were considered as not related to AG019 treatment. No severe TEAEs have been reported in any of the AG019 monotherapy cohorts.

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There was no evidence of an increased rate of infections in any of the cohorts. Viral reactivation, measured as a positive polymerase chain reaction (PCR) test after study treatment initiation, was reported most often in the adult combination group, but also in a placebo treated patient.

There was no evidence nor any trend suggesting that AG019 negatively impacted the safety profile of teplizumab infusions. The TEAEs and transient changes in lab safety assessments reported in the AG019/teplizumab combination cohorts are in line with the safety profile reported for teplizumab in its Investigator Brochure and no unexpected TEAEs were identified.

Sepsis or bacteremia were not reported in any of the AG019 monotherapy cohorts or AG019/teplizumab combination cohorts.

PHARMACOKINETIC RESULTS:

Adult and adolescent patients receiving AG019 monotherapy and AG019/teplizumab combination therapy did not show AG019 bacteria in blood. Also, no systemic exposure of AG019 secreted hPINS and hIL-10, as measured by enzyme-linked immunosorbent assay (ELISA) in plasma, could be demonstrated. These results indicate no risk for systemic exposure in adult and adolescent T1D patients receiving AG019 monotherapy or AG019/teplizumab combination therapy during and up to 1 month (34 days) after the last AG019 dose.

AG019 bacteria were demonstrated in fecal samples of 82% of the T1D patients treated with AG019 monotherapy and AG019/teplizumab combination therapy at one or more of the sampling timepoints, indicating GI exposure to AG019 after oral dosing. There was no evidence for persistence, accumulation, or colonization of AG019 bacteria in the GI tract after end of treatment.

PHARMACODYNAMIC RESULTS:

<u>AG019 monotherapy:</u>

A treatment period of 8 weeks of oral AG019 monotherapy in both adult and adolescent T1D patients was associated with a stabilization of stimulated C-peptide levels at 6 months in 7/16 (44%) of all PD-PP patients in this treatment group (median value in responders of 104% of baseline C-peptide value). In adults, 5/9 patients (56%) were classified as responders[3], whereas in adolescents a favorable metabolic outcome based on C-peptide stabilization was demonstrated in 2/7 (29%) patients.

In adults treated with AG019 monotherapy, HbA1c levels were significantly decreased as compared to baseline at month 3 and 6 of the study. At baseline, 7/9 (78%) of adult patients had HbA1c levels <7% which is in line with the ADA recommended targets for glycemic control. Following an 8-week treatment with AG019 monotherapy, all adult patients (9/9) had HbA1c <7% both at 6 and at 12 months. In adolescents treated with AG019 monotherapy, no significant decrease in HbA1c levels were seen compared to baseline.

Insulin dose adjusted HbA1c (IDAA1c) levels decreased during AG019 treatment in both adults and adolescents. At baseline, 6/8 (75%) of adult patients had IDAA1c levels ≤9. Following treatment, 9/9 (100%) and 8/9 (89%) of adult patients had IDAA1c levels ≤9, indicating partial disease remission at 6 and 12 months, respectively. In adolescent patients, partial remission

[3] Patients were classified as a 'responder' when his or her C-peptide change from baseline was either non-negative or, if negative, represented a coefficient of variance (CV) less than or equal to 9.7% (Greenbaum et al., 2012).

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rates decreased after treatment; while 6/8 (75%) of adolescents' patients had IDAA1c levels ≤9 at baseline, 3/5 (60%) and 4/7 (57%) of adolescent patients still met this partial remission criterion at 6 and 12 months, respectively.

Insulin use throughout the study remained virtually stable in all cohorts, except in the adult low dose AG019 monotherapy cohort (with an increase of 0.23 international un(U)/kg/day at Visit 19 compared to baseline).

Analysis of antigen-specific immune markers for therapy in peripheral blood demonstrated that AG019 monotherapy was associated with an antigen-specific immune response, including an increased frequency of the preproinsulin (PPI)- and islet-reactive CD4+ T-cells in the (memory) regulatory compartment in adults and a decrease/stabilization in the frequency of PPI-specific (memory) conventional CD4+ T-cells (Tconv cells) in adults and adolescents. In AG019 monotherapy-treated adolescents, there was also a trend towards an increase in antigen-specific regulatory T-cel(Tregs). The analysis of the PPI-specific CD8+ T-cells indicated that the frequency of these antigen-specific cells was significantly ($P<0.05$) decreased in the peripheral blood of patients treated with AG019 monotherapy at 3 months (adolescents and adults combined). This decrease in PPI-specific CD8+ T-cells tended to be more substantial for responders as compared to non-responders.

<u>AG019/teplizumab combination therapy</u>

In the patients (both adults and adolescents) treated with AG019/teplizumab combination therapy, 11/14 (79%) showed stabilization/increase in their C-peptide levels at 6 months. In adults, 7/10 (70%) patients and in adolescents, 4/4 (100%) patients were classified as responders at 6 months. The median change from baseline (in the 6-month responder group, n=11) at 6 months corresponds to 126% and 105% at 12 months. At 12 months, 10/13 (77%) of all (adult and adolescent) patients showed stabilization/increase in their C-peptide levels. In adults, 6/9 patients (67%) and in adolescents 4/4 patients (100% were responders at 12 months.

HbA1c levels in this treatment arm were significantly decreased in the adult population at month 2 and 3 as compared to baseline. This decrease was seen up to 12 months, although not significant. In adolescents, non-significant decreases in HbA1c were also seen up to 12 months. In the AG019/teplizumab combination cohort, 6/10 (60%) and 2/4 (50%) of adult and adolescent patients, respectively, had HbA1c levels% at baseline. Following treatment, the percentage of adult patients in the AG019/teplizumab combination cohort with HbA1c (indicating good glycemic control) increased to 6/8 (75%) and 7/9 (77.7%) at 6 and 12 months, respectively. In the adolescent AG019/teplizumab combination cohort, 4/4 (100%) and 3/4 (75%) of patients had HbA1c levels below the ADA recommended target of 7% at 6 and 12 months, respectively.

Both in adults and adolescents treated with AG019/teplizumab combination therapy, IDAA1c levels decreased from baseline. These decreases, although not significant, were maintained up to 12 months. In the adults treated with AG019/teplizumab combination therapy, 6/10 (60%) of patients had IDAA1c whereas all adult patients met the criterion for partial disease remission (i.e. IDAA1c ≤ 9) at 6 and 12 months. In adolescents, the percentage of patients in partial remission increased from 50% (2/4) at baseline to 75% (3/4) at 6 months. At 12 months, 2/4 (50%) were still in partial remission.

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Name of Active Ingredient: *Lactococcus lactis* sAGX0407		

Insulin use throughout the study remained virtually stable in all cohorts, except in the adult placebo combination cohort (with an increase of 0.24 IU/kg/day at Visit 19 compared to baseline).

In adult patients treated with AG019/teplizumab combination therapy, 4/9 patients had increased levels of PPI-reactive or islet-reactive memory Tregs at 3 or 6 months as compared to baseline. In adolescents, there was a trend to an increase of PPI-specific Tregs at 3 months. Additionally, adults treated with AG019/teplizumab combination therapy had increased expression of the PD-1 inhibitory receptor on islet- (6/9) and PPI-specific (4/9) Tconv cells up to 3 or 6 months, whereas in adolescents' patients, the expression of the inhibitory receptor PD-1 on antigen-reactive Tconv cells mostly decreases.

The analysis of the PPI-specific CD8+ T-cells indicated that the frequency of these antigen-specific cells significantly ($P<0.05$) decreased in the peripheral blood of (adult and adolescent) patients treated with AG019/teplizumab combination therapy patients at 6 months. Also here, this decline in PPI-specific CD8+ T-cell frequency in patients treated with AG019/teplizumab combination therapy tended to be more substantial for patients with a more favorable metabolic outcome (responders) as compared to patients with a less favorable metabolic outcome (non-responders) and was equally seen in adults and in adolescents. In (adult and adolescent) patients treated with AG019/teplizumab combination therapy, CD8+ T-cells with a partially exhausted phenotype (eomesodermin [EOMES]+ T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain [TIGIT+]) were expanded at 3 months (not significant) and at 6 months ($P<0.05$) as compared to baseline.

In placebo-treated adult and adolescent patients, no metabolic responders could be identified at 6 months or at 12 months, and no significant differences could be detected in HbA1c or IDAA1c levels over time. The antigen-reactive regulatory T-cell compartment remained mostly stable and Tconv cells expressing the inhibitory receptor PD-1 decreased over time. No significant decrease in PPI-specific CD8+ T-cell frequency was seen as compared to baseline levels.

CONCLUSIONS:

The primary endpoint of both the Phase 1b AG019 monotherapy and the Phase 2a AG019 combination therapy was met; AG019 was well tolerated and safe when administered to adults and adolescents either as monotherapy or in combination with teplizumab.

There were no serious adverse events (SAEs) and no deaths. No AG019 treatment discontinuation occurred due to a treatment emergent adverse event (TEAE).

There was no evidence of dose-related adverse events in the AG019 monotherapy cohorts, and the AG019 safety profile was similar between adults and adolescents.

The TEAEs reported were mostly of mild and sometimes of moderate severity. The vast majority of TEAEs were considered as not related to AG019 treatment. No severe TEAEs have been reported in any of the AG019 monotherapy cohorts.

There was no evidence nor any trend suggesting that AG019 negatively impacted the safety profile of teplizumab infusions. The TEAEs and transient changes in lab safety assessments reported in the AG019/teplizumab combination cohorts are in line with the safety profile reported for teplizumab in its Investigator Brochure and no unexpected TEAEs were identified.

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Sepsis or bacteremia were not reported in any of the AG019 monotherapy cohorts or AG019/teplizumab combination cohorts.

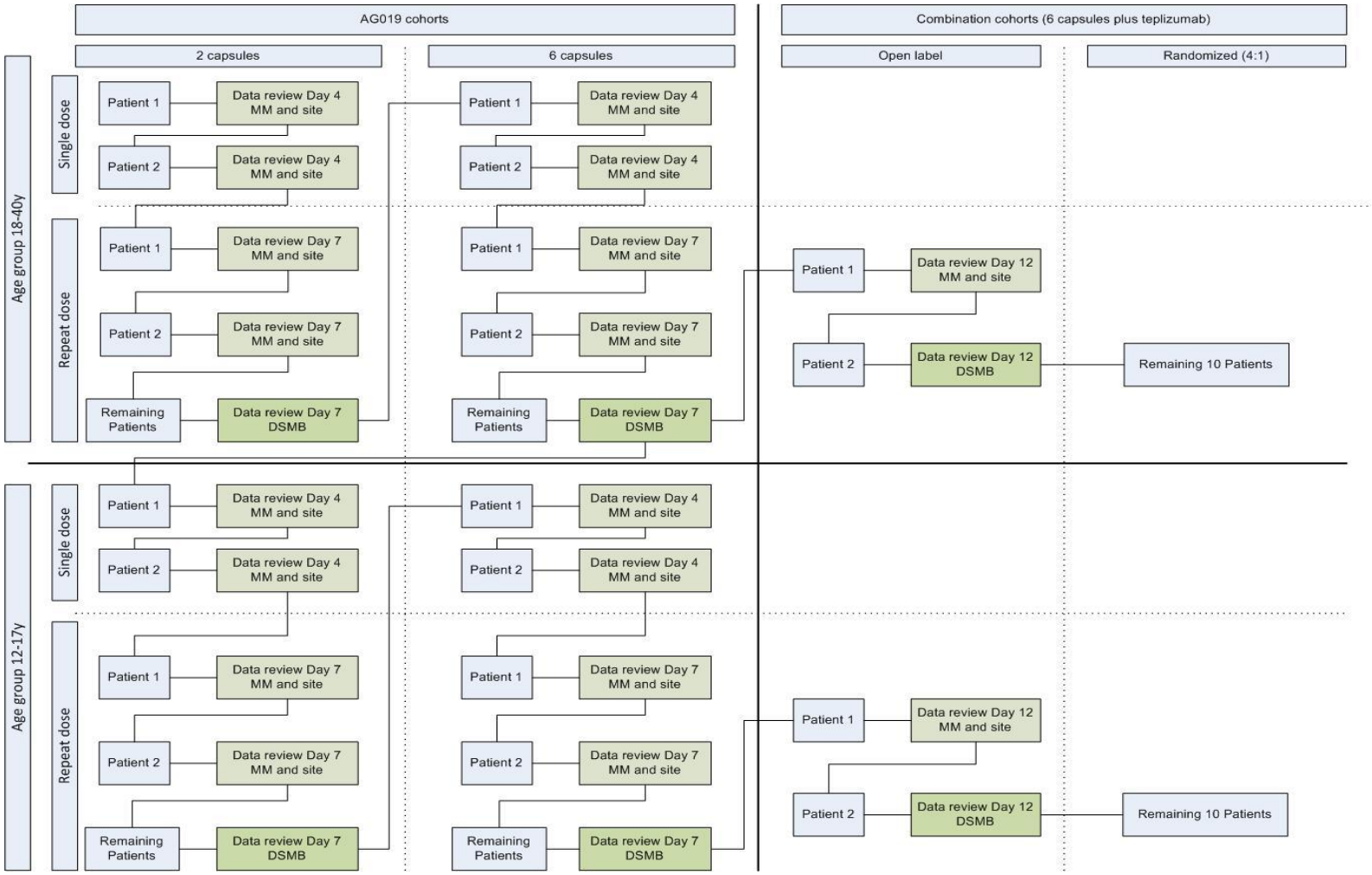
In addition, pharmacokinetic analyses demonstrated no systemic exposure of hPINS, hIL-10 and of AG019 bacteria in the blood of the patients, confirming the safety profile of AG019. Local exposure of AG019 in the GI tract, as assessed by analysis of fecal samples, could be demonstrated in the majority of patients. Moreover, encouraging metabolic and antigen-specific immunological effects, which is the keystone for the mechanism of action of AG019, was seen in the Phase 1b/2a clinical study.

A treatment period of 8 weeks of oral AG019 monotherapy was associated with a stabilization of stimulated C-peptide levels at 6 months in 7/16 (44%) patients (responders). In adults' stabilization of stimulated C-peptide levels at 6 months was observed in 5/9 (56%) patients (responders) and with stabilization of HbA1c <7% (indicating good glycemic control) and IDAA1c ≤9 (indicating partial disease remission) up to 12 months. In adolescents, stabilization of stimulated C-peptide levels at 6 months was observed in 2/7 (29%) patients (responders). HbA1c and IDAA1c trends observed in adolescents were similar to those observed in adults. AG019 monotherapy was associated with an antigen-specific immune response in the circulation, including an increase in antigen-specific Tregs up to 6 months and a significant decrease in disease-specific CD8+ T-cells at 3 months (in adolescents and adults combined). This decrease was more substantial for responders as compared to non-responders. In adolescents, metabolic control and immune modulation was overall more modest.

In patients treated with AG019/teplizumab combination therapy, 11/14 or 79% of the T1D patients (both adults and adolescents) were responders at 6 months and 6/9 (67%) of the adult patients and 4/4 (100%) of the adolescents were still responders at 12 months. HbA1c levels in this treatment arm were significantly decreased in the adult population at month 2 and 3 as compared to baseline, and average values of both HbA1c and IDAA1c remained below or equal to the target values of 7% and 9, respectively, in adults and adolescents up to 12 months. In adult patients treated with a combination of AG019 and teplizumab, an increase in antigen-reactive CD4+ Tregs was seen in combination with an increased expression of the PD-1 inhibitory receptor on antigen-specific Tconv cells. The frequency of disease-specific CD8+ T-cells was significantly decreased at 6 months in adults and in adolescents, with a more substantial decreased in responder patients as compared to non-responder patients. AG019/teplizumab combination therapy was associated with an expansion of total CD8+ T-cells with a partially exhausted phenotype, which is in line with the known pharmacodynamic effects of teplizumab.

Overall, oral AG019 monotherapy and AG019/teplizumab combination therapy were safe and well tolerated which, together with the ease of administration, could provide an opportunity for chronic treatment in different age-groups and stages of T1D. C-peptide stabilization or increase in the first 6 months in the AG019 monotherapy group and up to 12 months in the AG019/teplizumab combination therapy group provides an opportunity to prolong the treatment effect by extending the treatment duration of AG019. Through its capacity to induce antigen-specific immune modulation, AG019 may have the potential to be effective in preserving insulin-production in recent-onset T1D, alone or in association with teplizumab.

Figure 1. Overall enrollment plan



Abbreviations: DSMB; data safety monitoring board; MM, medical monitoring; y, years.

Table 1. Visit Schedule and Assessments – Single Dose Patients

Study Procedure	Screening	Treatment	Post treatment	Unscheduled
Visit	1	2	3	99[1]
Week	-4 to -1	1	1	N/A
Study Day	-29 to -1	1	4	N/A
Visit Window	N/A	0	0	N/A
GENERAL ASSESSMENTS				
Written informed consent	X			
Eligibility verification	X			
Register patient/visit through interactive response technology (IRT)	X[2]	X		X
Medical History / Demography	X			
Adverse Events	X	X	X	X
Concomitant medications	X	X	X	X
Physical Examination	X	X	X	X
Vital Signs[3]	X	X	X	X
Tuberculosis test	X			
12-lead electrocardiogram (ECG)	X		X[4]	X[4]
LABORATORY ASSESSMENTS – Local Laboratory				
Drugs of abuse test[5]	X			
Serum pregnancy test[6]	X			
Urine pregnancy test[6]		X	X	X
Hematology[7]	X		X	X
Chemistry[8]	X		X	X
Additional screening blood analysis[9]	X			
Autoantibodies[10]	X			
Viral Loads - Serology[11]	X			
STUDY DRUG ADMINISTRATION AND RELATED ASSESSMENTS				
Administer AG019		X		
Study drug accountability			X	

[1] If a patient returned for an unscheduled visit and it was determined that the patient had to withdraw, all End Of Study assessments were performed.

[2] Registration was done as soon as possible after confirmation of eligibility and completion of all screening assessments to allow for timely shipment of study drug.

[3] Vital signs included at least weight, blood pressure, respiratory rate, heart rate, temperature. Height was only measured at the visit 1.

[4] 12-lead ECG was only done if there was suspicion of cardiac problems.

[5] It was recommended that following drugs were assessed at a minimum: cannabis, cocaine, ecstacy, amphetamines.

[6] Only required for women of childbearing potential.

[7] Red blood cell (RBC) count, Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), red blood cell distribution width (RDW), white blood cell count, differential count, platelet count

[8] Blood glucose, sodium, potassium, chloride, calcium, CO_2/bicarbonate, total protein, albumin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), INR.
[9] Following additional parameters were assessed at screening: uric acid, urea/blood urea nitrogen (BUN), creatinine, estimated glomerular filtration (eGFR), total cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) (optional), thyroid stimulating hormone (TSH). Assessments for which the result was within the normal lab ranges were not repeated at follow-up visits.
[10] If evidence of autoantibody positivity is found in the patient's medical file, this assessment does not have to be repeated at screening.
[11] Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV).

Table 2. Visit Schedule and Assessments – Repeat Dose Patients in AG019 Monotherapy Cohorts and AG019/teplizumab Combination Cohorts

Study Procedure	Screening	Treatment									Post treatment									Unscheduled
Visit	1	2	3[1]	4[1]	5	6[1]	7[1]	8	9[1]	10[1]	11[1]	12[1]	13	14	15	16	17	18	19	99[2]
Week	-4 to -1	1	1	1	1	1	1	1	2	2	2	2	2	4	8	13	26	39	52	N/A
Study Day	-29 to -1	1	2	3	4	5	6	7	8	9	10	11	12	28	56	90	180	270	360	N/A
Visit Window[17]	N/A	0	0	0	0	0	0	0	0	0	0	0	0	±2	±2	±7	±7	±7	±7	N/A
GENERAL ASSESSMENTS																				
Written informed consent	X																			
Eligibility verification	X																			
Register / randomize patient through interactive response technology (IRT)	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X						X
Medical History / Demography	X																			
Tuberculosis test	X																			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X			X			X					X	X	X	X	X	X	X	X
Vital Signs[4]	X	X			X			X					X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X														X		X[5]		X	X[5]
DISEASE SPECIFIC ASSESSMENTS																				
Insulin use	X	X			X			X					X	X	X	X	X	X	X	
hypoglycemic events	X	X			X			X					X	X	X	X	X	X	X	
Electronic patient reported outcomes (ePRO) training/review	X	X			X			X					X	X	X	X	X	X	X	
Continuous glucose monitoring (CGM) placement		X																		
CGM readings					X			X					X	X	X	X	X	X	X	

Study Procedure	Screening	Treatment									Post treatment									Unscheduled
Visit	1	2	3[1]	4[1]	5	6[1]	7[1]	8	9[1]	10[1]	11[1]	12[1]	13	14	15	16	17	18	19	99[2]
Week	-4 to -1	1	1	1	1	1	1	1	2	2	2	2	2	4	8	13	26	39	52	N/A
Study Day	-29 to -1	1	2	3	4	5	6	7	8	9	10	11	12	28	56	90	180	270	360	N/A
Visit Window[17]	N/A	0	0	0	0	0	0	0	0	0	0	0	0	±2	±2	±7	±7	±7	±7	N/A
LABORATORY ASSESSMENTS - Local Laboratory																				
Drugs of abuse test[6]	X																			
Serum pregnancy test[7]	X																			
Urine pregnancy test[7]		X			X			X					X	X	X	X	X	X	X	X
Hematology set & coagulation test (INR)[8, 10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Chemistry set[9, 10]	X	X			X			X					X	X	X	X	X	X	X	X
Infusion Safety Chemistry set[10]			X	X		X	X		X	X	X	X								
Additional screening blood analysis[11]	X																			
Autoantibodies[12]	X																			
SARS-CoV-2 test – Polymerase chain reaction (PCR)	X	X[18]																		
Viral Loads – Serology[13]	X																			
Viral Loads – PCR[13]	X												X	X	X	X			X	X
LABORATORY ASSESSMENTS - Central Laboratory																				
HbA1c	X														X	X	X	X	X	
C-peptide (from 4h Mixed Meal Tolerance Test)	X															X	X		X	
Glucose (from 4h Mixed Meal Tolerance Test)	X															X	X		X	
Blood for PK	X												X		X	X				
Feces for PK[14]	X														X					

Study Procedure	Screening	Treatment									Post treatment									Unscheduled
Visit	1	2	3[1]	4[1]	5	6[1]	7[1]	8	9[1]	10[1]	11[1]	12[1]	13	14	15	16	17	18	19	99[2]
Week	-4 to -1	1	1	1	1	1	1	1	2	2	2	2	2	4	8	13	26	39	52	N/A
Study Day	-29 to -1	1	2	3	4	5	6	7	8	9	10	11	12	28	56	90	180	270	360	N/A
Visit Window[17]	N/A	0	0	0	0	0	0	0	0	0	0	0	0	±2	±2	±7	±7	±7	±7	N/A
MECHANISTIC ASSESSMENTS[15]																				
Serum	X	X											X		X	X	X	X	X	
Cellular Assays (Screening)	X																			
Cellular Assays (Follow-up)		X											X		X	X	X	X	X	
Gene Expression	X														X	X	X	X	X	
Bulk RNA	X														X	X	X	X	X	
DNA	X														X	X	X	X	X	
STUDY DRUG ADMINISTRATION AND RELATED ASSESSMENTS																				
teplizumab/placebo infusion[1, 16]		X	X	X	X	X	X	X	X	X	X	X	X							
AG019/placebo dispensing		X												X						
Study drug accountability					X			X					X	X	X					

[1] Only applicable for patients in the combination cohorts
[2] Registration was done as soon as possible after confirmation of eligibility and completion of all screening assessments to allow for timely shipment of study drug
[3] If a patient returned for an unscheduled visit and it was determined that the patient had to withdraw, all End Of Study assessments were performed.
[4] Vital signs included at least weight, blood pressure, respiratory rate, heart rate, temperature. Height was only measured at visit 1.
[5] 12-lead ECG was only done if there was suspicion of cardiac problems.
[6] It was recommended that following drugs were assessed at a minimum: cannabis, cocaine, ecstasy, amphetamines. The method of testing was left to the discretion of the investigator.
[7] Only required for women of childbearing potential.
[8] Complete Blood Count (CBC): RBC count, Hb, Hct, MCV, MCH, MCHC, RDW, white blood cell count, differential count, platelet count, INR.
[9] Blood glucose, sodium, potassium, chloride, calcium, CO_2/bicarbonate, total protein, albumin, total bilirubin, ALP, AST, ALT, LDH, CRP.
[10] Total bilirubin, AST, ALT, and LDH were evaluated, in addition to the Full Hematology set and INR, before each (potential) teplizumab infusion to verify the need to withhold teplizumab infusion
[11] Following additional parameters were assessed at screening: uric acid, urea/BUN, creatinine, eGFR, total cholesterol, triglycerides, HDL, LDL, VLDL (optional), TSH. Assessments for which the result was within the normal lab ranges were not repeated at follow-up visits.

Study Procedure	Screening	Treatment									Post treatment									Unscheduled
Visit	1	2	3[1]	4[1]	5	6[1]	7[1]	8	9[1]	10[1]	11[1]	12[1]	13	14	15	16	17	18	19	99[2]
Week	-4 to -1	1	1	1	1	1	1	1	2	2	2	2	2	4	8	13	26	39	52	N/A
Study Day	-29 to -1	1	2	3	4	5	6	7	8	9	10	11	12	28	56	90	180	270	360	N/A
Visit Window[17]	N/A	0	0	0	0	0	0	0	0	0	0	0	0	±2	±2	±7	±7	±7	±7	N/A

[12] If evidence of autoantibody positivity was found in the patient's medical file, this assessment was not repeated at screening.
[13] EBV, CMV, HCV, HIV, HBV
[14] Feces samples were only collected from patients in AG019 cohorts 2 and 4 and the Combination cohorts. Feces were collected at screening, on the last day of treatment, and every 2 days thereafter for a total of 5 sampling points (Day 56, 58, 60, 62, 64). On collection days, one feces sample was collected in a separate container and labelled with date and time of sample collection. A pick-up was arranged after Day 64.
[15] Mechanistic assessments were only done for patients in AG019 cohorts 2 and 4 and the Combination cohorts.
[16] If teplizumab dosing was withheld, all evaluations outlined in Section 11.4.3.6. of the study protocol (see Appendix 16.1.1) were needed to be performed.
[17] Due to the COVID-19 pandemic, sites could be closed for patient follow-up visits or patients could not be willing to travel to the sites for assessments. For this reason, follow-up visits from Day 90 onwards could fall outside the foreseen visit window and investigators could record the actual date of collection of all data in the electronic data capture (EDC).
[18] To be completed no more than 3 days before the scheduled start of treatment.