2 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 (USA)

STUDY CENTERS:

3 study centers in Belgium and 13 in the USA.

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 (FOCIS) 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 publicly 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, a high proportion of T1D patients do not achieve the glycemic targets. The complexity and demands of day-to-day 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

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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 destruction process and is by itself not without risks. Insufficient insulin levels can put the patient in a hyperglycemic state, which can result in nausea, vomiting, dry mouth, shortness of breath and ultimately life-threatening diabetic ketoacidosis. Left untreated, diabetic ketoacidosis can cause potentially fatal complications, such as severe dehydration, coma and swelling of the brain. On the other hand, insulin overdose can cause serious 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 potentially even death. Preservation of residual β-cell function in T1D patients is known to improve glycemic control, and to reduce risks of 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 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 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 GM *L. lactis* sAGX0407, secreting hPINS and hIL-10, alone or in association with a short-term treatment with a systemic surrogate anti-CD3 monoclonal antibody (mAb), reverted recent-onset diabetes in nonobese diabetic (NOD) mice. Therapeutic success (defined as the return to stable normoglycemia) 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 was via an increased frequency of functional PINS-specific Foxp3+ regulatory T-cells (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 was 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.

Following the positive results obtained in the NOD mouse model, AG019 has been studied as monotherapy as well as in association with teplizumab, 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 obtain pharmacokinetics data: determine the potential presence of AG019 or its secreted proteins in systemic circulation (safety – systemic exposure) and the presence of *L. lactis* AG019 bacteria in fecal excretion (PK - local exposure).

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METHODOLOGY:

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

Eight (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)
- 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 1 plus 3 additional days), after which they completed their study participation (Day 4) (see Figure 1 and Table 1).

After study completion by 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

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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).

- **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)

[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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- 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 AG019/teplizumab 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 potentially considerable study timeline 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 provides an overview of all inclusion criteria for:

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- AG019 monotherapy cohorts: column 'AC'
- 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	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 75g 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
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) ***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 (CGM) device and willingness to comply with the protocol-defined glucose monitoring *(note: this inclusion criterion does not apply to single dose patients)*	X	X

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• 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 (Hg) ≥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:

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

All patients in the repeat dose AG019 monotherapy cohorts were treated for 8 weeks with AG019 with one of the doses listed below. All patients in the AG019/teplizumab combination cohorts who were randomized to active treatment, were treated for 8 weeks with the high dose of AG019 as listed below.

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.

Teplizumab:

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

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Teplizumab batch number: 1-FIN-2543.

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

Placebo:

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

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 (up to the 12-month follow-up visit).

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, mean, median, standard deviation standard error of the mean, minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term “treatment group” refers to assigned dose group or cohort.

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

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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 (safety analysis set).

AG019 monotherapy cohorts:

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

Sepsis or bacteremia was not reported in any of the AG019 monotherapy cohorts.

The incidence of TEAEs up to the 6-months follow-up visit (i.e., the primary endpoint) was highest in the adolescent low dose cohort (7.0 TEAEs/patient), followed by the adult and adolescent high dose cohorts (3.8 TEAEs/patient each).

Overall, the highest frequency of TEAE reporting in the AG019 monotherapy cohorts occurred in the Infections and Infestations SOC, which included mainly upper respiratory tract infections and nasopharyngitis. Most other TEAEs were reported in the Gastrointestinal Disorders SOC, Blood and Lymphatic System Disorders SOC, and the Investigations SOC, but no clear pattern can be discerned across repeat dose cohorts.

All TEAEs reported in the AG019 monotherapy cohorts were of mild (80.4%) or moderate (19.6%) severity. No severe TEAEs have been reported in any of the AG019 monotherapy cohorts.

The vast majority of TEAEs (89.7%) were considered as not reasonably related to AG019 treatment. Most TEAEs reported as reasonably related to AG019 were in the Gastrointestinal Disorders SOC with diarrhea being the most reported.

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

Although the total number of patients is too limited to draw firm conclusions, there was no evidence of an increased rate of infections in any of the AG019 monotherapy cohorts. Viral reactivation, measured as a positive polymerase chain reaction (PCR) test after study treatment initiation, was not observed in any of the AG019 monotherapy cohorts.

AG019/teplizumab combination cohorts:

There were no serious adverse events (SAEs) and no deaths. No AG019 treatment discontinuation occurred due to a TEAE. Six (6) patients prematurely discontinued teplizumab infusions, in accordance with the protocol defined infusion withholding criteria.

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

The incidence of TEAEs up to the 6-months follow-up visit (i.e., the primary endpoint) was highest in the adult placebo combination cohort (12.5 TEAEs/patient) and in the adult active AG019/teplizumab combination cohort (9.1 TEAEs/patient). In the adolescent combination cohorts, the incidence of TEAEs up to the 6-month follow-up visit was 4.4 TEAE/patient in the active combination cohort, and 1TEAE/patient in the placebo combination cohort, respectively.

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Overall, the highest frequency of TEAE reporting in the AG019/teplizumab combination cohorts occurred in the Gastrointestinal Disorders SOC, which included mainly diarrhea and vomiting. Most other TEAEs were reported in the Investigations SOC, Nervous System Disorders SOC, and Blood and Lymphatic System Disorders SOC.

The TEAEs reported in the AG019/teplizumab combination cohorts were mostly of mild (67.2%) or moderate (28.1%) severity. Eight (8) grade 3 TEAEs were reported in the active AG019/teplizumab combination cohorts. Of these, 2 were assessed as being reasonably related to AG019 and teplizumab (diarrhea and vomiting) while the other 6 grade 3 TEAEs were assessed as being reasonably related to teplizumab but not to AG019 (lymphopenia, maculopapular rash, increased blood bilirubin and decreased lymphocyte count). One non-serious grade 4 TEAE (lymphopenia) was reported in the adult active AG019/teplizumab combination cohort. The TEAE was assessed as being reasonably related to teplizumab but not to AG019.

The majority of TEAEs were considered as not reasonably related to AG019 treatment (66.7%). Sixty-four (64) TEAEs were assessed as being reasonably related to AG019 (including 41 TEAEs in the adult active combination cohort, 22 TEAEs in the adult placebo cohort, and 1 TEAE in the adolescent active combination cohort). Most TEAEs reported as being reasonably related to AG019 occurred in the Gastrointestinal Disorders SOC (mainly diarrhea and vomiting).

Although the total number of patients is too limited to draw firm conclusions, there was no evidence of an increased rate of infections in the AG019/teplizumab combination cohorts. Viral reactivation, measured as a positive polymerase chain reaction (PCR) test after study treatment initiation, was detected in 4 patients in the adult active AG019/teplizumab combination cohort, and in one placebo treated patient. For 3 of these 5 reactivations, a TEAE was reported.

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 (including transient decreases in lymphocytes and transient increases in alanine aminotransferase) reported in the AG019/teplizumab combination cohorts were in line with the safety profile reported for teplizumab in its Investigator Brochure and no unexpected TEAEs were identified.

PHARMACOKINETIC RESULTS:

Adult and adolescent patients receiving AG019 monotherapy and AG019/teplizumab combination therapy did not show AG019 bacteria in blood. Also, there was no evidence of systemic exposure of AG019 secreted hPINS and hIL-10 in plasma. These results indicate no risk for systemic exposure in adult and adolescent T1D patients receiving AG019 monotherapy or AG019/teplizumab combination therapy during treatment 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>

Stimulated C-peptide, measured during an MMTT, was used to identify responders with stabilized C-peptide levels. Patients were classified as a ‘responder’ when his/her C-peptide change from

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baseline was either non-negative or, if negative, represented a coefficient of variance (CV) less than or equal to 9.7%[2].

An 8-week treatment period with oral AG019 monotherapy in 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 at 6 months was 104% of baseline C-peptide value). In adults, 5/9 patients (56%) were classified as responders, whereas in adolescents a favorable metabolic outcome based on C-peptide stabilization was demonstrated in 2/7 (29%) patients.

At baseline, 7/8 (87%) of adult and adolescent PD-PP patients had HbA1c levels in line with the ADA recommended targets for glycemic control, i.e., <7%. Following an 8-week treatment with AG019 monotherapy, all adult patients (9/9, 100%) had HbA1c <7% both at 6 and at 12 months, and HbA1c levels were significantly decreased as compared to baseline at month 3 and 6 of the study ($p<0.05$ at both timepoints). In adolescents treated with AG019 monotherapy, no significant decrease in HbA1c levels were seen compared to baseline, and 80% (4/5) and 57% (4/7) of patients had HbA1c <7% at 6 months and 12 months, respectively.

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

Patients in the adolescent monotherapy cohort (PD-PP) had an average insulin requirement of 0.50 IU/kg/24h at baseline, whereas insulin requirements at 12 months was 0.53 IU/kg/24h (change from baseline at study completion of +0.03 IU/kg/24h). For the adult monotherapy cohorts, insulin use at baseline was 0.23 IU/kg/24h and 0.40 IU/kg/24h at Visit 19 (+0.16 IU/kg/24h).

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-cells (Tregs). The analysis of the PPI-specific CD8+ T-cells indicated that the frequency of these antigen-specific cytotoxic 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.

AG019/teplizumab combination therapy

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; 7/10 (70%) adult patients and 4/4 (100%) adolescent patients were classified as responders at 6 months. The median

[2] Greenbaum, C.J., Beam, C.A., Boulware, D., et al. Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012; 61, 2066–2073.

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change from baseline in the 6-month responder group (N=11) corresponds to 126% at 6 months and 105% at 12 months. At 12 months, 10/13 (77%) of all patients (6/9 adults and 4/4 adolescents) showed stabilization/increase in their C-peptide levels.

HbA1c levels in this treatment arm were significantly decreased in the adult population at month 2 ($p<0.01$) and at month 3 ($p<0.05$) as compared to baseline. This decrease was seen up to 12 months, although not statistically significant. In adolescents, a non-significant decrease in HbA1c levels was 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 <7% at baseline. Following treatment, the percentage of adult patients in the AG019/teplizumab combination cohort with HbA1c <7 (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 ($p<0.05$ in adults at 2 months). These decreases were maintained up to 12 months, although not significant. In the adults treated with AG019/teplizumab combination therapy, 6/10 (60%) of patients had IDAA1c ≤ 9 at baseline, whereas all adult patients (100%) 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%) adolescent patients were still in partial remission.

Adolescents had an average insulin requirement of 0.51 IU/kg/24h at baseline, whereas average insulin requirements in the adult AG019/teplizumab combination cohorts was 0.37 IU/kg/24h (in placebo 0.38 IU/kg/24h). For the adult AG019/teplizumab combination cohorts, the average insulin requirement at 12 months was 0.35 IU/kg/24h (change from baseline -0.02 IU/kg/24h). Patients treated with placebo had increased insulin requirements at study completion (+0.42 IU/kg/24h), whereas insulin requirements in AG019/teplizumab treated adolescents decreased during the study (-0.02 IU/kg/24h).

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 adolescent patients, the expression of the inhibitory receptor PD-1 on antigen-reactive Tconv cells mostly decreased.

The analysis of the PPI-specific CD8+ T-cells indicated that the frequency of these antigen-specific cytotoxic cells decreased in the peripheral blood of (adult and adolescent) patients treated with AG019/teplizumab combination therapy patients at 3 months (not significant) and 6 months (significantly, $p<0.05$). Also here, the 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 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

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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, and partially exhausted CD8+ T-cells were not expanded during treatment.

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 SAEs and no deaths. No AG019 treatment discontinuation occurred due to a TEAE.

The TEAEs reported were mostly of mild and sometimes of moderate severity. No severe TEAEs have been reported in any of the AG019 monotherapy cohorts.

The vast majority of TEAEs were considered as not reasonably related to AG019 treatment.

There was no evidence nor any trend suggesting that AG019 negatively impacted the safety profile of teplizumab infusions

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

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 most patients.

Pharmacodynamic analysis demonstrated that a treatment period of 8 weeks of oral AG019 monotherapy was associated with a stabilization of stimulated C-peptide levels at 6 months in 44% of patients (responders). In adults, stabilization of stimulated C-peptide levels at 6 months was observed in 56% of patients (responders) along with stabilization of HbA1c <7% (indicating good glycemic control), insulin use 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 29% of patients (responders). HbA1c, insulin use 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 patients treated with AG019/teplizumab combination therapy, 79% of the patients (70% of adults and 100% of adolescents) were responders at 6 months and 77% at 12 months (67% of adults and 100% of adolescents). 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. Also, daily insulin use appeared to stabilize in adults and adolescents up to 10 months after treatment completion. 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 decrease 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.

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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 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. Trends showing stabilization or improvement of HbA1c, IDAA1c and daily insulin dose levels further supported C-peptide findings and pointed towards a potential broader improvement of metabolic response. 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.