2 SYNOPSIS

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Study Title:
"A Multicenter, Multinational Extension of Study CP-MGA031-01 to Evaluate the Long-Term Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus" (Protocol CP-MGA031-02; the Protégé Extension study)

Investigators and Study Centers:
Multicenter, 56 centers in North America, Europe, Israel, and India.

Publication (reference): None

Study Period:

- 14 Feb 2009 (first subject enrolled)
- 23 Nov 2010 (sponsor decided to terminate the study based on study **CP-MGA031-01** results)
- 08 Feb 2011 (last subject completed)

Study Phase:: 2/3

Objectives:

- The primary objective of the extension study was to assess longer-term safety, with particular focus on the development of serious adverse events (SAEs), adverse events of special interest (AESIs) including opportunistic infections and lymphoproliferative disease, and other immediately reportable events (IREs), in subjects with recent-onset type 1 diabetes mellitus (T1DM) who completed CP-MGA031-01.
- The secondary objectives planned for the extension study were to assess longer-term efficacy of teplizumab, evaluate immunologic effects (in Canada and the United States [US] only), measure anti-teplizumab antibody levels, and assess patient-reported outcomes (PRO) in adults and children with recent-onset T1DM

Methodology:
CP-MGA031-02, the Protégé Extension study, was designed as a 3-year extension of study CP-MGA031-01 (also known as the Protégé study). All investigators and subjects blinded to study treatments and laboratory measurements taken in CP-MGA031-01 were to remain

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blinded throughout CP-MGA031-02. Subjects kept their same subject identifier as they had in CP-MGA031-01 and no drug (or placebo) was administered during this extension study. Subjects who completed CP-MGA031-01 and met all other entry criteria were invited to participate in CP-MGA031-02. Subjects were to be seen for a follow-up visit every 6 months, blood samples drawn, AESIs and SAEs recorded, and concomitant medications monitored. Subjects were also to be contacted by telephone every 3 months. Subjects were to record insulin use and glucose measurements on a diary card.

Number of Subjects (Planned and Analyzed):
It was planned that CP-MGA031-02 would involve up to 80 international sites, with an anticipated range of 1 to 26 subjects per site. Of the 497 subjects eligible for the extension study, 219 subjects were enrolled, and none completed this extension study. All 219 enrolled subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:
The main inclusion criterion was that subjects complete the evaluations for the Study Day 728 visit of the Protégé study (**CP-MGA031-01**), regardless of how many doses of teplizumab or placebo were received. Written informed consent was to be obtained after all procedures for Study Day 728 were completed. Written assent was obtained for subjects under age 18, according to all applicable regulations) including consent for the use of research-related health information.

Test Product, Dose and Mode of Administration, Lot Number:
Not applicable, as no study drug or placebo was administered.

Duration of Treatment:
Not applicable as no study drug or placebo was administered.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable as no study drug or placebo was administered.

Criteria for Evaluation:

Efficacy and Pharmacodynamics:
Efficacy assessments were to include hemoglobin A1c (HbA1c) values, insulin use, glucose, C-peptide levels, and PROs (patient-reported outcomes). Pharmacodynamics evaluations were to include measurements of human anti-human antibody (HAHA) levels, and mechanistic measurements of Fox P3 and various clusters of differentiations.

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Pharmacokinetics and Immunogenicity:
Pharmacokinetics were not evaluated in this extension study. Antidrug antibody levels were obtained to evaluate immunogenicity.

Safety:
Safety was assessed in this study by the recording of SAEs and AESIs. Laboratory evaluations, including hematology, serum chemistry, urinalysis, and serology, were periodically evaluated as well as vital signs. Subjects were to be monitored throughout the study for the occurrence of new SAEs and AESIs that began in the extension study, as well as ongoing events that began during the Protégé study. The new AESIs and SAEs were to be monitored from Study Day 0 of the extension study until resolution to baseline status (Study Day 0 of the extension study). Any AESIs and SAEs from Protégé that continued into the extension study were to be monitored until they returned to baseline status (Study Day 0 status of Protégé).

Statistical Methods:
All data were provided in data listings sorted by age group (open-label segment subjects) or treatment group (double-blind segment subjects) and subject number. All tabular summaries were by age group (open-label segment subjects) or treatment group (double-blind segment subjects). In general, categorical data were summarized by number and percentage of subjects falling within each category. Continuous variables were summarized by descriptive statistics including mean, standard error or deviation, median, minimum, and maximum.

Summary of Results:

Study Subjects:
A total of 497 adults and children with T1DM were eligible for the extension study. Of these, 219 subjects were enrolled, and none completed the extension study. All 219 subjects received at least one dose of study drug or placebo in the Protégé study. A total of 219 (100.0%) subjects discontinued from the study. The most common reason for discontinuation from the study was study terminated by sponsor (90.6% and 96.3% in the open-label and double-blind subjects, respectively). Of the 32 subjects enrolled in the extension study from the open-label segment of the Protégé study, only one (3.1%) subject remained enrolled at Month 21. Of the 187 subjects enrolled in the extension study from the double-blind segment of Protégé, very few subjects were still enrolled in the study even at 12 months of participation (4.7% of all teplizumab subjects and 5.3% of the placebo subjects). The following discussion compares the extension subjects and all Protégé subjects at baseline of the Protégé study. At Protégé baseline, the extension subjects were approximately 1 year older than all Protégé subjects. In both the extension and Protégé

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studies, the number of males was higher than the number of females, and the majority of subjects were white (~85% in subjects from the open-label segment and ~65% in subjects from the double-blind segment) with another portion Asian (~16% in subjects from the open-label and ~35% in subjects from the double-blind segment). Like the Protégé study, a large majority of subjects in the extension study had positive Epstein-Barr virus (EBV) or cytomegalovirus (CMV) immunoglobulin G values at baseline of the extension study. Only 7 subjects had positive EBV immunoglobulin M values at extension baseline. No subjects had positive CMV polymerase chain reaction values at extension baseline.

Efficacy and Pharmacodynamics results:
The primary efficacy objective of this extension study was to assess longer-term efficacy. The original composite endpoint (HbA1c<6.5% and insulin<0.5U/kg/day) as well as C-peptide, insulin use, HbA1c, and the new composite (HbA1c<7.0% and insulin<0.25U/kg/day) were to be assessed as was done in Protégé. Because the study was terminated early with a limited number of subjects and subject visits the data were only summarized. Too few data were available for meaningful results for any efficacy endpoint. No meaningful results related to pharmacodynamics were obtained.

Pharmacokinetics and Immunogenicity results:
Pharmacokinetics were not evaluated in this extension study. No meaningful results related to immunogenicity were obtained due to the early termination of this study and the subsequent limited amount of samples collected. Of the 41 subjects enrolled from the Protégé double-blind segment with values measured, the majority of subjects had HAHA counts less than or equal to 100 ng/mL.

Safety:
There were no new or unexpected safety findings in the results of this study. Adverse events that did not meet one of the criteria for AESI or SAE were not to be collected in this study; however, they were not deleted if recorded inadvertently into the system. One subject died during this extension study (unknown cause with gastrointestinal symptoms), 13 subjects had SAEs, and 26 subjects had AESIs.

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CONCLUSIONS

Efficacy Conclusions:

Due to the early termination of this study and the subsequent limited amount of efficacy data obtained, no efficacy conclusions can be drawn. Too few data were available for meaningful conclusions about any efficacy endpoint.

Safety Conclusions:

This longer-term extension study was terminated early, and limited data were available. However, no new or unexpected safety findings were detected in the results during this extension study.

Final Date: 05 October 2012