2 SYNOPSIS

Sponsor: MacroGenics, Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
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Study Title:
A Phase 3, Randomized, Double-Blind, Multinational, Placebo-Controlled Study to Evaluate 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-MGA031-03; the Encore study)

Investigators and Study Centers:
Multicenter, 75 sites in India, Poland, Romania, United States, Spain, Germany, Czech Republic, Ukraine, Israel, Great Britain, Belgium, Finland, and Mexico

Publication (reference): None

Study Period:
15 Sep 2009 (first patient enrolled)

20 Oct 2010 (sponsor decided to terminate enrollment and dosing in the study based on study **CP-MGA031-01** results)

18 Apr 2012 (last patient completed; NOTE: 3 unscheduled laboratory draws occurred after that date with the last occurring on 08 May 2012)

Study Phase: 3

Objectives:
The primary objective of this study was to assess, relative to placebo, the efficacy, tolerability, and safety of teplizumab when administered according to 3 different teplizumab dosing regimens in subjects with recent-onset (onset within past 12 weeks) type 1 diabetes mellitus (T1DM). All regimens were administered in addition to standard of care (ie, insulin treatment). The secondary objectives were to assess the durability of clinical benefit, the impact of teplizumab on health-related quality of life, and the safety and tolerability of teplizumab.

Methodology:
CP-MGA031-03, the Encore study, was designed to address the safety and therapeutic activity of teplizumab in relation to duration of treatment and total dose administered in subjects (aged 8 – 35 years) with recent-onset T1DM. Subjects were no longer being

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enrolled, randomized, or dosed in this study as of 20 Oct 2010. Enrollment and dosing under this protocol was suspended, based on results demonstrating lack of efficacy based on the primary endpoint in another teplizumab study similar to this study in design (Protocol **CP-MGA031-01**, the Protégé study). Subject follow-up for safety and some efficacy parameters continued. The study was 18 to 24 months duration, depending on whether subjects received 1 or 2 cycles of treatment or portion thereof, before dosing for this study was discontinued by the Sponsor. Subjects were followed for 18 months after their first dose of their last cycle of study medication. Subjects who received some or all of 1 cycle of treatment participated for 18 months; subjects who received some or all of a second cycle of treatment 6 months after their first cycle participated for 24 months. Subjects continued to the end of the study. Subjects who consented (and assented for children under age 18) and met the entry criteria at Study Day 1 were randomized to 1 of 4 study arms. The randomization was stratified by country and age (18-35 years, 12–17 years, and 8-11 years). All treatments were to be repeated at Week 26. As of 20 Oct 2010, 254 subjects had been randomized into the study. Blood samples were drawn, AESIs and SAEs recorded, and concomitant medications monitored.

Number of Subjects (Planned and Analyzed):
It was planned that CP-MGA031-03 would involve 400 subjects; 254 actual subjects were enrolled before enrollment and dosing in the study was terminated early. Subjects received treatment with teplizumab (3 study arms of 100 planned subjects each [Arms 1−3, respectively]) or placebo only (1 study arm of 100 planned subjects [Arm 4]). All 254 enrolled subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion:
The main inclusion criteria were male and female subjects aged 8-35 currently receiving insulin (or the use of insulin in the recent past) and recently diagnosed, according to the American Diabetes Association criteria, with T1DM (within 12 weeks from first visit to any physician for symptoms or signs of T1DM), able to provide written informed consent/assent, with a detectable fasting or stimulated C-peptide level, one positive relevant antibody test at screening, able and willing to be available for the duration of the study, willing to follow study restrictions/procedures, and willing to forego other forms of experimental treatment during the study, particularly immunomodulatory agents and agents that stimulate pancreatic beta cell regeneration or insulin secretion.

Test Product, Dose and Mode of Administration, Lot Number:
Teplizumab intravenous (IV) doses ranged from 51 $\mu g/m^2$ to 826 $\mu g/m^2$. The MGA031 final

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drug product lot numbers for this study were 1-FIN-0618, 1-FIN-0694, 1-FIN-0762, and FIN-0478. [redacted]

Duration of Treatment: One dose per day for 14 days, repeated at Week 26

Reference Therapy, Dose and Mode of Administration, Lot Number:
Placebo dose administered IV. Placebo lot numbers used in this study were 1-FIN-0681, FIN-0183, 1-FIN-0684, FIN-0196, 1-FIN-0685, 1-FIN-0763, and 1-FIN-0846.

Criteria for Evaluation:

Efficacy:
Efficacy assessments included C-peptide levels, glycosylated hemoglobin (HbA1c) values, insulin use, hypoglycemia, glucose, and quality of life evaluations.

Pharmacodynamics:
Pharmacodynamic assays included immunophenotyping, CD3 coating and modulation, flow cytometry, and FoxP3.

Pharmacokinetics and Immunogenicity:
Serum teplizumab and antidrug antibody levels were obtained and analyzed in combination with the pharmacokinetic data from the Protégé study (**CP-MGA031-01**).

Safety:
Adverse events (AEs), adverse events of special interests (AESIs), and serious adverse events (SAEs) were assessed through Day 365 through a symptom-directed medical history. After Day 365, only non-serious AEs assessed as treatment related, AESIs, and SAEs were required to be reported. Other safety assessments included blood chemistry, serology, complete blood counts with differential, platelets, urinalysis, vital signs, and laboratory studies when indicated.

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Statistical Methods:
All data were provided in data listings sorted by treatment group and subject number. All tabular summaries were by treatment group. 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.

The composite endpoint of HbA1c and insulin was considered the primary endpoint. If a statistically significant difference was observed between any dose group and placebo in the composite endpoint analysis, the secondary endpoints were then analyzed in a hierarchical order. The secondary endpoints were compared to placebo only for those groups that differed from placebo in the composite endpoint analysis.

Summary of Results:

Study Subjects:
A total of 505 adults and children with T1DM were screened for this study; 254 adults and children with recent-onset T1DM were randomized and enrolled in this study. Of the 254 subjects enrolled into the study, all 254 subjects received at least one dose of study drug (placebo or teplizumab); 89.8% completed 52 weeks of follow-up, but only 29.1% completed 104 weeks of follow-up. During the study, a total of 44 (71.0%) subjects in the placebo group and 151 (78.6%) subjects in the all teplizumab group withdrew from dosing. The most common reasons for discontinuation from study treatment were “other”, including subjects who stopped dosing when study dosing was stopped by the sponsor on 20 Oct 2010, (67.7% of subjects in the placebo group and 62.5% of subjects in the all teplizumab group), and adverse event (3.2% of subjects in the placebo group compared to 12.5% of subjects in the all teplizumab group).

The majority of double-blind subjects in this study were adult and white. Approximately 67% of subjects were male. Mean ages were similar across treatment groups. Three separate age groups were enrolled into the double-blind segment, in a stratified manner: adults (18 to 35 years), adolescents (12 to 17 years), and children (8 to11 years). The distribution of subjects into these age groups was similar across the treatment groups. Baseline viral status was similar across treatment groups. Approximately 78% of all enrolled subjects were immunoglobulin G (IgG) or immunoglobulin M positive at baseline for Epstein-Barr virus (EBV), and approximately 26% of subjects were IgG positive at baseline for cytomegalovirus. No statistically significant differences were observed among the treatment

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groups in time from diagnosis to enrollment, C-peptide and HbA1c levels, insulin use at baseline, ketoacidosis between onset and enrollment, and presence of T1DM autoantibodies.

Efficacy and Pharmacodynamics results:
No significant differences were observed at 52 weeks between placebo and any of the teplizumab treatment groups in the primary endpoint, the composite of insulin less than 0.5 U/kg/day and HbA1c less than 6.5%.

Pharmacokinetics and Immunogenicity results:
The results of the pharmacokinetic analysis indicated that teplizumab concentration time profiles for subjects of this study (Encore) could be described by the model developed with the Protégé study data, with the addition of study corrections for humanized anti-human antibody (HAHA) assay, clearance and volume parameters. The estimate of the HAHA assay correction provided by the model was in agreement with the observed differences in HAHA distributions of the two studies. Clearance and volume for patients of this study (Encore) were estimated to be 46% (95% confidence interval [CI]: 36-56%) and 32% (95% CI: 24 - 40%) higher than those for patients from the Protégé study. The reason for the differences is not clear although differences in sampling schedule between studies may have contributed to the differences in the parameter estimates.

Safety:
The safety results of this study are consistent with the safety results of the Protégé study, a sister study to this study. As in the Protégé study, no difference was seen in the frequency of overall AEs between teplizumab and placebo subjects, and no difference was seen in the rate of AEs, including SAEs, in children versus adults. Drug-related AEs, SAEs, AEs leading to withdrawal either from study drug or the study, and AEs of grade 3 or higher were more common in all teplizumab groups compared to placebo. Receipt of one or two cycles of treatment did not make a difference on the percentage of subjects who had any AE as all subjects had at least one AE. However, a higher percentage of subjects who received two cycles of treatment had treatment-related AEs, SAEs, and grade 4 AEs. As in the Protégé study, the AEs were usually transient, grade 1 or 2, with the exception of the teplizumab mechanism-based lymphopenia that usually resolved in 14 days, but no more than 28 days.

Based on safety data from this study and the Protégé study, the main risks of teplizumab over 2 years consisted of transient cytopenias (predominantly lymphopenia), transient (mostly mild) elevations in LFTs, and mild to moderate (if pre-medicated) cytokine release, and infusion related symptoms including rash. The main hematologic changes seen with

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teplizumab were a mechanism-based transient decrease in lymphocytes in over 80% of teplizumab subjects (commonly grade 3 or lower) and a mild decrease in neutrophils and platelets. These values typically began to resolve after Day 7 while dosing was continuing. Other less common hematologic changes included transient eosinophilia; these changes were not associated with clinical manifestations. In this study, where the difference between the cycles of dosing was examined, there was not a detectable difference in these patterns of mean changes in these hematologic parameters between the two cycles of dosing.

As in the Protégé study, liver function abnormalities (grade 1 and 2) appear transient, are not associated with clinical disease, and may be consistent with cytokines in the liver. Of note, the pattern of mean changes in liver function abnormalities was less pronounced during cycle 2 dosing. Liver events of grade 3 or higher are not higher in teplizumab-treated subjects compared to placebo-treated subjects. Mean liver function transaminases also began to resolve after Day 7 while dosing was still continuing. As in the Protégé study, rigorous, conservative dose-stopping rules included in and specific to the protocol could have mitigated the potential for the development of select SAEs and should be used in future studies.

CONCLUSIONS:

Efficacy Conclusions

As a result of the premature termination of this study, only 63.5% (254/400) of the planned subjects actually enrolled. Thus, efficacy analyses are under powered, limiting any conclusions and interpretation of outcomes. No significant differences were observed at 52 weeks between placebo and any of the teplizumab treatment groups in the primary endpoint, the composite of insulin less than 0.5 U/kg/day and HbA1c less than 6.5%.

Pharmacokinetic data from this study and the Protégé study were combined, and the earlier developed population PK model was evaluated and updated based on the combined data. The pharmacokinetics of teplizumab following intravenous administration was described by the two-compartment model developed previously, with saturable binding in central and peripheral compartments. Clearance and volume for this study (Encore) were estimated to be 46% and 32%, respectively - higher than those for the Protégé study.

Safety Conclusions

In a population of early T1DM who were pre-treated with antihistamines and anti-pyretics the main risks of teplizumab over 18 months after the last dose consist of:

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- transient cytopenias (predominantly lymphopenia)
- transient (mostly mild) elevations in liver function tests
- mild to moderate transient rash
- mild to moderate (if pre-medicated) cytokine release
- infusion-related AEs also included headache, nausea, vomiting, pyrexia, and chills/rigors.

With regard to infection, at the doses used in this study, EBV reactivation is transient and uncommon and acute mononucleosis syndrome is not increased versus placebo. The number of herpes zoster events was small with both placebo and teplizumab.

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