2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: IMLYGIC®

Name of Active Ingredient: Talimogene laherparepvec

Title of Study:

A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX Sponsored Clinical Trials

Investigator(s) and Study Center(s):

This study was conducted at 52 centers in Canada, Europe, South Africa, South Korea, and the US (see Section 16.1.4).

Publication(s):

None.

Study Period:

26 April 2010 (first subject enrolled) – 23 September 2021 (final subject exited).

Development Phase: Phase 4 Registry

Previous Reports for This Study:

Synopsis Clinical Study Report: 009/07, dated 17 September 2013

Study Rationale:

The purpose of this observational registry study was to monitor subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial ("parent study") for any tumor type for overall survival and long-term safety. Subjects enrolled in the registry study were to be contacted every 3 months (± 30 days) to assess long-term safety, survival data, and use of subsequent anti-cancer therapy. The data collected by this registry study, along with safety data collected during long-term follow-up (LTFU) in the parent studies, was intended to provide information to better characterize the long-term effects of subjects that have received talimogene laherparepvec.

Objectives, Endpoints:

Objectives	***Endpoints***
Primary	
• To evaluate the long-term safety of talimogene laherparepvec	• Long-term safety as assessed by subject incidence of all post-treatment talimogene laherparepvec related adverse events (AEs) of any grade, grade ≥ 3 adverse events, serious adverse events (SAE), fatal adverse events, and adverse events of interest (EOI)

• To monitor subject overall survival	• Survival status
• To monitor use of subsequent anti-cancer therapy, for the tumor indication in the prior Amgen or BioVex-sponsored clinical trial, including retreatment with marketed talimogene laherparepvec in subjects previously enrolled in Amgen or BioVex-sponsored talimogene laherparepvec clinical trials	• Use of subsequent anti-cancer therapy for indicated tumor type in prior Amgen or BioVex-sponsored talimogene laherparepvec clinical trial
Secondary	
• To monitor subject enrollment in the registry from parent studies	

Methodology:

This was an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial and have ended treatment and participation, including long-term follow-up (if applicable) in that trial. No experimental intervention was involved. Thus, subjects underwent clinical assessments and received the standard of care treatment as determined by the subject's physician. Subjects who consented to and were eligible to enroll in this registry study were monitored 1) for adverse events deemed by the investigator to be related to treatment with talimogene laherparepvec, 2) for overall survival every 3 months (± 30 days) until withdrawal of consent, death, or end of study, whichever occurs first, and 3) use of subsequent anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.

If retreatment with marketed talimogene laherparepvec for approved indication was indicated during participation in the registry study, a subject continued participation in the study and the retreatment was reported.

The study began in 2010 and the database cutoff date was 03 November 2021, which included the period during which the COVID-19 pandemic was occurring globally. The study was at the stage of recruitment and follow-up when the pandemic occurred. Contingency measures were implemented to manage study conduct during the COVID-19 pandemic. These measures included remote monitoring visits, including remote source data verification (where allowed per local regulations), and documentation of COVID-19 related protocol deviations. This study also permitted telephone follow up visits.

Number of Subjects Planned:

The total number of subjects who participated in the registry was determined by the number of subjects who remained alive at the end of the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial in which they participated for any tumor type and who consented and were deemed eligible to participate in this registry study.

Diagnosis and Main Criteria for Eligibility:

Key Inclusion Criteria:

All subjects must have provided informed consent prior to initiation of any study activities. When the subject was legally too young to provide informed consent/assent, subject's legally acceptable representative must have provided informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities.

All subjects must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial for any tumor type and must have discontinued treatment and participation, including long-term follow-up (if applicable) in that trial.

Key Exclusion Criteria:

Subjects who were currently receiving talimogene laherparepvec in Amgen or BioVEX-sponsored clinical trial.

Subjects who were currently participating, including for long-term follow-up (if applicable), in other Amgen-sponsored talimogene laherparepvec clinical trial.

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number:

No investigational product was administered during the course of this registry study.

Duration of Treatment:

Duration of the study varied for each subject. Subjects who ended talimogene laherparepvec treatment on an Amgen or BioVEX-sponsored clinical trial for any tumor type and who consented to and were deemed eligible for participation in this registry study were monitored for 1) adverse events deemed by the investigator to be related to treatment with talimogene laherparepvec for 2) overall survival every 3 months (± 30 days) until withdrawal of consent, death, or end of study, whichever occurs first, and 3) for use of anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.

Statistical Methods:

The statistical reporting of the safety endpoints and overall survival will be entirely descriptive (summary statistics), with no formal statistical testing performed. Categorical outcomes were summarized using frequency and percent. Continuous outcomes were summarized using the mean, median, standard deviation, minimum, and maximum. Overall survival (OS) was estimated using the Kaplan-Meier method; estimates of event time quartiles, event-free rates at selected times, and the corresponding 95% CIs were provided.

In addition to data collected from subjects enrolled in registry study 20120139, data from subjects with LTFU (follow-up visit or any reported AE with onset > 30 days from last dose) in their parent study were analyzed (post-treatment analysis set).

Summary of Results:

Subject Disposition:

Registry Study

One hundred eighty-six subjects were enrolled in the registry study. Of these, 113 subjects completed the study and 57 exited the study due to death. Five subjects were lost to follow-up, 5 were withdrawn due to sponsor decision (2 were enrolled in error while still on their parent study, 2 were deemed ineligible due to a change in exclusion criteria when amending the protocol, and 1 was due to an unspecified reason), 4 failed to meet protocol-specified criteria, and 2 withdrew consent to participate. The median (range) post-treatment follow-up time in the registry study was 147.7 (0.1, 592.3) weeks.

Post-treatment Analysis Set

One thousand one hundred and forty-eight (1148) subjects were identified from parent studies who had at least 1 post-treatment follow-up > 30 days after their last dose of talimogene laherparepvec in either their respective parent study, after enrolling in the registry only, or who participated in both the registry and LTFU in their parent study. Of these 1148, 970 participated in LTFU in their parent study only, 71 had LTFU in the registry study only, and 107 had LTFU in both their parent study and the registry. The median (range) post-treatment follow-up time in the parent studies was 65.6 (0, 399.7) weeks.

Baseline Demographics:

Sex:

Registry Study: 95 men (53.4%), 83 women (46.6%)
Post-treatment Analysis Set: 650 men (56.6%), 498 women (43.4%)

Age:

Registry Study: Mean (SD, range) 63.7 (15.1, 19 to 96) years
Post-treatment Analysis Set: Mean (SD, range) 62.8 (14.4, 11 to 96) years

Race:

Registry Study: 175 white (98.3%), 3 other (1.7%)
Post-treatment Analysis Set: 1115 white (97.1%), 33 other (2.9%)

Ethnicity:

Registry Study: 3 Hispanic or Latino (1.7%), 174 not Hispanic or Latino (97.8%), 1 missing (0.6%)
Post-treatment Analysis Set: 31 Hispanic or Latino (2.7%), 1114 not Hispanic or Latino (97.0%), 3 missing (0.3%)

Efficacy Results:

Median OS in the post-treatment analysis set (N = 1148) was 47.57 (95% CI: 39.95, 60.88) months post-first dose.

Safety Results:

Ninety-nine subjects (8.6%) in the post-treatment analysis set reported at least 1 post-treatment related adverse event (AE), including 97 subjects in the post-treatment long-term follow-up in the parent study and 2 subjects in the registry study. The most commonly reported post-treatment related AEs in the post-treatment analysis set were rash (9 subjects, 0.8%), vitiligo (9 subjects, 0.8%), fatigue (8 subjects, 0.7%), and pruritus (7 subjects, 0.6%). The two post-treatment related AEs reported by the 2 subjects in the registry study were capillary leak syndrome and diabetic metabolic decompensation.

Fifteen subjects (1.3%) in the post-treatment analysis set reported at least 1 grade ≥ 3 AE; no grade 3 or 4 AE preferred term was reported in more than 1 subject.
Ten subjects (0.9%) had serious post-treatment related AEs in the post-treatment analysis set. One of these SAEs (diabetic metabolic decompensation) was reported in a subject enrolled in the registry study, while the remaining 9 were reported during post-treatment LTFU in parent studies. No SAE preferred term was reported for > 1 subject. One subject in the post-treatment analysis set had fatal adverse events of cytokine release syndrome and pleural effusion; these events occurred during the long-term follow-up in the parent study.

The percentage of subjects receiving subsequent anti-cancer therapies was 38.0% and 37.6% in the post-treatment analysis set and registry study set, respectively. The most commonly reported therapies used were pembrolizumab, nivolumab, and ipilimumab.

The most common primary tumor type reported for subsequent cancer therapy in the post-treatment analysis set and registry study was melanoma. The most common subsequent anti-cancer therapy type was immunotherapy.

Conclusions:

The primary objective of the Study 20120139 registry was to evaluate the long-term safety of talimogene laherparepvec and to monitor survival and subsequent anti-cancer therapy in subjects who received at least 1 dose of talimogene laherparepvec in an Amgen/BioVex sponsored clinical trial (parent study). The median (range) post-treatment follow-up in the parent studies was 65.6 (0, 399.7) weeks, while the median post-treatment follow-up time in the registry study was 147.7 (0.1, 592.3) weeks. Few (1.3%) subjects reported at least one grade 3 or higher post-treatment related AE. No long-term safety concerns for talimogene laherparepvec were identified.