Amsterdam, 10 November 2022
EMA/CHMP/831598/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Imlygic

International non-proprietary name: talimogene laherparepvec

Procedure no.: EMA/H/C/002771/P46/011

seq 0114

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	12 Sep 2022	12 Sep 2022	☐
☐	CAT Rapporteur Assessment Report	17 Oct 2022	14 Oct 2022	☐
☐	CAT and CHMP members comments	27 Oct 2022	27 Oct 2022	☐
☐	Updated CAT Rapporteur Assessment Report	28 Oct 2022	n/a	☐
☐	CAT conclusions	04 Nov 2022	04 Nov 2022	☐
☒	CHMP conclusion	10 Nov 2022	10 Nov 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Declarations

☒ The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments or development plans etc), irrespective from which entity was received*.

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1. Introduction

The MAH submitted a completed paediatric study for Imlygic, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

The global end of the study has not yet been reached. These interim data do not require an update of the Product Information.

2. Scientific discussion

2.1. Clinical aspects

2.1.1. Introduction

The MAH submitted the clinical study report for:

- study 20110261, titled "A Phase 1, Multi-center, Open-label, Dose

De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Paediatric

Subjects with Advanced Noncentral Nervous System Tumors That are Amenable to Direct Injection".

Talimogene laherparepvec (IMLYGIC) is an oncolytic viral therapy to treat unresectable and metastatic melanoma. In the EU, talimogene laherparepvec was approved in December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease.

2.1.2. Clinical study

Study 20110261, titled "A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Paediatric Subjects with Advanced Noncentral Nervous System Tumors That are Amenable to Direct Injection"

Study 20110261 is a paediatric study and listed as PIP study 3 in the PIP EMEA-001251-PIP01-11-M05 (EMA agency decision P/0005/2022). As talimogene laherparepvec has not been evaluated in a paediatric population, the first step to the evaluation was determination of safety. Hence, this phase 1 dose de-escalation study was proposed starting with the recommended adult dose. Only paediatric subjects with advanced non-CNS tumours amenable to direct injection (excluding visceral organ injection) were enrolled.

Enrolment started with the oldest age cohort (12 to 21 years of age). The most likely eligible tumour types in this cohort were expected to be Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissues sarcoma or rhabdomyosarcoma. After review of the safety data in the oldest cohort, recruitment was opened for the younger patients (2 to <12 years of age). Subjects younger than 2 years of age were not included in this study due to the lack of eligible tumour types amenable for direct intratumoural injection and availability of effective treatment options. Subjects were to have histologically or cytologically confirmed non-CNS solid tumours that recurred after standard/frontline therapy (or for which there is no standard/frontline therapy available).

The study was initiated in August 16 2017 and is ongoing. The analyses presented are based on a database snapshot date of 14 March 2022.

Methodology:

This was a phase 1, multicenter, open-label study of talimogene laherparepvec in paediatric subjects with advanced non-CNS tumours that were amenable to direct injection in the clinical setting.

Approximately 18 to 24 paediatric subjects were to be enrolled and treated with at least 1 dose of talimogene laherparepvec in 2 cohorts stratified by age (permissible based on the incidence of DLTs, a minimum of 18 dosed subjects total for the primary analysis).

- Cohort A1 (12 to ≤21 years of age)
- Cohort B1 (2 to <12 years of age)

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of talimogene laherparepvec, as assessed by incidence of dose-limiting toxicities (DLT), in pediatric subjects with advanced non-central nervous system (CNS) tumors that are amenable to direct injection.	• Subject incidence of DLTs
Key Secondary	
• To evaluate the anti-tumor activity of talimogene laherparepvec, as assessed by: ○ overall response rate (ORR), duration of response (DOR), time to response (TTR), time to progression (TTP) ○ progression-free survival (PFS) using immune-related response criteria RECIST 1.1 (modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors [irRC-RECIST]) ○ overall survival (OS).	• ORR, DOR, TTR, TTP, and PFS using modified irRC-RECIST • OS
Safety	
• To evaluate the safety and tolerability of talimogene laherparepvec	• Subject incidence of adverse events and clinically significant laboratory abnormalities

Subjects:

A total of 15 subjects were enrolled in Cohort A1 (n = 13) and Cohort B1 (n = 2). All subjects received talimogene laherparepvec during the study. The mean age was 14.3 years (range 7 to 21 years) and there were 10 males and 5 females. 7 subjects (46.7%) had soft tissue sarcoma, 3 subjects (20.0%) had melanoma, 3 subjects (20.0%) had bone tumor, 1 subject (6.7%) had neuroblastoma, and 1 subject (6.7%) had nasopharyngeal carcinoma. Seven subjects (46.7%) were herpes simplex virus (HSV) positive at baseline.

Results:

At the time of data cutoff, 14 subjects (93.3%) had discontinued investigational product due to death (1 subject, 6.7%), disease progression (10 subjects, 66.7%), requirement for alternative therapy (2 subjects, 13.3%), and adverse event (1 subject, 6.7%). The median (range) actual follow-up time was 6.867 (1.12, 51.06) months. At the time of the data cutoff date, 12 subjects (80%) had discontinued the study due to death and 3 subjects continued in the study.

Efficacy results

Analysis of Best Overall Response per Modified irRC-RECIST Criteria by Investigator (Safety Analysis Set)

	T-VEC Cohort A1 (N = 13)	T-VEC Cohort B1 (N = 2)	Total (N = 15)
Response assessment based on Investigator - n (%)			
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (PR)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD)	2 (15.4)	1 (50.0)	3 (20.0)
Progressive disease (PD)	4 (30.8)	1 (50.0)	5 (33.3)
Unable to evaluate (UE)	4 (30.8)	0 (0.0)	4 (26.7)
Missing	3 (23.1)	0 (0.0)	3 (20.0)
Objective response rate (CR/PR) - n (%)	0 (0.0)	0 (0.0)	0 (0.0)
95% CI[a]	(0.00, 24.71)	(0.00, 84.19)	(0.00, 21.80)

Source: Table 14-4.1

The median OS was 8.80 months (95% CI: 3.06, 16.85).

Safety results

Subjects received talimogene laherparepvec for a median (range) of 5.14 (0.1, 39.4) weeks. The mean (SD) volume for the first injection was 3.50 (0.78) of 106 PFU/mL. For all other doses, the mean (SD) volume of injection was 3.73 (0.58) mL of 108 PFU/mL talimogene laherparepvec.

Thirteen subjects were included in the DLT analysis set. No subject had a DLT during the DLT evaluation period. Overall, all subjects (15 subjects, 100.0%) experienced at least 1 treatment-emergent adverse event and 8 subjects (53.3%) reported grade ≥ 3 adverse events.

The most frequently reported adverse events (≥ 20.0% of subjects) were anemia (3 subjects, 20.0%), fatigue (4 subjects, 26.7%), increased gamma-glutamyltransferase (3 subjects, 20.0%), headache (6 subjects, 40.0%), influenza-like illness (3 subjects, 20.0%), nausea (4 subjects, 26.7%), pain in extremity (5 subjects, 33.3%), pyrexia (11 subjects, 73.3%), and vomiting (7 subjects, 46.7%). One subject (6.7%) had a treatment-emergent adverse event leading to withdrawal of talimogene laherparepvec (wound dehiscence). Four subjects (26.7%) reported treatment-emergent serious adverse events (musculoskeletal chest pain, nausea, pulmonary embolism, skin ulcer, and vascular device infection). Two subjects (13.3%) reported treatment-related treatment-emergent serious adverse events (pulmonary embolism and skin ulcer).

2.1.3. Discussion on clinical aspects

According to the CSR at data cut-off one subject was continuing talimogene laherparepvec and three subjects had not discontinued from the study. According to the cover letter by the MAH August 22 2022, two subjects were in long term follow-up. According to the MAH the projected global end of study/last subject last visit will be in Q4 2023, if the long-term follow-up goes to the full duration as per the protocol. An addendum to the CSR will be provided in Q2 2024 or within 6 months of the global end of study date, which will include the final analysis results for the 20110261 study.

Regarding efficacy, there were no complete or partial responses. The median treatment time was short (5.14 weeks) indicating that the treatment was typically discontinued after the 2nd injection, which takes place 21 days (+ 3 days) after the 1st injection.

In this phase 1, open-label, dose de-escalation study in paediatric subjects with advanced non-central nervous system tumours amenable to direct injection, no subject had a DLT. No dose de-escalation was needed. The ORR per modified irRC-RECIST was 0% (95% CI: 0.00, 21.80). The most frequent AEs were anemia (20.0%), fatigue (26.7%), increased gammaglutamyltransferase (20.0%), headache (40.0%), influenza-like illness (20.0%), nausea (26.7%), pain in extremity (33.3%), pyrexia (73.3%), and vomiting (46.7%). Of these the only AE not described in the current SmPC for Imlygic is increased gammaglutamyltransferase which was detected in three subjects in the study (grade 1 in 2 patients and grade 2 in one patient). No increases in aspartate aminotransferase or alanine aminotransferase were reported within the AEs. Thus, the safety data seems to be nearly consistent with the known safety profile of talimogene laherparepvec in adults. The subjects' underlying disease could be related to the increase in gammaglutamyltransferase, noting also the relative non-specificity of gamma-glutamyltransferase.

The MAH has not proposed any changes to the product information.

In conclusion, the MAH has submitted results from a paediatric study, which was listed as a PIP study 3 in the PIP EMEA-001251-PIP01-11-M05 (EMA P/0005/2022). As also concluded by the MAH, no changes to the PI are needed. The study results do not impact the benefit/risk balance of Imlygic in the approved indication. The benefit-risk balance of Imlygic remains positive.

3. Rapporteur's overall conclusion and recommendation

In conlusion, the MAH has submitted results from a paediatric study, which was listed as a PIP study 3 in the PIP EMEA-001251-PIP01-11-M05 (EMA P/0005/2022). No changes to the PI are needed. The study results do not impact the benefit/risk balance of Imlygic in the approved indication. The benefit-risk balance of Imlygic remains positive.

☒ Fulfilled:

No further action required, however further data are expected prior to any conclusion on product information amendments is made.

The MAH has provided a commitment that addendum to the CSR will be provided in Q2 2024 or within 6 months of the global end of study date, which will include the final analysis results for the 20110261 study.