International Regulatory Affairs

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A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection.

Replacement of the Environmental Risk Assessment (ERA) For Talimogene Laherparepvec Associated With Clinical Trial Applications With the Approved ERA Associated With the Marketing Authorisation.

Dear Sir/Madam,

This letter is to justify that the submission of environmental risk assessments (ERAs) in association with clinical trial applications (CTAs) for talimogene laherparepvec in pediatric subjects with advanced non-central nervous system tumors that are amenable to direct injection is no longer necessary following the inclusion of the product in the European Community register of medicinal products approved for human use 16 December 2015 (invented name, Imlygic®).

Talimogene laherparepvec, a genetically modified organism (GMO), is a disabled recombinant herpes simplex type 1 virus (HSV-1). Talimogene laherparepvec was generated by modifying the wild type HSV-1 genome (new isolate JS1) to functionally delete both copies of ICP34.5 and the ICP47 gene from the viral backbone and to insert an expression cassette encoding the human granulocyte macrophage colony-stimulating factor (hGM-CSF) gene in both ICP34.5 regions.

As part of the centralised Marketing Authorisation (MA) assessment, an ERA was submitted both to the European Medicines Agency and to national environmental agencies. Following assessment, it was concluded by the Committee for Medicinal Products for Human Use (CHMP) that the overall risk posed by talimogene laherparepvec for human health (to the unintended recipient) and to the environment is considered low. As sponsor, Amgen proposes that a requirement to submit an ERA associated with a CTA can now be removed, as the

environmental risk of the product has been reviewed as part of the MA assessment.

This proposal is being submitted to competent authorities and national environmental agencies with new CTA applications and alongside substantial amendments for ongoing and new clinical studies with solid tumours. Amgen contends that the environmental risks associated with talimogene laherparepvec have been thoroughly assessed and approved by the relevant EU competent authorities and national agencies. The risks and impact of talimogene laherparepvec administration and release detailed in the ERA submitted with the MA are applicable to its use in all solid tumours. The route of administration is consistently intralesional administration across all solid tumour types being studied. Further, the inclusion criteria including the immune status of the patients enrolled in the clinical trials targeting solid tumours is similar. Patients with evidence of clinically significant immunosuppression, such as primary immunodeficiency state such as Severe Combined Immunodeficiency Disease (SCID), will be excluded from the studies.

The biodistribution and shedding of intralesionally administered talimogene laherparepvec were investigated in a phase 2, single-arm clinical study that measured talimogene laherparepvec DNA in blood, urine, injection site, occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions among subjects with unresected, stage IIIB to IVM1c melanoma.

Among 60 subjects with melanoma who received talimogene laherparepvec intralesional injection, talimogene laherparepvec DNA was present in all sites during the study. The proportion of samples and subjects with talimogene laherparepvec DNA was highest during cycle 2 of treatment for the blood, urine, injection site, and occlusive dressings; highest in cycle 1 of treatment for the oral mucosa; and highest in cycles 1 and 2 for the anogenital area. Among subjects with detectable talimogene laherparepvec DNA, no samples had detectable talimogene laherparepvec DNA in the blood, urine, oral mucosa and anogenital area 30 days after the end of treatment, and from injected lesions 60 days after end of treatment. Three of 19 subjects with lesions of suspected herpetic origin had talimogene laherparepvec DNA present at any time during the study.

Viral activity was measured in samples that were positive for talimogene laherparepvec DNA from the injection site, occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions. No viral activity was detected in samples of the occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions. Infectious talimogene laherparepvec virus was detected at the site of injection in 7 (11%) subjects at multiple time points in the study; no samples were positive for viral infectivity after cycle 2 or after the end of treatment.

In particular relation to clinical trials in advanced non-central nervous system tumors:

- The Exploratory objective for the 261 study includes estimating clearance of talimogene laherparepvec DNA from blood and urine, detecting talimogene laherparepvec DNA and virus in swab samples taken from cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any), exterior of occlusive dressings, surface of injected lesions, and oral mucosa.

- Although the location of injection sites is different in this study to that of the market authorised indication, the mode of injection is consistent for all solid tumours, with direct injection into lesions. Additionally, the administered dose is the same as that given for the authorised indication. Replication in the patient is expected to be self-limiting and dependent on tumour burden.

- Injected lesions may shed live virus at times during treatment. Therefore, patients and close contacts are advised to avoid direct contact with injected lesions. Occlusive dressings are to be applied for the first week after treatment when the risk of viral shedding is highest (and longer if the lesion is weeping).

- Administration of talimogene laherparepvec in clinical studies is only to be performed by medical professionals in an approved study site facility, using appropriate precautions. Given the minimal manipulations required in drawing the dose from a vial into a syringe (with unlikely potential aerosol from the dead space of the needle) the potential for exposure during administration is low.

This approach is supported by Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, which includes the following statements:

> **Recital (56):** *When a product containing a GMO, as or in products, is placed on the market, and where such a product has been properly authorised under this Directive, a Member State may not prohibit, restrict or impede the placing on the market of GMOs, as or in products, which comply with the requirements of this Directive.*
> *A safeguard procedure should be provided in case of risk to human health or the environment*.
>
> **Part B, Art 6 (4):** *The competent authority may accept that releases of the same GMO or of a combination of GMOs on the same site or on different sites for the same purpose and within a defined period may be notified in a single notification*.

In the context of 2001/83/EC, “placing on the market” means making available to third parties whether in return for payment or free of charge, i.e. either as marketed product or via a clinical trial.

Amgen believes that the use of talimogene laherparepvec is considered to have the same environmental risk whether administered as marketed product under the MA or in the clinical trial setting where the route of administration intralesionally into solid tumours is the same as for the marketed product.

In conclusion, as talimogene laherparepvec now has a marketing authorisation for deliberate release, an assessment of the ERA documents by the environmental authorities as a prerequisite for clinical trial approval is no longer necessary.

Yours sincerely,

Lori Mulcahy
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Amgen, Inc