International Regulatory Affairs

Amgen Limited
240 Cambridge Science Park
Milton Road
Cambridge
CB4 0WD
Direct Dial: +44 (0) 1223 420305
UK Freephone: 0800 243104

FAMHP
Research and Development
Victor Portplein 40 Bus 40
B - 1060 Brussel

31 July 2017

A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases (20140299)

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 the treatment of solid tumours 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.

Biodistribution and shedding of talimogene laherparepvec are being investigated in subjects with unresected, stage IIIB to IVM1c melanoma. Interim results from 30 patients show no evidence of live virus.

In particular relation to clinical trials in triple negative breast cancer and colorectal cancer with liver metastases:

- 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.
- There is no evidence to date of the impact of combination therapy of talimogene

laherparepvec and atezolizumab compared to the therapy without atezolizumab in terms of biodistribution and shedding of talimogene laherparepvec by the treated subjects. Atezolizumab is a humanised monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors, administered by intravenous infusion. As a monoclonal antibody, it is not subject to viral shedding.

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,

Michelle Pernice, Pharm.D.
Senior Manager, Regulatory Affairs
Regional Regulatory Lead
Amgen, Inc