



INFORMATION FOR THE PUBLIC

Amgen Ltd., on behalf of Amgen Inc.

A Phase 1b/3 Multicenter, Randomized, Open-label Trial of Talimogene Laherparepvec in combination with Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

European Notification Number

B/BE/15/BVW2

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 12 March 2001 repealing directive 90/220/EEC and at Belgian level by a new Royal Decree, "regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment" repealing the Royal Decree of 18 December 1998.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorisation from the competent Minister, the company Amgen submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant a permission to Amgen to conduct experiments with talimogene laherparepvec as stipulated in application B/BE/15/BVW2.

The release will take place at one or more experimental locations in Belgium:

Hospital Name	Address
Institut Jules Bordet	Boulevard de Waterloo 121, 1000 Bruxelles
GasthuisZusters Antwerpen - Sint Augustinus	Oosterveldlaan 24, 2610 Wilrijk

It is expected to start in March 2016 and to be completed by March 2022.

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1. General Information

1.1 Description of the Genetically Modified Micro-organism (GMM)

Talimogene laherparepvec is a modified herpes simplex virus (HSV) type-1 (the 'cold sore' virus) that has a medicine called human granulocyte macrophage colony stimulating factor (GM-CSF) added to it. Human GM-CSF is a medicine used to treat patients with blood cell counts that are too low. Talimogene laherparepvec is administered by injection with a needle directly into one or more tumor(s). Administration may occur using an ultrasound for some tumours that are below the surface of the skin.

Talimogene laherparepvec is designed to work in two complementary ways. It directly destroys cells in the tumor into which it is injected, and it activates the body's own immune fighting cells to destroy the tumor cells throughout the body, not just the area where it is injected.

The original version (the "wild type") of HSV type-1 can cause a variety of symptoms, like cold sores. Due to the modifications of HSV type-1 in talimogene laherparepvec, it is not likely that talimogene laherparepvec will cause these symptoms.

1.2 Type and Purpose of the Envisaged Trial

The purpose of this study is to find out more about talimogene laherparepvec in people with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). Metastasis means that the tumor has spread to other parts of the body. Recurrence is defined as the return of a tumor after a previously successful treatment and after a period of time during which the cancer cannot be detected.

Approximately 490 subjects will be enrolled in this phase 1b/3 study, which will be conducted in Europe, Australia and North America and Canada. Approximately a total of 10 subjects will participate in the study at the following sites in Belgium:

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Institut Jules Bordet	Boulevard de Waterloo 121, 1000 Bruxelles
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Talimogene laherparepvec will only be administered to subjects by trained healthcare professionals at the sites stated. The subject will have each injection site covered with an occlusive (air-tight and water-tight) dressing before being allowed to leave the study site. They will need to keep the dressing(s) on for a week.

It is not considered necessary, ethical or practical to isolate patients receiving this treatment.

2. Research/Development Activities

2.1 Previous Development Activities

Talimogene laherparepvec has already been extensively tested.

Ten clinical studies have been or are being conducted in several advanced tumour types with a total of 430 patients treated with talimogene laherparepvec as of 05 May 2014 (according to the Investigational Brochure V12, dated October 2014). To date Austria, Italy, Poland and the United Kingdom are European countries participating in the talimogene laherparepvec clinical programme, where it was considered 'contained use'.

2.2 Knowledge and Experience Obtained in Previous Development Activities

Results from non-clinical studies have shown talimogene laherparepvec can eradicate tumours or substantially inhibit their growth at doses comparable to those used in clinical studies. It was also shown that talimogene laherparepvec affects not only the tumours into which it is injected, but also distant non-injected tumours, demonstrating a systemic beneficial effect from local administration. Non-clinical evaluation has also confirmed that GM-CSF enhances the immune response generated, enhancing both injected and uninjected tumor responses.

The talimogene laherparepvec phase 3 clinical program is currently focused on melanoma and other tumor types, including SCCHN. An optimised dosing regimen for treating SCCHN has been determined from a dose-ranging study that demonstrated the dosing as being well tolerated. This trial will allow the investigators to obtain additional information which may support and inform its use in routine clinical practice.

No evidence of herpes infection attributable to talimogene laherparepvec outside of the tumour has been documented during development. A number of individuals (patients or medical personnel) have reported reactivations of wild type HSV-1, which is not unexpected in the population as a whole, since the virus is so common. These cases were investigated and it was determined by culture of the virus and identification of selected genes not to be caused by talimogene laherparepvec. No additional reports have been made relating to viral transmission in the environment or to close contacts of treated patients.

Most adverse events reported in subjects administered talimogene laherparepvec have been non-serious and primarily include flu-like symptoms and injection site reactions.

2.3 Future Activities

Further to this clinical trial, additional clinical studies may be conducted to investigate the use of talimogene laherparepvec in other types of cancer. It is hoped that such studies will provide scientific evidence that talimogene laherparepvec can safely treat these cancers, so that it can be used in routine clinical practice as a marketed medicinal product to benefit patients.

3. Benefits

Head and neck carcinomas (HNC) are the fifth most common cancer in the world and annual incidence appears to be increasing. In 2014, it was estimated that about 55,070 new cases of oral cavity, pharyngeal, and laryngeal cancers would occur, which would account for about 3% of new cancer cases in the United States. An estimated 12,000 deaths from HNC would occur during the same time period ([Siegel et al, 2014](#)). SCCHN or a variant is the histologic type seen in more than 90% of these tumors. The four most common primary sites of SCCHN in the United States and Europe are the oral cavity, oropharynx, hypopharynx, and larynx. HNC are strongly associated with tobacco use and with excessive alcohol abuse in 80% of oral cancers. Other risk factors include HPV for oropharyngeal cancer, Epstein-Barr virus (nasopharyngeal), exposure to asbestos, Barrett's esophagus in the case of hypopharyngeal cancer, and sun exposure in the case of lip cancer.

The purpose of this study is to evaluate that a regimen of an oncolytic immunotherapy (talimogene laherparepvec) and an immune checkpoint inhibitor (pembrolizumab) is safe and tolerable, and that the combination treatment might enhance the clinical efficacy shown when pembrolizumabis administered alone to subjects with recurrent or metastatic squamous cell carcinoma of the head and neck.

4. Risks

4.1 Potential Risks to the Environment

Humans are the only natural host for wild type HSV-1 infection. It does not infect plants, rarely infects animals, and does not contribute to environmental ecosystems or processes.

Outside of the host (humans), HSV-1 is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It does not form survival structures and its survival outside the host organism is limited to short periods of time.

None of the genetic modifications made to wild type HSV-1 during construction of talimogene laherparepvec would be expected to alter its effect on environmental processes or have an effect on sensitivity to inactivating agents or survivability in the environment.

4.2 Potential Risks to Human Health

Wild type HSV-1 survives in the environment in the host species (humans) as a persistent infection or as a latent infection in the nucleus of some infected cells (principally neurons of the trigeminal ganglion), where it may remain inactive indefinitely, or be reactivated giving rise to secretion of virus and sometimes (though not always) clinical symptoms.

Its mode of transmission is through direct contact with infected secretions or mucous membranes/skin with lesions from an asymptomatic or symptomatic patient shedding the virus. Transmission of HSV-1 can also occur by respiratory droplets.

None of the precise genetic modifications made to wild type HSV-1 during construction of talimogene laherparepvec would be expected to have an effect on the mode of transmission.

Therefore, a potential risk exists from the accidental transmission of talimogene laherparepvec to another human. The most likely individuals who may be at risk are healthcare workers administering talimogene laherparepvec or individuals who come into close contact with the subject such as caregivers, partners or family members.

Accidental transmission of talimogene laherparepvec may occur via direct contact with a patient's injection site, body fluids or with the inside of the dressing(s) covering used to cover a patient's injection site(s). Spreading of talimogene laherparepvec may be more likely if a close contact has a break in the skin or mucous membranes that come into contact with the patient's injection site or body fluids.

In humans treated with talimogene laherparepvec in clinical trials, the virus has been found on the surface of the injected tumors within the first few hours and up to 7 days after the injection, although it is not known exactly how long it may be present. Although there has been no detection of live virus on the outside of the occlusive dressing that is placed on top of the injected lesions in subjects participating in clinical trials

If a close contact is exposed to talimogene laherparepvec, it is possible that they could develop symptoms of a herpes type infection. The likelihood of this occurring is

expected to be very low due to the design of talimogene laherparepvec that makes it different from the naturally occurring wild type HSV-1 virus.

5. Containment, Control and Monitoring Measures

5.1 Control of GMM and Gene Spreading

Talimogene laherparepvec is an investigational medicinal product for use only in approved clinical trials by trained medical professionals at an authorised study site.

It will be supplied by Amgen directly to the study site and appropriate records/ traceability of shipments will be maintained in line with the requirements of Good Clinical Practice (GCP).

After talimogene laherparepvec has been administered the injection site is covered with a dry occlusive (air-tight and water-tight) dressing before the patient leaves the medical facility. The occlusive dressing covers the injection site for up to 1 week. Given the nature of the product administration directly into the patient's tumours, the use of an occlusive dressing provides a physical barrier to virus leakage. The risk of exposure of the medical professionals involved in the patients' care and the patients' family on returning home from the study site facility to talimogene laherparepvec is also minimised by the data already obtained on talimogene laherparepvec which demonstrates the absence or low levels of shedding of virus.

5.2 Genetic Stability of the GMM

The genetic stability of talimogene laherparepvec in isolation has been demonstrated and continues to be monitored.

A genetic variant of talimogene laherparepvec could theoretically occur spontaneously if a cell containing talimogene laherparepvec also was infected with wild type HSV-1. It is unlikely that a wild type virus would be in the same tissue as talimogene laherparepvec since the latter is directly injected into tumour cells and cannot spread effectively into normal tissue, while the pre-existing HSV-1 would be in the mucosal tissues or neuronal ganglia of the patient. The possibility of the creation of stable genetic variants with unintended characteristics is also minimised by the design of the talimogene laherparepvec genetic construct.

5.3 Destruction of GMM Containing Material

Following administration of talimogene laherparepvec at a study site, used vials, syringes, needles and any disposable instruments or other materials used during the

procedure should be disposed of following appropriate local/regional and institutional requirements for biohazardous waste.

Accidental spills should be treated with a virucidal agent and absorbent materials. All materials contaminated with talimogene laherparepvec must be disposed of in compliance with local institutional guidelines.

Each subject is provided with instructions to follow to ensure that disposal of any soiled dressings occurs via the study site at their next scheduled visit. The subject is provided with additional dressings, disposable gloves and resealable bags, and specific instructions to be followed to minimise the risk of unintended exposure to the environment.

At the end of the study all unused product must be returned to Amgen for destruction or will be destroyed at the study site if authorized by Amgen.

5.4 Training Requirements

All healthcare professionals participating in the study will be qualified by education, training and experience to assume responsibility for the proper conduct of the trial.

All study sites will be thoroughly evaluated prior to the initiation of the trial to ensure that the facilities are sufficient for storing and administering talimogene laherparepvec, as well as having the appropriate facilities for the collection and storage of human specimens. Additionally, all clinical site personnel involved in the handling or administration of talimogene laherparepvec will be trained accordingly.

5.5 Emergency Situations

Instructions are provided to the study sites to follow in the event of an accidental occupational exposure or exposure of talimogene laherparepvec to close contacts of the subject (eg caregivers, family members, or healthcare professionals). Any potential or known unintended exposure should be reported by the study site to the sponsor of the clinical trial.

In the unlikely event of the transmission of talimogene laherparepvec to an unintended human recipient, the affected patient can be treated with approved antiviral treatments such as acyclovir, if clinically indicated to alleviate any symptoms of primary infection and potential recurrence (if deemed necessary). Further spread from the individual can be mitigated by educational materials to increase awareness of the infection and preventative measures which can be taken to prevent transmission to close contacts.

5.6 Other Containment, Control and Monitoring Measures

Amgen will conduct a surveillance program to aid the assessment of any potential risks to third parties following treatment of subjects with talimogene laherparepvec. Surveillance of the potential for talimogene laherparepvec to be transmitted to third parties will be assessed through a subject interview which will ask subjects regarding any possible signs or symptoms amongst their contacts which may be attributable to their participation in a talimogene laherparepvec clinical trial. Subjects will be asked to have their possible affected close contacts contact the study staff or Amgen to provide more information. Additionally, health care providers, other staff in contact with talimogene laherparepvec will also be asked to report any contact with or symptoms that maybe related to talimogene laherparepvec exposure. Information will be gathered by the study staff and forwarded to Amgen.

5.7 Responsibilities of the Notifier

The consent that could be given to the study Sponsor by the competent Minister stipulates that Amgen takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals or environment.

The notifier's civilian liability shall not apply when the damage is due to a third party being negligent (e.g. investigator not complying with protocol).

5.8 Inspection by the Public Authorities

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. In cases where mismanagement or fraud is identified specific sanctions will be imposed.

5.9 Activity Report

At the end of the trial an activity report will be prepared by Amgen to be delivered to the competent authority. This activity report will include at least the following data:

- the site and period of release,
- the precise nature of the actually released GMMs,
- the aim(s) of the trial,
- the measures that were taken to prevent unwanted release of transgenic material, if applicable, the measures that were taken to protect the relatives of the treated patients, the measures that were taken to protect the workers who had to manipulate the GMM-containing material,
- the method used for the destruction of the unused or contaminated material,
- the results obtained during the trial,
- the measures that were taken to prevent unwanted release of transgenic material,

- if applicable, the measures that were taken to protect the subject (patient/animal) during administration of the GMM-containing study drug,
- if applicable, the measures that were taken to protect the relatives of the treated patients, the measures that were taken to protect the workers who had to manipulate the GMM containing material,
- the method used for the destruction of the unused or contaminated material,
- the results obtained during the trial,
- an overview of the monitoring of the patient/animal for GMM shedding,
- an overview of the monitoring of GMM or recombinant DNA in the environment.

6. References

Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. CA Cancer J Clin. 2014;64:9-29.

7. Contact

If you have any comment on the public dossier or our activities or wish to obtain additional information on the deliberate release, please contact us at the following address.

You can also have access to a summary of the notification (SNIF) on the web site of the Joint Research Centre of the European Commission (<http://gmoinfo.jrc.it/>). Comments can be addressed to the Commission via this web site.

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