22 October 2015
EMA/734400/2015/ corr. 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imlygic

International non-proprietary name: talimogene laherparepvec

Procedure No. EMEA/H/C/002771/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BHK	Baby hamster kidney
BRAF	v-raf murine sarcoma viral oncogene homolog B
CHMP	Committee for Medicinal Products for Human Use
CI(s)	Confidence interval(s)
COP	Cyclic olefin polymer
CR	Complete response
CRO	Contract research organization
CRSI	Core Reference Safety Information
CTCAE	Common Terminology Criteria for Adverse Events
CZ	Crystal Zenith
DFS	Disease-free survival
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DP	Drug product
DRR	Durable response rate
DS	Drug substance
EAC	Endpoint Assessment Committee
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EUS	Endoscopic ultrasound
FACT-BRM	Functional Assessment of Cancer Therapy – Biologic Response Modifier
FBS	Foetal bovine serum
FNA	Fine needle aspirate
GCP	Good Clinical Practice

GM-CSF	Granulocyte macrophage colony stimulating factor
GMO	Genetically modified organism
hGM-CSF	Human granulocyte macrophage colony stimulating factor
HSV	Herpex simplex virus
HSV-1	Herpes simplex virus type-1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IEX	Ion exchange chromatography
IFNγ	interferon gamma
Ig	Immunoglobulin
IPC	In-process control
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive Voice Response System
IPCW	inverse probability censoring weighting
LDH	Lactate dehydrogenase
LoQ	List of Questions
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OR	Overall response
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive Disease
PDn	Clinically Not Relevant PD
PDr	Clinically Relevant PD
PET	Positron Emission Tomography
PFU	Plaque forming units
PhEur	European Pharmacopoeia
PR	Partial response

qPCR	Quantitative polymerase chain reaction
qRT-PCR	Quantitative reverse phase polymerase chain reaction
RECIST	Response Evaluation Criteria In Solid Tumours
RI	Response Interval
RO	Response Onset
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SCCHN	Squamous cell carcinoma of the head and neck
SCID	severe combined immunodeficiency
SD	standard deviation
SEC	Size exclusion chromatography
SMQ	Standardized MedDRA query
SmPC	Summary of Product Characteristics
TNM	Tumour, Node, Metastasis
TOI	Trial Outcome Index
TSE	Transmissible spongiformic encephalopathy
T-VEC	Talimogene laherparepvec
UF/DF	Ultrafiltration/diafiltration
UK	United Kingdom
ULN	Upper limit of the normal range
US	United States
USP	United States Pharmacopoeia
WCB	Working cell bank
WHO	World Health Organization
WT	Wild-type
WVSS	working virus seed stock

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 28 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Imlygic, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment of adults with melanoma that is regionally or distantly metastatic.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant indicated that talimogene laherparepvec was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0047/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0047/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance talimogene laherparepvec contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 October 2008 and 30 May 2013. The

Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States of America.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Olli Tenhunen
Co-Rapporteur:	Marit Hystad

- The application was received by the EMA on 28 August 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on 12 December 2014. The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on 12 December 2014.
- During the meeting on 15-16 January 2015, the CAT agreed on the consolidated List of Questions to be sent to the applicant.
- During the meeting on 19-22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 29 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CAT and CHMP members on 1 June 2015.
- During the CAT meeting on 18-19 June 2015, the CAT agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During the meeting on 22-25 June 2015, the CHMP agreed on the consolidated list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant. The final consolidated list of outstanding issues was sent to the applicant on 25 June 2015.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- The Rapporteur's Joint Assessment Report on the responses provided by the applicant was circulated to all CAT and CHMP members on 01 September 2015
- During a meeting of a SAG on 10 September, experts were convened to address questions raised by the CAT and CHMP.
- During the CAT meeting on 17 September 2015, outstanding issues were addressed by the applicant during an oral explanation before the CAT.

- During the meeting on 17-18 September 2015, the CAT agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant
- During the meeting on 21-24 September 2015, the CHMP agreed on the second consolidated list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant. The final consolidated list of outstanding issues was sent to the applicant on 28 September 2015.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 September 2015.
- The Rapporteur's Joint Assessment Report on the responses provided by the applicant was circulated to all CAT and CHMP members on 07 October 2015.
- During the meeting on 17-18 October 2015, the CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Imlygic on 18 October 2015.
- During the meeting on 19-22 October 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Imlygic on 22 October 2015.

2. Scientific discussion

2.1. Introduction

Melanoma is the sixth and seventh most common malignancy in men and women, respectively: in Europe in 2012, the incidence was 39.6 cases /100.000 men and 42.5 cases /100.000 women, the mortality was approximately 8.8 cases/100.000 in males and 6.9 cases/100.000 in females, with median age at diagnosis of 59 years[1].

There are several types of melanoma such as superficial spreading melanoma, lentigo malignant melanoma, acral lentiginous melanoma and nodular melanoma amongst others. The clinical appearance of melanoma is characterised by the ABCD rule where A=Asymmetry, B=Border, C=Colour, D=Diameter and the evolution in size, colour and depth of the lesion. Typical features of melanoma lesions are asymmetry of the lesion, irregular borders, variability in colour, diameter of 5 mm and more, growth of nodules. The pathological staging of melanoma tumours is based on the AJCC staging and classification system, which includes sentinel node staging[2]. The AJCC staging provides information on the thickness of the lesions (Breslow), information on the mitotic rate and ulceration, number of lymph nodes involved and regression or progression of the lesion to loco-regional sites (subcutaneous invasion, lymph nodes) or distant lesions with or without the presence of elevated LDH (Table 1) [3]. The clinical staging of melanoma patients is primarily based on the physical examination, imaging tests and biopsies looking at the location and size the primary tumour, degree of lymph node involvement, and presence and location of metastases[4]. The clinical staging can be divided into several groups: Stage 0, Stage I (A,B), Stage II (A,B,C), Stage III (A,B, C) and Stage IV depending on the pathological findings of the tumour characteristics (Table 2). Where Stage I and II is limited primarily at the site of the primary tumour, Stage III involves dissemination to regional lymph nodes and Stage IV includes distant disease where M1a defines metastases distant from the skin, subcutaneous or nodal, M1b metastases to the lung and M1c metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH (Table 1).

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 07 Jan 2014.
[2] Balch CM, Gershenwald JE, Soong SJ et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009; 27: 6199–6206.
[3] NCCN clinical practice guidelines in oncology accessed 11 September 2015 on http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf
[4] American Joint Committee on Cancer quick reference tools accessed on the 11 September 2015 https://cancerstaging.org/references-tools/quickreferences/documents/melanomasmall.pdf

Table 1: AJCC staging system of melanoma

T classification	Thickness (mm)	Ulceration status/mitosis
T1	≤1.0	a: without ulceration and mitosis <1/mm^2 b: with ulceration or mitoses ≥1/mm^2
T2	1.01–2.0	a: without ulceration b: with ulceration
T3	2.01–4.0	a: without ulceration b: with ulceration
T4	>4.0	a: without ulceration b: with ulceration
N classification	**No. of metastatic nodes**	**Nodal metastatic mass**
N0	0	N/A
N1	1 node	a: micrometastasis[a] b: macrometastasis[b]
N2	2–3 nodes	a: micrometastasis[a] b: macrometastasis[b] c: in transit metastases/satellites 'without' metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit metastases/satellites 'with' metastatic nodes	
M classification	**Site**	**Serum LDH**
M0	No distant metastasis	N/A
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

[a]Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if carried out).
[b]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
AJCC, American Joint Committee on Cancer; N/A, not applicable; LDH, lactate dehydrogenase.

Table 2: Staging of melanoma of the skin (AJCC 7th edition)

ANATOMIC STAGE/PROGNOSTIC GROUPS							
	Clinical Staging[3]				Pathologic Staging[4]		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

About 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis and the tumour-specific 10-year-survival for such tumours is 75–85%[5]. The 10-year-survival for patients with micrometastasis in the regional lymph nodes is 30–70%, 30–50% for patients with satellite (defined as up to 2 cm from the primary tumour) and in-transit (located in the skin between 2 cm from the site of the primary tumour and the first draining lymph node) metastases and 20–40% for those with clinically apparent regional lymph node metastases. Distant metastases have a median survival in untreated patients of only 6–9 months, although there is considerable variation[6].

Whenever a suspicious skin lesion is removed, a histological examination is performed to investigate the pathologic characteristics and other features such as growth phase and level of invasion. Surgical removal is indicated in case of localised and locoregional disease with, in certain cases, radiotherapy and IFN gamma[7]. For systemic metastatic disease (stage IV) surgery, radiotherapy and systemic therapy, are indicated. The currently approved systemic treatment options include:

- ipilimumab, an anti-CTLA4 approved to treat previously untreated adults with unresectable or metastatic melanoma; it has shown a statistically significant improvement in overall survival (OS) compared with the gp100 vaccine (10.1 versus 6.4 months; HR: 0.66; p= 0.003).
- nivolumab, an anti-PD1 monoclonal antibody approved for the treatment of advanced (unresectable or metastatic) melanoma in adults; the median OS reported was >14 versus 10.84 (HR=0.46;(95% CI: 0.31, 0.69; p=0.000085) for dacarbazine.
- pembrolizumab, an anti-PD1 humanised monoclonal antibody approved for the treatment of advanced (unresectable or metastatic) melanoma in adults; it has shown a median PFS of 5.5 months (HR= 0.58; 95% CI: 0.46, 0.72; p<0.00001) and 4.1 (HR=0.58; 95% CI: 0.47, 0.72; p<0.00001) versus 2.8 compared to ipilimumab.
- chemotherapy with dacarbazine (DTIC), used in EU countries for many years as standard first line treatment of patients with metastatic melanoma. It has shown response rates ranging from 11% to 25% with 3 to 6 months of duration and a median survival time from 4.5 to 6 months[8, 9, 10, 11].

For melanoma tumours that have been screened and tested positive for the BRAF V600 mutation, systemic treatment options include:

- vemurafenib, a BRAF inhibitor, approved for adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, which has shown a median progression-free survival (PFS) of 6.9 vs 1.6 months, respectively (HR 0.38, 95%CI: 0.32-0.46, p<0.0001) and median OS 13.6 vs 9.7 months (HR: 0.70, 95%CI: 0.57-0.87, p<0.0001) compared with DTIC.
- dabrafenib, a BRAF kinase inhibitor approved for treatment of unresectable or metastatic melanoma with a BRAF V600 mutation; it has shown a median PFS of 6.9 vs 2.7 months compared

[5] Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2012. Eur J Cancer. 2012; 48:2375-2390.
[6] Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199-6206.
[7] Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G; ESMO Guidelines Working Group. Ann Oncol. 2012 Oct;23 Suppl 7:vii86-91.
[8] Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res. 2000 Mar;19(1):21-34.
[9] Luce JK, Thurman WG, Isaacs BL, Talley RW. Clinical trials with the antitumour agent 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide(NSC-45388). Cancer Chemother Rep. 1970 Apr;54(2):119-24.
[10] Hill GJ 2nd, Moss SE, Golomb FM, Grage TB, Fletcher WS, Minton JP, Krementz ET. DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. Cancer. 1981 Jun 1;47(11):2556-62.
[11] Falkson G, Van der Merwe AM, Falkson HC. Clinical experience with 5-(3,3-bis(2-chloroethyl)-1-triazeno)imidazole-4-carboxamide (NSC-82196) in the treatment of metastatic malignant melanoma. Cancer Chemother Rep. 1972 Oct;56(5):671-7.

to DTIC (HR: 0.37; 95% CI: 0.24, 0.58; p-value<0.0001) and a 12 month OS of 70 % versus 63 % of the DTIC treatment.

- trametinib, a MEK inhibitor, approved as monotherapy and in combination with dabrafenib treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation; a median PFS 4.8 vs 1.5 months, respectively (HR 0.45; 95%CI:0.33, 0.63; p-value <0.0001) and median OS of 15.6 vs 11.3 months (HR 0.78; 95%CI 0.57, 1.06) were reported for trametinib and dacarbazine respectively.

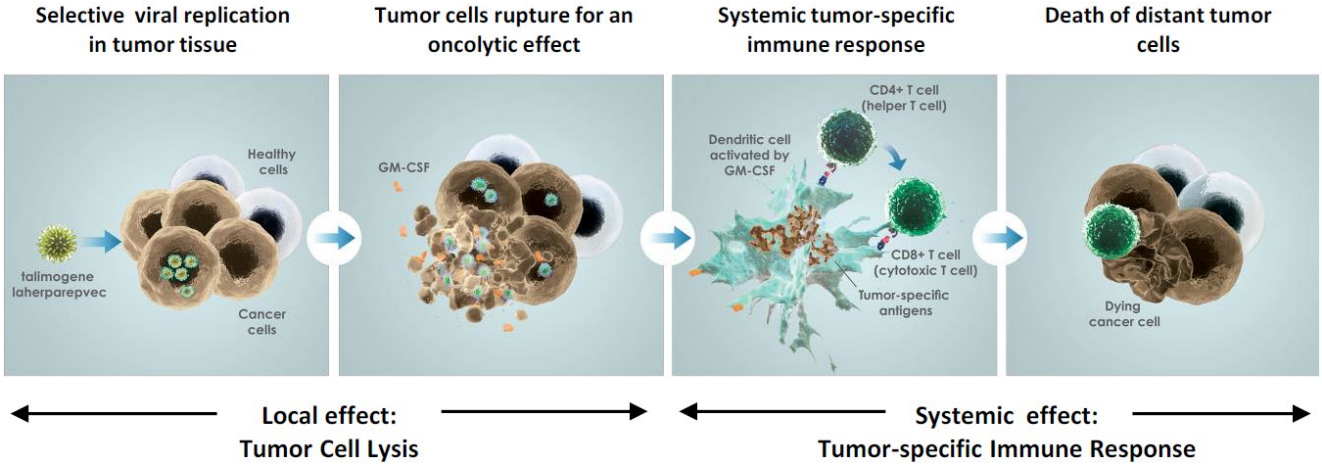
Talimogene laherparepvec is an oncolytic immunotherapy that is derived from HSV-1. Talimogene laherparepvec has been modified to replicate within tumours and to produce the immune stimulatory protein human GM-CSF. Talimogene laherparepvec causes the death of tumour cells and the release of tumour-derived antigens. It is thought that together with GM-CSF, it will promote a systemic anti-tumour immune response and an effector T-cell response. Mice that had complete regression of their primary tumours following treatment were resistant to subsequent tumour rechallenge (section 5.1 of the SmPC).

The modifications to talimogene laherparepvec from HSV-1 include deletion of ICP34.5 and ICP47. Whereas anti-viral immune responses defend normal cells following infection by talimogene laherparepvec, tumours have been shown to be susceptible to injury and cell death from ICP34.5-deficient HSV-1 viruses, including talimogene laherparepvec. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, thereby enhancing viral replication in tumour cells (section 5.1 of the SmPC).

In addition, the coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF), has been inserted in place of ICP34.5. GM-CSF is a cytokine involved in the stimulation of immune responses through its effect on antigen-presenting cells. GM-CSF can activate dendritic cells to increase antigen presentation and can potentiate both cell-mediated and humoral immune responses[12, 13, 14]. The activation of the adaptive immune system following tumour cell lysis is thought to contribute to local and systemic immune-mediated tumour destruction of distant tumours and possibly lead to the development of immunological memory and long term control of tumour growth through immune surveillance (Figure 1). Moreover, at the time when the clinical trials for talimogene laherparepvec were being designed, results from a single-arm phase 2 study suggested that overall and disease-free survival (DFS) were significantly prolonged (compared with matched historical controls) in subjects who received post-surgical treatment with GM-CSF, and that this treatment was well-tolerated[15, 16].

[12] Inaba K, Inaba M, Romani N, Aya H, Deguchi M, Ikehara S, Muramatsu S, Steinman RM. Generation of large numbers of dendritic cells from mouse bone marrow cultures supplemented with granulocyte/macrophage colony-stimulating factor. J Exp Med. 1992 Dec 1;176(6):1693-702.
[13] Fischer HG, Frosch S, Reske K, Reske-Kunz AB. Granulocyte-macrophage colony-stimulating factor activates macrophages derived from bone marrow cultures to synthesis of MHC class II molecules and to augmented antigen presentation function. J Immunol. 1988 Dec 1;141(11):3882-8.
[14] Weisbart RH, Golde DW, Clark SC, Wong GG, Gasson JC. Human granulocyte-macrophage colony-stimulating factor is a neutrophil activator. Nature. 1985 Mar 28-Apr 3;314(6009):361-3.
[15] SpitlerLE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. J Clin Oncol. 2000; 18(8):1614-1621.
[16] Lawson DH, Lee SJ, Tarhini AA, Margolin KA, Ernstoff MS, Kirkwood JM. E4697:Phase III cooperative group study of yeast-derived granulocyte macrophage colonystimulating factor (GM-CSF) versus placebo as adjuvant treatment of patients with completely resected stage III-IV melanoma [abstract]. J Clin Oncol 2010;28(supp):Abstract 8504

Figure 1: Proposed Mechanism of Action for Talimogene Laherparepvec



The applicant applied for the following indication: "Talimogene laherparepvec is indicated for the treatment of adults with melanoma that is regionally or distantly metastatic (see section 5.1)".

The final proposed indication is as follows:

Imlygic is indicated 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 (see section 4.4 and 5.1).

Treatment with talimogene laherparepvec should be initiated and supervised by a qualified physician experienced in the treatment of cancer.

Posology (SmPC section 4.2)

Imlygic is provided in single use vials of 1 mL each in two different concentrations:

- 10^6 (1 million) PFU/mL - For initial dose only.
- 10^8 (100 million) PFU/mL - For all subsequent doses.

The total injection volume for each treatment visit should be up to a maximum of 4 mL. The initial recommended dose is up to a maximum of 4 mL of Imlygic at a concentration of 10^6 (1 million) PFU/mL. Subsequent doses should be administered up to 4 mL of Imlygic at a concentration of 10^8 (100 million) PFU/mL.

The recommended dosing schedule for Imlygic is shown in table 1 in the SmPC section 4.2.

2.2. Quality aspects

2.2.1. Introduction

Talimogene laherparepvec is an oncolytic immunotherapy derived from the wild-type HSV-1 genome. It is an attenuated non-integrating HSV-1 that has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein GM-CSF.

The therapeutic strategy of talimogene laherparepvec intralesional administration is to produce a direct oncolytic effect by replication of the modified virus in cancer cells, resulting in their lysis and local release of potential tumour antigens, and to promote a systemic anti-tumour immune response enhanced by the local expression of human granulocyte macrophage colony stimulating factor (hGM-CSF) to promote antigen presentation.

Talimogene laherparepvec drug product is presented as a sterile, preservative-free solution for intralesional injection, formulated at a nominal concentration of either 10^6 PFU/mL or 10^8 PFU/mL. The drug product is supplied at a deliverable volume of 1.0 mL in single use vials to be stored, transported and supplied frozen at -80°C ± 10°C.

The 10^6 PFU/mL presentation is intended as an initial dose to be administered once to the patient, enabling HSV seroconversion prior to subsequent dosing. The 10^8 PFU/mL dose is administered subsequently for the remaining duration of treatment. The product is administered by intralesional injection into cutaneous, subcutaneous and nodal lesions. A dose up to a maximum of 4 mL is recommended for either presentation.

2.2.2. Active Substance

General information

The general information on nomenclature, structure and general properties is considered sufficient.

Talimogene laherparepvec was generated by modifying the wild type HSV-1 genome (new isolate JS1) in two regions. The nature of the modifications and the resulting phenotypic changes that bring about the therapeutic effects of talimogene laherparepvec are as follows:

• Functional deletion of the ICP34.5 gene enabling suppression of virus replication in normal tissue.

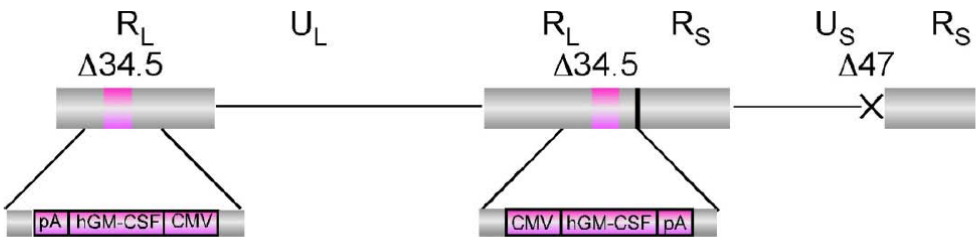
• Deletion of the ICP47 gene enabling up-regulation of the US11 gene, resulting in increased replication of ICP34.5 deleted HSV, without reducing tumour selectivity.

• Deletion of ICP47 gene ensuring display of cytoplasmic antigens on MHC Class I molecules enabling immunosurveillance by CD8+ T-cells.

• Insertion of the human granulocyte macrophage colony-stimulating factor (hGM-CSF) expression cassette into the ICP34.5 loci, causing production and release of biologically active hGM-CSF stimulating a systemic cytotoxic immune response against tumour cells at distal locations.

Each hGM-CSF expression cassette consists of the major immediate early promoter from cytomegalovirus (CMV), the cDNA encoding hGM-CSF and a bovine growth hormone polyadenylation signal (pA). A schematic representation of the talimogene laherparepvec genome is presented below:

Figure 2: Schematic representation of talimogene laherparepvec genome



The talimogene laherparepvec genome is shown with the positions of the ICP34.5 and ICP47 deletions marked as Δ34.5 and Δ47, respectively. The genome is composed of a unique long region (U_L) flanked by long repeats (R_L) and a unique short region (U_S) flanked by short repeats (R_S). The site of the hGM-CSF cassette insertion is shown in pink and expanded to show the composition of the hGM-CSF expression cassette; the CMV promoter, hGM-CSF cDNA and a pA signal.

Manufacture, characterisation and process controls

Manufacturer

The sites participating in the manufacture, testing, and storage of active substance and their responsibilities were listed in the dossier and GMP certificates were provided.

Description of manufacturing process and process controls

The talimogene laherparepvec active substance manufacturing process has been sufficiently described including information on manufacturing steps, operating parameters and in process controls. Adequate information on batch formula and batch size was submitted as well as flow charts (Figure 3).

In summary, the active substance manufacturing process includes cell expansion, virus infection and production (in roller bottles), harvest, recovery, and purification stages. The purification process consists of endonuclease digestion, clarification by filtration, ultrafiltration/diafiltration (UF/DF), two chromatography steps (IEX, SEC) and a final sterile filtration to produce the active substance. No additional filtration occurs beyond this step in drug product manufacture. The sterile filtration step therefore provides the terminal sterile filtration for the drug product.

The scale of the active substance manufacturing process is defined by the expected volume of a single bulk harvest produced by pooling the supernatants from the production roller bottles at the end of virus production, which is nominally 40 L. A single bulk harvest is purified to produce a single lot of active substance.

Control of materials

The Applicant provides adequate information on the raw materials used in the manufacturing of talimogene laherparepvec.

Standard cloning techniques were applied to construct the plasmids used to: 1) functionally delete the two copies of the ICP34.5 gene and to insert the hGM-CSF gene into the ICP34.5 loci, and 2) to delete the ICP47 gene. Correct structure of the plasmids was confirmed by restriction digest analysis or by DNA sequencing. The cloning steps are described in the dossier to a sufficient level of detail.

The JS1/34.5-/47-/hGM-CSF talimogene laherparepvec recombinant virus was initially constructed in BHK cells through a series of transfections and homologous recombinations. The cell line was subsequently changed to Vero cells. The steps involved in the generation of the final talimogene laherparepvec virus are described in sufficient detail. Also the characterisation of the virus is adequately addressed.

For commercial production of talimogene laherparepvec, the Applicant utilises three working cell banks (WCB) originating from two different master cell banks (MCB Lot 2003-0049 (initial MCB produced at BioReliance); MCB Lot 5000-00001 which both derive from the same parental WHO Vero cell bank. Both the new and the old MCBs and WCVs have been adequately characterised and qualified in accordance with the recommendation given in ICH Q5D and ICH Q5A(R1) guidelines, as well as relevant Ph. Eur. monographs and general texts. Comparative characterisation results demonstrate that the properties of the new and old cell banks are fundamentally similar. During commercial production the oldest manufactured lot will be used until inventory is exhausted. Therefore, the approach with the multiple cell banks can be accepted, although not fully in line with the general expectations for a two-tiered cell banking system.

Control of critical steps and intermediates

The manufacturing process is controlled through critical and key operating parameters (input parameters) and critical and key in-process controls (IPC, output performance parameters). Although this classification is not in line with ICH terminology, it was considered acceptable for the control strategy of this particular product. Based on process understanding and product quality considerations, testing for process impurities, safety related and microbial control and for process consistency has been established.

Process validation

The talimogene laherparepvec commercial active substance manufacturing process (Process C) was validated at the BioVex Inc., Woburn facility (AWM) by demonstrating that the process when executed within defined operating parameter ranges, is robust, performs consistently and meets pre-established performance parameter acceptance criteria.

Manufacturing process development

During the development of talimogene laherparepvec, three main manufacturing processes have been used. These manufacturing processes are designated Process A, B and C. Only three Process A batches were produced. These batches were used for non-clinical toxicology studies, as well as for an early phase I study. Process B material was applied in additional non-clinical toxicology studies and phase II clinical studies. Commercial talimogene laherparepvec will be produced using Process C which is the same manufacturing process as used for manufacture of Phase III material.

Comparability between batches manufactured using the different manufacturing processes has been adequately demonstrated. This control approach can be supported.

Characterisation

For characterisation of talimogene laherparepvec, the Applicant has considered viral structure (size, density, purity by SEC), genomic sequence, protein and glycan content, as well as biological characteristics. The studies are considered relevant and adequately conducted.

Specification

The test methods and acceptance criteria used to assure the quality of talimogene laherparepvec active substance were listed in the application dossier.

An assessment of the appropriate placement for testing has been conducted by the Applicant. Based on this assessment, certain tests, such as the tests for process-related impurities and safety tests, have been moved upstream to be included as critical in-process controls with associated rejection limits. Although a conventional strategy is not applied, overall the control strategy is considered acceptable.

Analytical methods

Summaries for each of the analytical procedures used to test each lot of active substance against the commercial specification are provided. Satisfactory method validation summaries are given.

Batch analysis

Batch analyses data from 36 GMP bulk harvest and active substance lots manufactured at the commercial manufacturing facility and in support of the clinical program, that were used to establish specification acceptance criteria or used as reference standard, are presented and reveal lot to lot consistency.

Reference materials

The description of the qualification of present and future reference standards is adequate and includes the relevant tests.

Stability

Due to the practically continuous manufacturing process, storage of the active substance has been validated as an in-process hold time (≤13 days at 5±3°C). Consequently, no stability data for the active substance is included in dossier.

Comparability exercise for Active Substance

As described above in the section on *Manufacturing process development* three primary manufacturing processes have been used for production of talimogene laherparepvec during product development. For the change from Process A to Process B, results of comparability assessment were submitted at the time of the original clinical trial application but were not included in the original MA submission. These comparability data were, however, submitted upon request. The analytical comparability between Process B and Process C, as well as between Process C pre- and post-facility and equipment modifications are adequately addressed and comparability between batches manufactured using the different manufacturing processes has been demonstrated.

New Active Substance Status – Quality Aspects

Talimogene laherparepvec (Imlygic) is an oncolytic immunotherapy derived from the wild-type herpes simplex virus type-1 (HSV-1) genome (newly isolated strain JS1; ECAAC Accession Number 01010209). It is an attenuated non-integrating HSV-1 that has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein GM-CSF.

Talimogene laherparepvec can be considered as a new active substance in the European Union as it has not previously been authorised as a medical product in this region or any of its Member States.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of drug product

Talimogene laherparepvec is supplied as a sterile, single use, preservative-free frozen liquid in a vial for intralesional injection. Each vial contains 1.0 mL deliverable volume of talimogene laherparepvec at a nominal drug product potency of 10^6 PFU/mL or 10^8 PFU/mL after product thaw.

Talimogene laherparepvec is formulated in a sodium phosphate buffer with sodium chloride as a tonicity modifier, and sorbitol and myo-inositol added as stabilizers. All excipients in the formulation are specified in the United States Pharmacopeia (USP), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP) or the European Pharmacopoeia (PhEur) as shown in 3.2.P.4 (Control of Excipients).

Pharmaceutical development

The product development has been adequately described and the rationale for the commercial formulation justified.

Manufacturing process development

The comparability between drug product batches manufactured using the different processes is discussed in detail in the dossier. Comparability between batches manufactured using the different manufacturing processes has been adequately demonstrated.

Manufacture of the product and process controls

Manufacturer

The sites participating in the manufacture, testing, and storage of drug product and their responsibilities were listed in the dossier and GMP certificates provided.

Description of manufacturing process and process controls

The drug product manufacturing process has been adequately described. In summary, in the drug product manufacturing process for 10^6 PFU/mL and 10^8 PFU/mL vials, the active substance is forward

processed by diluting with diluent buffer in an aseptic dilution step to a target concentration in order to achieve a nominal drug product potency of 10^6 PFU/mL or 10^8 PFU/mL after product thaw. The resulting drug product formulated bulk is aseptically filled into vials, and the vials are sealed with a stopper and cap. The drug product vials undergo visual inspection and primary labelling before being frozen using a controlled rate freezing process. The finished medicinal product is stored frozen at -80°C ± 10°C. Data supporting the applicability of the ranges/limits established for operating parameters have been provided.

Process validation

The manufacturing process for both drug product presentations has been validated at the commercial manufacturing site according to an approved protocol with predefined acceptance criteria. All lots also met the release specification requirements. Furthermore, the fill weight checks performed confirmed consistency in the filling volume of the validation lots.

Control of excipients

All excipient comply with Ph. Eur requirements and are widely used in pharmaceutical formulations.

Product specification

The test methods and acceptance criteria used for control and release of talimogene laherparepvec drug product are listed in the application dossier.

The proposed release testing of talimogene laherparepvec drug product is considered adequate.

In order to test for potency, three separate measurements are used. These are together evaluating the key biological functions of the virus; infection of the target cells, hGM-CSF production and hGM-CSF biological activity.

The quality of the drug product is controlled by assessing the infectious particles to viral protein ratio. As a correlation between total viral protein and total viral particles has been established, the total viral protein is considered a suitable surrogate for total viral particles. Therefore the infectious particle to total particle ratio is also covered by assessing the infectious particles to viral protein ratio.

As a release control, the Applicant is testing for visible particles in accordance with Ph. Eur 2.9.20.

Analytical methods

Analytical methods used for drug product batch release are sufficiently described and their validity has been confirmed.

Batch analysis

Batch analysis data for drug product lots used during clinical development and lots manufactured at the commercial manufacturing site are provided. The 59 drug product lots filled (from 36 active substance lots) include 43 at 10^8 PFU/mL nominal dose, and 16 at 10^6 PFU/mL nominal dose lots. Batch data reveal lot to lot consistency.

Reference materials

The characterisation and qualification of the current reference standard BP1104HA, as well as the

testing and qualification program established for future reference standards, is adequate.

Container closure system

The container closure system consists of a 2 mL 13 mm cyclic olefin polymer (COP) plastic resin vial, a 13 mm elastomeric stopper with a fluoropolymer laminated plug and a cross-linked silicon top, and an aluminium seal with a flip-off dust cover. All product contact container closure components are manufactured to comply with United States Pharmacopeia (USP) and European Pharmacopoeia (PhEur) requirements.

Stability of the product

The provided stability data support the claimed shelf life in the SmPC.

For assessing drug product stability, the Applicant has conducted real time, real-condition stability studies using a large number of drug product batches produced with the commercial manufacturing). The data set includes 42 lots of 10^8 PFU/mL and 16 lots of 10^6 PFU/mL, with stability data available for 48 months from seven primary lots of 10^8 PFU/mL drug product and three primary lots for the 10^6 PFU/mL drug product. The stability indicating properties of the assays used in the studies have been adequately addressed. Based on the results from the real-time, real-condition studies, the recommended long-term storage condition of -80°C for 48 months is considered acceptable.

In addition to the real time, real-condition stability studies, the Applicant has provided limited stability data from studies conducted under accelerated and stressed storage conditions, as well as from light exposure, thaw temperature and 5°C post thaw storage studies. As expected, decreased stability was seen for samples stored at evaluated temperatures, with faster degradation of 10^6 PFU/mL batches compared to 10^8 PFU/mL batches. Based on the thaw temperature studies and the 5°C post long-term storage studies, the Applicant has established the thawing and in use stability conditions as following "thawing drug product at room temperature for a maximum of 30 minutes followed by storage at 5°C for up 48 hours for 10^8 PFU/mL drug product and up to 12 hours for 10^6 PFU/mL drug product strengths". This is considered acceptable.

The post-approval stability program and commitment are considered adequate. In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Comparability exercise for finished medicinal drug product

Active substance and drug product process, analytical, non-clinical and clinical comparability data has been submitted. An assessment of drug product, including stability evaluations was performed for each comparability exercise and comparability was shown, also between the commercial and clinical trial formulations.

Adventitious agents

Non-viral adventitious agents

The talimogene laherparepvec manufacturing process incorporates control measures to prevent contamination and maintain microbial control. Assessments were performed by Amgen on all raw materials used to produce talimogene laherparepvec, from the working cell banks and working virus seed stocks (WVSS) through the final drug product, to determine if any of the raw materials are of

animal origin or have product contact with materials of animal origin. An assessment of the transmissible spongiform encephalopathy (TSE) risk was conducted by the Applicant according to the principles in the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01). Based on the assessment, the TSE risk associated with talimogene laherparepvec was determined to be negligible.

Viral adventitious agents

Due to the intrinsic properties of the talimogene laherparepvec virus, viral clearance steps that are typically applied in the purification process of a biologic would inactivate or remove the desired product. Thus, the approach to viral safety in the talimogene laherparepvec manufacturing process is based on multiple layers of risk mitigation, including rigorous control of raw and starting materials, use of a cell substrate (Vero) with a proven safety profile, appropriate cGMP procedures and facility design features, extensive viral testing of cell banks, virus seed stocks, end of production cells and viruses at the limit of manufacturing age, and viral testing at strategic points in the manufacturing process. This multilayered approach minimizes the risk of viral contamination to provide assurance of safety.

As requested, the Applicant has removed the in vivo test for viral contaminants performed at the viral harvest stage. Based on a risk assessment, the Applicant will maintain the existing in vitro assay for viral contaminants performed on each production lot. This approach is endorsed.

In conclusion, the adventitious agents safety evaluation has been properly addressed and adequately presented.

GMO

The GMO, talimogene laherparepvec (JS1/ICP34.5-/ICP47-/hGM-CSF), 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. (See *Environmental Risk Assessment*).

Post approval change management protocol

As part of the MA application for Imlygic, Amgen has submitted a post-approval change management protocol (PACMP). The purpose of the PACMP is to scale up the cell build process for talimogene laherparepvec. Following approval of the marketing authorisation and the PACMP, the changes described in the protocol will be introduced through a type IB variation application procedure.

The proposed changes have been adequately presented and discussed. The minor revisions and/or clarifications requested have been agreed by the Applicant, the final updated PACMP will be submitted with the eCTD closing sequence.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The documentation in the quality dossier gives an adequate description of the characterisation, manufacture and control of the active substance and drug product. The information provided demonstrates consistent batch-to-batch production of Imlygic achieving a well-defined quality for the active substance and the drug product. The adventitious agents safety evaluation has been properly addressed and the non-viral and viral safety of the product is considered demonstrated.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Imlygic is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP endorse the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends two points for further investigation.

The CHMP endorse the CAT assessment regarding the recommendation(s) for future quality development as described above.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical pharmacology and toxicology programs have included studies designed to evaluate the mechanism of action, biodistribution and shedding, general safety of talimogene laherparepvec following single and repeat administration, and effects on embryo-foetal development. *In vivo* pharmacodynamics studies were performed in nude (xenograft studies) or immunocompetent (syngeneic studies) BALB/c mice. A mouse surrogate HSV-1 vector encoding the murine GM-CSF (OncoVEX$^{mGM\text{-}CSF}$; JS1/34.5-/47-/mGM-CSF) was developed and used for the *in vivo* mouse studies because of the inability of human GM-CSF to bind to mouse GM-CSF receptor. Such studies include the analysis of anti-tumour effect of OncoVEX$^{mGM\text{-}CSF}$ on mice previously exposed to wild type HSV-1. Nonclinical pharmacokinetic evaluation included studies addressing biodistribution, viral shedding, and replication of talimogene laherparepvec. The nonclinical toxicology studies consisted of general toxicity studies up to 12 weeks in mice and an embryo-foetal development study in mice. Additional single dose studies were also conducted in rats and dogs. Pivotal repeat-dose toxicology, biodistribution, and embryo-foetal development studies were performed in accordance with Good Laboratory Practice (GLP) regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Assessment of the in vitro lysis of human tumour cells by OncoVEX^{GM-CSF} (*talimogene laherparepvec) using a CPE (cell pathological effect) assay (Studies 4648-00035, 4648-00055)*

The lytic effect of talimogene laherparepvec was assessed in a range of human tumour cell lines (melanoma, colorectal, breast, brain, pharynx, prostate, and squamous cell carcinoma cell lines). Cells were infected with talimogene laherparepvec at MOI 0.1 and 1 and lytic effect (% of cell death) and analysed at 24 and 48 hours by differential cell count using trypan blue staining. The single incubation time (24 h or 48 h), for each cell line with the greatest range of % cell death, was selected for the analysis of secreted hGM-CSF and measured by ELISA. The results are presented in Table 3 and showed dose– and time dependent response. Melanoma cell line (SK-MEL-28) was highly susceptible to infection with talimogene laherparepvec, resulting in 48% and 89 % cell death at MOI of 0.1 and 1, respectively after 24 hours of infection, and 84 % and 100% cell death at MOI 0.1 and 1, respectively after 48 hours of infection. After 24 hours of infection, melanoma cell line (SK-MEL-28) secreted hGM-CSF 69 ng/mL and 140 mg/mL at MOI of 0.1 and 1, respectively.

Table 3: *In vitro* efficiency of talimogene laherparepvec (shown as cancer cell death %)

Cell Line	24 HR incubation				48 HR incubation			
	MOI=0.1		MOI=1		MOI=0.1		MOI=1	
	% cell death	hGM-CSF (ng/mL)	% cell death	hGM-CSF (ng/mL)	% cell death	hGM-CSF (ng/mL)	% cell death	hGM-CSF (ng/mL)
FaDu	36.4	21.9	100	213.5	100	nt	100	nt
HT-29	15	33.8	58.3	176.2	84.6	nt	100	nt
SK-MEL-28	**48.3**	**69.3**	**84.1**	**140.6**	**89.4**	**nt**	**100**	**nt**
U-87 MG	0	nt	54.4	nt	47.1	37.1	95.2	41.4
MDA-MB-231	12.7	nt	13.6	nt	0	153.9	64.4	283.9

FaDu: human squamous cell carcinoma (pharynx) cell line, HT29: human colorectal cancer cell line, SK-MEL-28: human melanoma cell line, U-87 MG: human glioblastoma cell line, MDA-MB-231: human breast adenocarcinoma cell line.

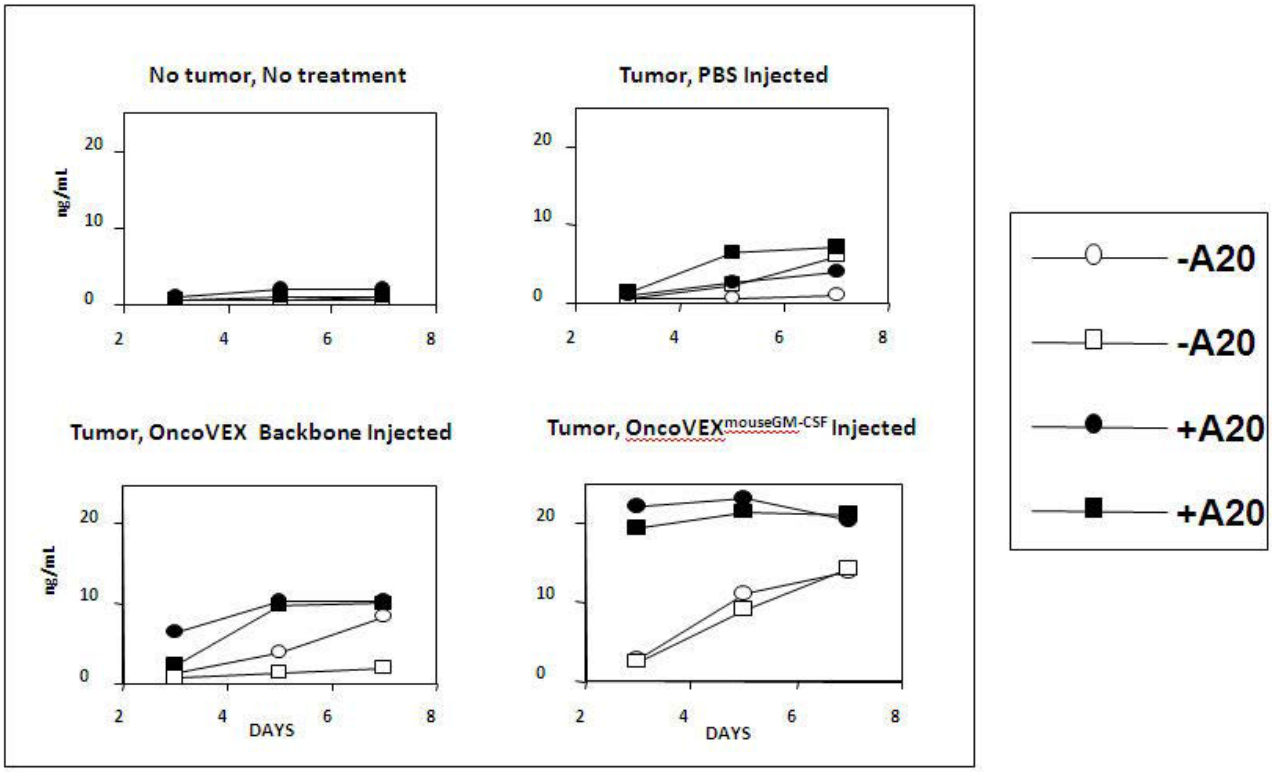
Cellular mediated immune response in A20 tumour bearing mice treated with JS1/34.5-/47- (Study 4648-00071)

Measurement of CT26-specific cytotoxic T- lymphocytes after intra-tumoral injection of mouse surrogate into CT26 tumour bearing female BALB/c mice (Study R20130079)

These studies investigated the T cell immune response in mice bearing A20 tumors treated with JS1/34.5-/47- (OncoVEX backbone). Immune-response was measured *ex vivo* by the T-lymphocyte activation as a response to IFNɣ release and by development of specific cytotoxic T-cells using cytotoxic T-lymphocyte assay (CTL). The IFNɣ release was stimulated most notably in splenocytes isolated from the mice treated with mouse surrogate and incubated with A20 tumour cells (Figure 3). The stimulation of IFNɣ release was seen at the earliest time point tested (3 days) and remained high during the study duration (up to 7 days). Moderate levels of IFNɣ release was detected at 5 days in

splenocytes isolated from the JS1/34.5-/47- treated mice as a specific response to the A20 tumour cells. Splenocytes were incubated with A20 tumour cells (+A20) or without (-A20).

Figure 3: IFNɣ release from splenocytes (including T-cells) isolated from JS1/34.5-/47- (OncoVEX backbone, hGM-CSF-deficient talimogene laherparepvec), mouse surrogate (OncoVEX mouseGM-CSF) or vehicle (PBS) –treated mice, or untreated naïve mice



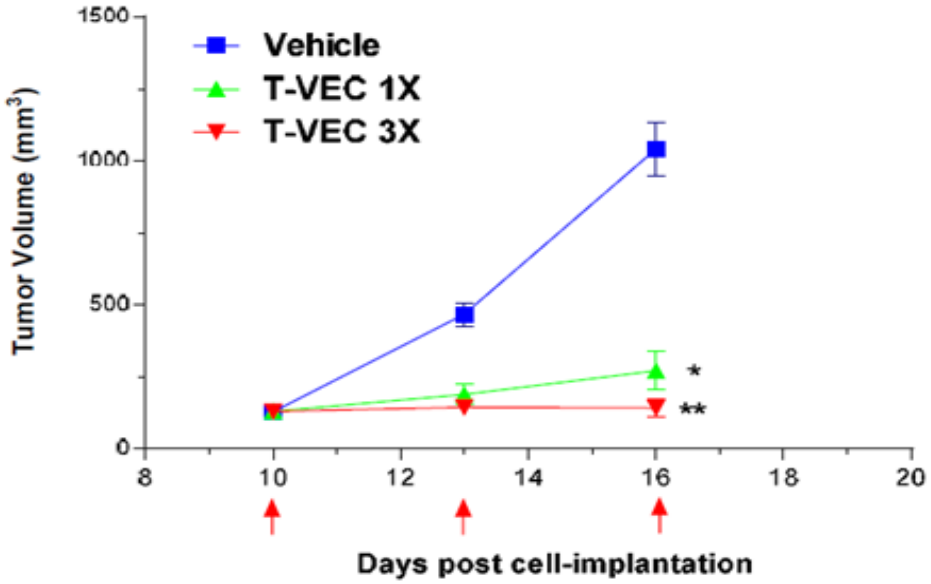
In vivo

*Efficacy of Talimogene Laherparepvec in the B16F10- muNectin1 Melanoma Syngeneic Tumour Model in Female C57BL/6 Mice (**Study R20150003**)*

Tumours were initiated by *SC* implantation of 1 x 10^5 B16F10/mNectin-1 tumour cells into the right flank of C57BL/6 mice. After 10 days, animals (n=10) received 3 intratumoural doses of 5 x 10^6 PFU (50 μL) of talimogene laherparepvec (or other viral constructs or vehicle) on days 10, 13, and 16. The animals in the control group received intratumoral injection of formulation buffer. One group of mice (n=10) received only one dose of talimogene laherparepvec at day 10 post tumour implantation.

Intratumoral administration of a single dose and 3 doses of talimogene laherparepvec produced statistically significant ($p<0.0001$) anti-tumour effect in the mouse syngeneic melanoma model (Figure 4).

Figure 4: Inhibition of B16F10-muNectin1 tumour growth by talimogene laherparepvec intratumoural injection



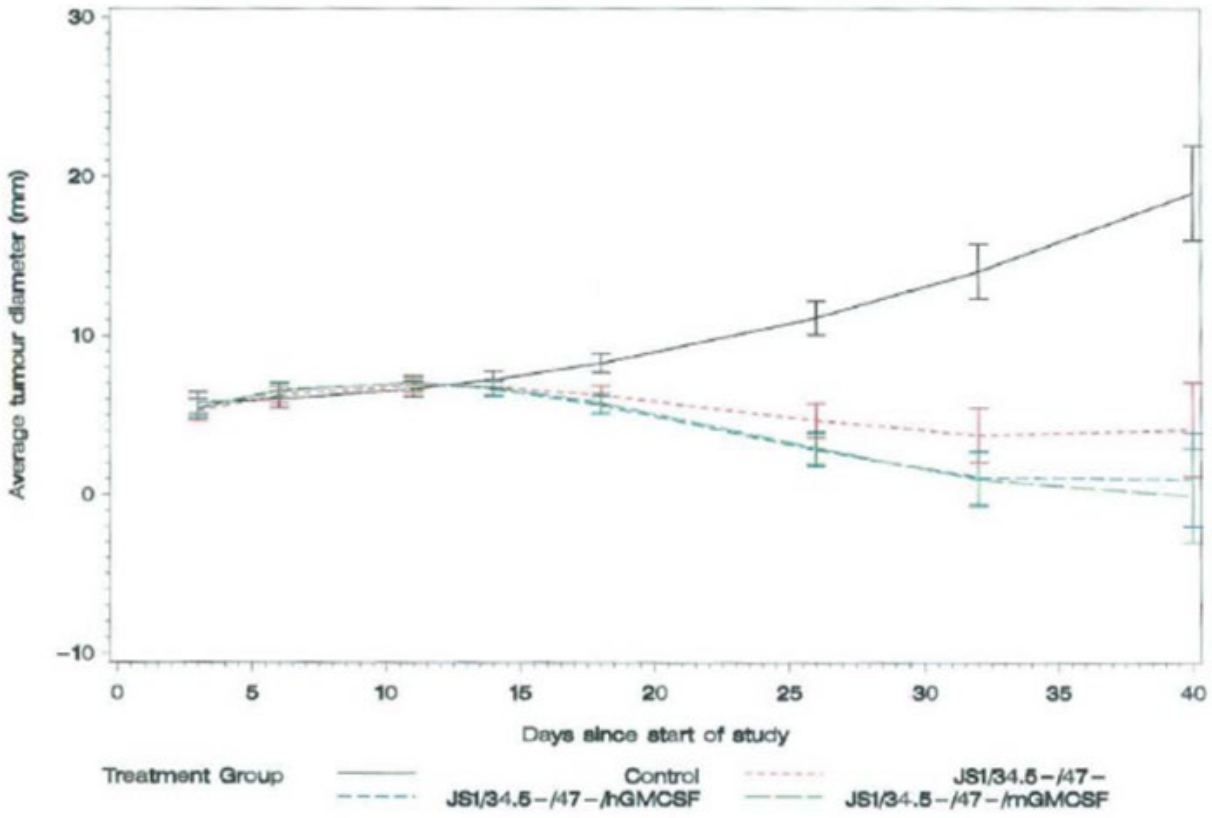
T-VEC 1x = one dose of 5 x 10^6 PFU, T-VEC 3x = three doses of 5 x 10^6 PFU

Assessment of anti-tumour effect of talimogene laherparepvec mouse surrogate *on mouse reticulum cell sarcoma (A20)-induced tumours in the Right Flank in Balb/c mice*

Direct anti-tumour effect (injected right flank tumours)

A study comparing the anti-tumour effect of talimogene laherparepvec mouse surrogate (mGM-CSF) in mouse reticulum cell sarcoma (A20) in BALB/c Mice was performed. The results are shown in Figure 5 which show anti-tumour activity of talimogene laherparepvec compared to control mice treated with vehicle after intra-tumoural injection ($p < 0.001$).

Figure 5: Efficacy of intratumourally administered talimogene laherparepvec and OncoVEX$^{mGM-CSF}$ in mouse reticulum cell carcinoma/ B-cell lymphoma tumour mice model - Study 4648-00002

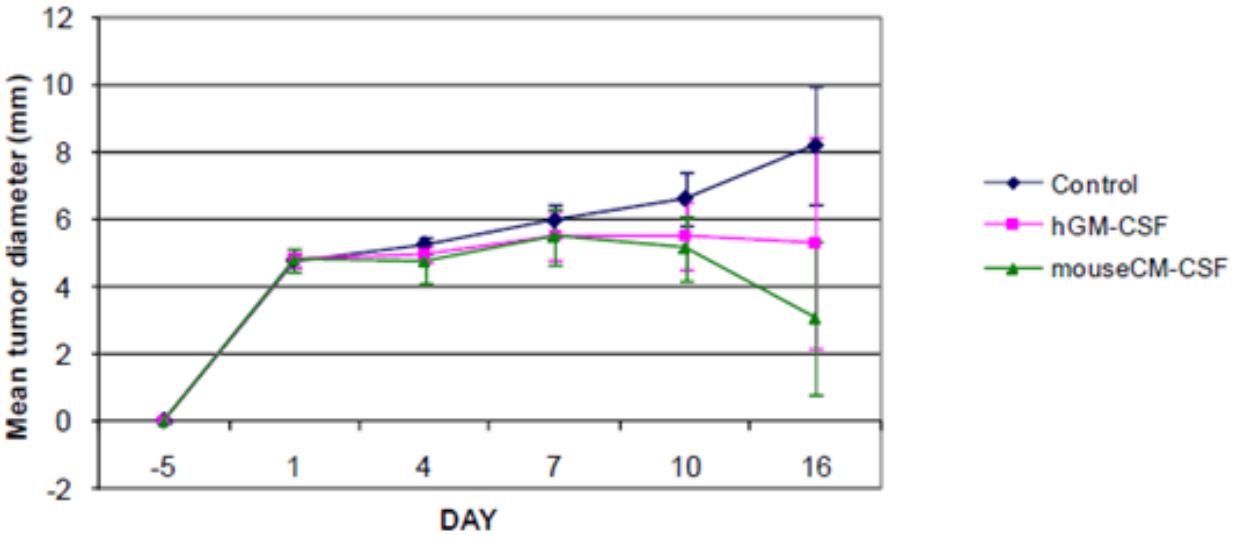


Tumours were injected with the following constructs; control: vehicle, JS1/34.5-/47-: hGM-CSF deficient talimogene laherparepvec, JS1/34.5-/47-/hGMCSF: talimogene laherparepvec, JS1/34.5-/47- /mGMCSF: mouse surrogate.

Systemic effect (uninjected left flank tumour)

The anti-tumour effect was seen on the uninjected (left flank) tumours (Figure 6 and Table 4). The mouse surrogate vector had a similar but slightly more potent anti-tumour effect. The anti-tumour effects of mouse surrogate and JS1/34.5-/47- (hGM-CSF deficient talimogene laherparepvec) did not differ significantly as compared to the talimogene laherparepvec.

Figure 6: Systemic effect of talimogene laherparepvec in mouse reticulum cell carcinoma/ B-cell lymphoma tumour mice model - Study 4648-00001



Tumours were injected with the following constructs; control: vehicle, hGM-CSF: talimogene laherparepvec, mouseGM-CSF: mouse surrogate.

Table 4: Efficacy of intratumorally administered viral vector constructs and the systemic effect - Study 4648-00051

Day	Mean Tumour Diameter (n)					
	Control		OncoVEX backbone		OncoVEX$^{mGM-CSF}$	
	Right Flank	Left Flank	Right Flank	Left Flank	Right Flank	Left Flank
1	6.83 (9)	7.01 (9)	6.72 (9)	7.62 (9)	7.11 (9)	7.37 (9)
5	8.22 (9)	8.53 (9)	6.48 (9)	7.62 (9)	7.26 (9)	8.19 (9)
8	9.43 (9)	10.11 (9)	6.87 (9)	9.13 (9)	7.32 (9)	9.07 (9)
11	10.62 (9)	11.32 (9)	6.60 (9)	8.76 (9)	5.52 (9)	9.22 (9)
18	13.94 (9)	15.34 (9)	1.69 (8)	10.0 (8)	0.86 (9)	8.06 (9)
26	N/A (0)	N/A (0)	0 (4)	5.9 (4)	0 (6)	4.58 (6)

Tumours were injected with the following constructs; control: vehicle, OncoVEX backbone: JS1/34.5-/47- (hGM-CSF deficient talimogene laherparepvec), OncoVEX$^{mouseGM-CSF}$: mouse surrogate.

Anti-tumour efficacy of Imlygic in immunosuppressed mice

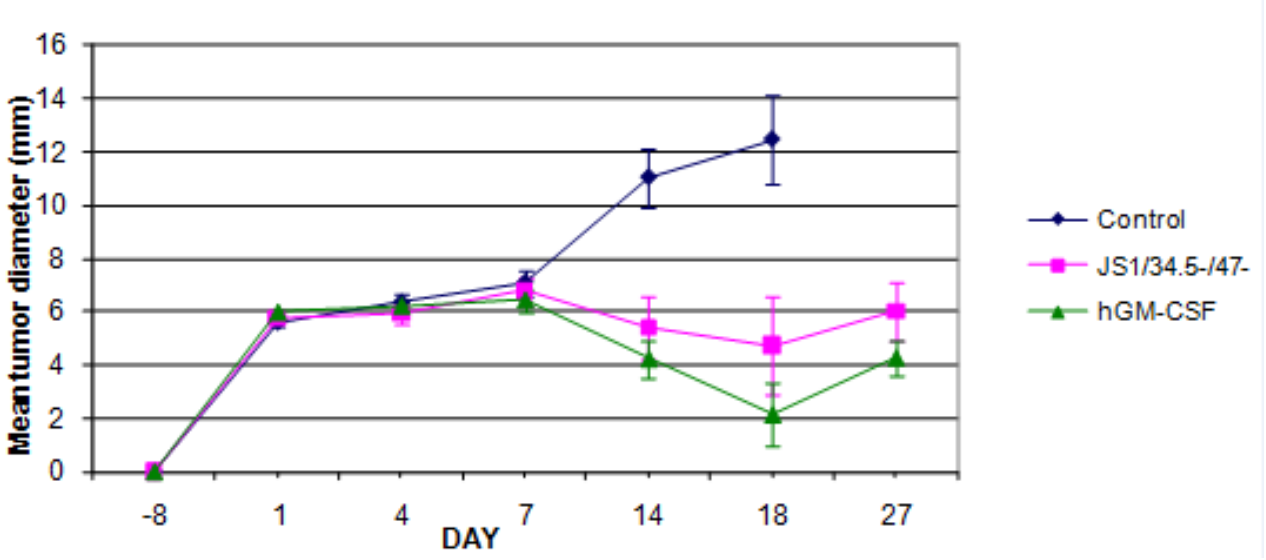
Assessment of the safety and anti-tumour efficacy in immunosuppressed BALB/c mice bearing A20 – induced tumours (Study 4648-00011)

This study evaluated the effect of induced immunosuppression on talimogene laherparepvec efficacy. A20 tumour bearing mice were given cyclosporin (50 mg/kg) from 2 days before first dose of talimogene laherparepvec (or hGM-CSF deficient talimogene laherparepvec) throughout the study. Control animals were terminated at day 18 due to tumour burden. The talimogene laherparepvec treated mice were terminated on day 27. One animal was found dead in the JS1/34.5-/47- (hGM-CSF

deficient talimogene laherparepvec) group at week 4. Death was thought to be due to peritonitis, possibly caused by *i.p.* administration of cyclosporin.

With immunosuppression the tumour diameters were significantly smaller in the talimogene laherparepvec (or GM-CSF deficient talimogene laherparepvec) groups as compared to the control at day 14 and 18 (Figure 7 $p<0.0001$). Significant levels of serum HSV antibodies were seen in treated animals on day 27. Antibody levels were similar in the talimogene laherparepvec and hGM-CSF deficient talimogene laherparepvec treated groups.

Figure 7: Anti-tumour efficacy in immunosuppressed mouse tumour model



Tumours were injected with the following constructs; control: vehicle, JS1/34.5-/47-: GM-CSF deficient talimogene laherparepvec, hGM-CSF: talimogene laherparepvec

Secondary pharmacodynamic studies

The applicant did not submit specific secondary pharmacodynamics studies (see non-clinical discussion).

Safety pharmacology programme

The applicant did not submit specific safety pharmacology studies (see non-clinical discussion).

Pharmacodynamic drug interactions

The applicant did not submit specific pharmacodynamics drug interaction studies (see non-clinical discussion). Drug interaction studies with combination treatment with cisplatin, 5FU and anastrazole were submitted (data not shown).

2.3.3. Pharmacokinetics

Biodistribution

The distribution and persistence of talimogene laherparepvec at the site of administration as well as in blood and all other tissues were evaluated based on qPCR results from the biodistribution studies conducted in naïve or tumour-bearing BALB/c mice following single or multiple subcutaneous, intravenous and intratumoral dosing (Table 5) and in addition, viral shedding was evaluated in tumour-bearing BALB/c mice (Study 115857). The study designs of biodistribution studies in mice are summarised in the Table 5.

Table 5: Nonclinical biodistribution study designs in mice

Study	Route	Dose Frequency	Dose Amount (PFU)	Assay	Collection Day(s)	Sample Collections
4648-00030	SC, IV	Single	Control or $0.6x10^7$ (n = 15/sex/route)	qPCR	24 hr and 15, 29, 57, and 85 days postdose; (n = 6/time point)[b]	blood, urine; injection site, spleen, lung, liver, heart, kidneys, gonads, trigeminal ganglion, brain, eyes, and sciatic nerve
4648-00027[a]	SC	multiple (Q3Dx5)	$1x10^7$ (n = 9/sex)	qPCR	Days 14, 42, and 70 (i.e. 24 hr, 29 and 57 days after the final dose); (n = 6/time point)[b]	blood, urine; brain, eyes, heart, injection site, kidney, liver, lungs, spleen, duodenum, trigeminal ganglia, gonads
4648-00028[a]	SC	multiple (QWx5)	$1x10^7$ (n = 15/sex)	qPCR	24hr, 4 and 12 weeks after the final dose (n = 10/time point)[b]	blood, urine; brain, eyes, heart, injection site, kidney, liver, lungs, spleen, duodenum, trigeminal ganglia, gonads
115857	intratumoral	multiple (Q3Dx3)	Control (n = 14/sex/dose); $1x10^5$ or $5x10^5$ (n = 24/sex/dose)	qPCR	Days 8, 14, or 91 (i.e. 24h hr, 7 and 84 days after the final dose); (n = 10/time point on Days 8 and 14; all others on Day 91 [n = 12-13] or at necropsy if before Day 91 [n = 1-12])[b]	blood; brain bone marrow, eye, gonads, heart, injection site, kidney, liver, lung, lymph node, spleen; specimens from possible sources for viral shedding (feces, lachrymal glands, nasal mucosa, urine, and salivary glands)

a Only the study design for the biodistribution arm is summarized;

bData from a fewer number of animals for each timepoint may have been available if animals were euthanized prior to schedule.

OncoVEX^{GM-CSF}: Single Dose Biodistribution Study in the Mouse with an 84-Day Observation Period (study 4648-00030)

In mice who received a single IV administration of $0.6x10^7$ PFU talimogene laherparepvec, viral DNA was detected in all samples collected from the site of administration (tail vein) at 24 hours post dose, but declined to 67% of samples testing positive at 14 days post dose, and 50% of samples testing positive at 28 days post dose. Viral DNA was not detected in any samples from the site of administration at 56 days post dose (Table 6). Viral DNA was detected in at least 1 sample from all of the tissues tested throughout the study. However, the majority of positive samples came from the site of administration (tail vein), blood, or organs with high blood perfusion (heart, liver, lungs, kidneys, and spleen). Of the mice who received a single SC administration of $0.6x10^7$ PFU talimogene laherparepvec, all tissues tested negative at 24 hours post dose with the exception of the injection site which tested positive in all animals.

Table 6: Detection of viral DNA in organs and tissues of BALB/c mice following single subcutaneous and intravenous injection

	Average copies in positive animals/ 0.1µg extracted DNA (# qPCR positive mice/# mice tested) qPCR assay LLOQ= 6.4 copies/0.1µg extracted DNA							
	Subcutaneous administration				**Intravenous administration**			
Tissues/organs/ Time after final dose	**24 hours**	**14 days**	**28 days**	**56 days**	**24 hours**	**14 days**	**28 days**	**56 days**
Brain	0 (0/6)	N/T	N/T	N/T	<6.4 (4/6)	6.71 (4/6)	<6.4 (4/6)	0 (0/6)
Eyes	0 (0/6)	N/T	N/T	N/T	6.56 (4/6)	<6.4 (3/6)	6.85 (4/6)	0 (0/6)
Heart	0 (0/6)	N/T	N/T	N/T	113.67 (4/6)	33.68 (6/6)	60.53 (6/6)	<6.4 (1/6)
Injection site	280.19 (6/6)	15.16 (1/6)[a]	0 (0/6)	N/T	4888.37 (6/6)	165.88 (4/6)[a]	888.41 (3/6)[b]	0 (0/6)c
Kidney	0 (0/6)	N/T	N/T	N/T	13.04 (4/6)	11.04 (6/6)	<6.4 (6/6)	0 (0/6)
Liver	0 (0/6)	0 (0/6)	N/T	N/T	514.21 (4/6)	16.93 (6/6)	19.03 (6/6)	<6.4 (5/6)
Lung	0 (0/6)	N/T	N/T	N/T	29 (5/6)	23.62 (6/6)	13.53 (5/6)	0 (0/6)
Sciatic Nerve	N/T	0 (0/5)	N/T	N/T				
Spleen	0 (0/6)	0 (0/6)	N/T	N/T	113.91 (4/6)	11.89 (6/6)	194.96 (6/6)	<6.4 (6/6)
Trigeminal ganglia	0 (0/6)	0 (0/6)	N/T	N/T	6.57 (4/6)	12.02 (5/6)	7.42 (6/6)	<6.4 (1/6)
Ovary	0 (0/3)	0 (0/3)	0 (0/3)	N/T	50.8 (1/3)	<6.4 (3/3)	<6.4 (1/3)	0 (0/3)
Testes	0 (0/3)	10.25 (1/3)	0 (0/2)	N/T	8.6 (3/3)	<6.4 (2/3)	0 (0/3)	0 (0/3)
Blood	0 (0/6)	0 (0/5)	N/T	N/T	3603.63 (5/6)	2132.39 (6/6)	3376.29 (6/6)	8.55 (5/6)

[a] One sample totally inhibitory. N/T not tested; when samples were negative or below the LLOQ (6.4 copies/0.1µg extracted DNA) samples from subsequent time points were not tested. Results are mean values for qPCR positive animals. Samples which were below the LLOQ (<6.4 copies) were assigned a value of 6.4 copies for the purpose of calculating mean values.	[a] One sample totally inhibitory and one sample partially inhibitory; [b] Three samples partially inhibitory; [c]Four samples totally inhibitory and 2 samples partially inhibitory. N/T not tested - if samples negative or below LLOQ (6.4 copies/0.1µg DNA) samples from subsequent time points not tested. Results are mean values for qPCR positive animals. Samples which were below the LLOQ (<6.4 copies) were assigned a value of 6.4 copies for the purpose of calculating mean values.

OncoVEX^{GM-CSF}: Repeat Dose Toxicity and QPCR Biodistribution Study in the Mouse Followed by a 24-hour, 28 or 56-Day Observation Period (Study 4648-00027)

The biodistribution arm of study was designed to examine the tissue distribution and duration of talimogene laherparepvec in BALB/c mice. After multiple SC administrations of $1x10^7$ PFU talimogene laherparepvec, all tissues tested did not have detectable viral DNA at 24 hours after the last dose, with the exception of the injection site in 5 of 6 animals and the blood of 2 of 6 animals (Table 7). At 29 days after the final dose (Day 42), only injection site and blood samples were tested ; one blood sample was below the LLOQ (<6.4 copies/0.1 µg extracted DNA).

Table 7: Detection of viral DNA in organs and tissues of BALB/c mice (study 4648-00027) following multiple subcutaneous injections

	Average copies in positive animals/ 0.1µg extracted DNA **(# qPCR positive mice/group)** qPCR assay LLOQ= 6.4 copies/0.1µg extracted DNA	
	Subcutaneous administration	
Tissues/organs/ Time after final dose	**24 hours**	**29 days**
Brain	0 (0/6)	N/T
Duodenum	0 (0/6)	N/T
Eyes	0 (0/6)	N/T
Heart	0 (0/6)	N/T
Injection site	848.29 (5/6)[a]	0 (0/5)[b]
Kidney	0 (0/6)	N/T
Liver	0 (0/6)	N/T
Lung	0 (0/6)	N/T
Spleen	0 (0/6)	N/T
Trigeminal ganglia	0 (0/6)	N/T
Ovary	0 (0/3)	N/T
Testes	0 (0/3)	N/T
Blood	8.11 (2/6)	<6.4 (1/5)

a One sample totally inhibitory; b All five samples totally inhibitory;

N/T not tested - if samples were negative or below the LLOQ (6.4 copies/0.1µg DNA) samples from subsequent time points were not tested.

Results are mean values for qPCR positive animals. Samples which were below the LLOQ (<6.4 copies) were assigned a value of 6.4 copies for the purpose of calculating mean values.

Across the nonclinical program, quantifiable levels of talimogene laherparepvec DNA in brain, assessed by quantitative PCR analysis, was observed in three samples collected at least 14 days after initiation of dosing. In Study 4648-00028, one animal dosed with talimogene laherparepvec ($1x10^7$ PFU, as 5 weekly intravenous doses) had quantifiable DNA in brain (Day 84, 2,427 copies/µg DNA). In Study 115857, two animals dosed with talimogene laherparepvec ($1x10^5$ PFU, as 3 intratumoral doses every third day) had quantifiable DNA in brain (Day 58: 13,325 copies/µg DNA; Day 91: 635 copies/µg DNA). In Study 115857, talimogene laherparepvec was studied following multiple intratumoral administrations and samples from brain and shedding tissues were analyzed through 84 days after dosing; analyses of eyes and gonads samples were curtailed after earlier results demonstrated no evidence indicating biodistribution to these tissues. Through up to 3 months post-dose, low copies of virus were detected only in liver, lymph node and spleen, indicating active immune surveillance and clearance of virus; no virus was detected in other tissues except one positive brain sample. No positive result was seen in ovaries or testes 7 days after dosing. Specific assessments of trigeminal ganglia (or other peripheral nerves) were not included in this study

Viral shedding

Viral shedding in BALB/c mice was measured by a plaque assay (Study 4648-00010). Viral shedding of talimogene laherparepvec in excreta (urine and feces) and shedding tissues (lachrymal glands, nasal mucosa, and salivary glands) were evaluated based on qPCR results from the biodistribution studies conducted in naïve or tumour-bearing BALB/c mice (Studies 4648-00030, 4648-00027, 4648-00028, and 115857).

Following a single IV or SC administration of $0.6x10^7$ PFU talimogene laherparepvec to naïve BALB/c mice (Study 4648-00030), urine samples were collected at 0 to 18 hours post dose from 10 mice (4M, 6F) in the IV dose group and from 9 mice (4M, 5F) in the SC dose group for analysis of viral DNA by qPCR. Of the urine samples from IV dosed animals one sample tested positive, five were marginally positive, and four samples were negative for viral DNA (Table 8). Of the urine samples from SC dosed animals two male and one female urine samples tested negative for viral DNA, and two male and 4 female urine samples were marginally positive.

Table 8: Detection of viral DNA in urine samples - Study 4648-00030

	Mouse, BALB/c		Mouse, BALB/c	
	Subcutaneous		**Intravenous**	
	0.6 x 10^7 PFU/animal		0.6 x 10^7 PFU/animal	
	talimogene laherparepvec		talimogene laherparepvec	
	qPCR		qPCR	
	Copies/ 0.1µg extracted DNA			
	Urine		**Urine**	
Gender (number of animals)	Males (1)	Females (2)	Males (2)	Females (3)

0-18 hours	0	0 6.86	<6.4 6.88	0 13.29 85.92
14 days	0 7.24 9.06	<6.4 <6.4 16.91	0 0	0 <6.4 11.69
qPCR values are given for individual mice.				

Following multiple SC doses of $1x10^7$ PFU talimogene laherparepvec to BALB/c mice (Study 4648-00027), 5 samples out of 6 were negative and 1 sample was marginally positive (Table 9). Of the 6 urine samples collected overnight on Days 14/15, 3 male samples were negative and 3 female samples were marginally positive.

Table 9: Detection of viral DNA in urine samples - Study 4648-00027

	4648-00027	**4648-00028**
	Mouse, BALB/c	Mouse, BALB/c
	3M/3F/timepoint	5M/5F (24h) 4M/4F (4w)
	Subcutaneous	**Subcutaneous**
	1 x 10^7 PFU/animal on Days 1, 4, 7, 10 & 13	1 x 10^7 PFU/animal once weekly for 5 weeks
	talimogene laherparepvec	talimogene laherparepvec
	aPCR	aPCR
	Copies/ 0.1µg extracted DNA	
	Urine	**Urine**
Day 13/14 (1-17h after final dose)	0 / 0 / 0 / 0 / 0 / 6.52	NA
Day 14/15 (17-41h after final dose)	0 / 0 / 0 / <6.4 / 6.44 / 6.76	NA
Week 5 (24h after final dose)		NQ / NQ / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0
Week 9 (4 weeks after final dose)		0 / 0 / 0 / 0 / 0 / 0 / 0 / 0[a]
[a] copies detected /µL urine extracted. NQ = not quantifiable; NA = Not applicable QPCR values are given for individual mice.		

Following multiple SC doses of $1x10^7$ PFU talimogene laherparepvec to BALB/c mice (Study 4648-00028), at 24 hours post dose, 8/10 urine samples were negative and 2 samples were below the assay limit of quantification. At 4 weeks post dose, all urine samples were negative. As the 4-week urine samples were negative, samples collected at 12 weeks post dose were not analysed.

Following three intratumoral injections of talimogene laherparepvec (Study 115857), viral DNA in urine samples could not be determined due to sample inhibition during qPCR analysis.

Following intraprostatic administration to dogs talimogene laherparepvec was not detected in urine at any time points (study 4648-00032).

Viral shedding was studied following three intratumoral injections of talimogene laherparepvec at $1x10^5$ or $5x10^5$ PFU/mouse/dose in A20-bearing BALB/c mice (Study 115857). Shedding tissues (lachrymal glands, nasal mucosa, and salivary glands) or excreta (urine and feces) samples were collected and evaluated on Day 8, 14 and 91 (ie, 24 hours, 7 days, and 84 days post last dose). Among shedding tissues or excreta, viral DNA was not detected in samples collected from lachrymal glands, nasal mucosa or feces. One animal was identified with a positive qPCR signal in salivary glands at 42 days post last dose.

2.3.4. Toxicology

Information on the acute tolerability of talimogene laherparepvec was obtained from short-term studies evaluating repeated-dose administration under clinically-relevant conditions. These studies include evaluation of intra-tumoral injection in tumour-bearing animals to assess tolerability under conditions allowing viral replication as anticipated in patients, and SC and IV injection in tumour-free mice to inform the safety of talimogene laherparepvec under conditions that are similar to the planned clinical dosing route in a study unconfounded by the presence of a tumour.

Single dose toxicity

Single-dose toxicity studies with talimogene laherparepvec were not conducted.

Repeat dose toxicity

Exploratory and GLP-compliant repeat dose toxicity studies were conducted in Balb/c mice with up to 12 weekly doses.

Table 10: Non-pivotal Repeat-Dose Toxicity Studies

Study number (GLP status)	Species/strain Gender and No. per group	Method of Administration	Doses (PFU/dose) Duration of Dosing	Findings NOAEL (PFU/dose)
4648-00012 (Non-GLP)	Mouse/ BALB/c Control: 14M/14F Virus: 6M/6F	Intra-tumoural into A20 mouse reticulum cell sarcoma tumours	OncoVEX^{GM-CSF}: 5 x 10^6 3 doses (on days 1, 4, and 7) 13-day observation period	OncoVEX^{GM-CSF}: 1M died and 1F euthanized moribund on day 11. There was no gross or microscopic evidence of any adverse effect of OncoVEX^{GM-CSF} at the final necropsy.
115857 (Non-GLP)	Mouse/ BALB/c Control: 14M/14F Virus: 24M/24F	Intra-tumoural into A20 B-cell lymphoma tumour xenografts	OncoVEX^{GM-CSF}:1 x 10^5 , 5 x 10^5 3 doses (on days 1, 4, and 7) 1-, 4-, 7- or 84-	No effect on behaviour, body weight, or body weight gain. No clinical signs. Unscheduled deaths were attributable to tumour growth that reached pre-defined limits.

			day observation period	
4648-00007 (Non-GLP)	Mouse/ BALB/c 20M/20F	Subcutaneous	OncoVEX^{GM-CSF}: 10^6, 10^7 OncoVEX$^{mouseGM-CSF}$: 10^7 5 doses (on days 1, 4, 7, 10, 13). 30-day observation period	10^7 OncoVEX^{GM-CSF}: 1 male died on day 14 with no previous adverse effects. 10^7 OncoVEX^{GM-CSF} and 10^7 OncoVEX$^{mouseGM-CSF}$: Enlarged spleens and increased extra-medullary haematopoiesis in one male of each group.

N/A: Not Applicable

Table 11: Pivotal Repeat-Dose Toxicity Studies

Study number (GLP status)	Species/strain Gender and No. per group	1. Method of Administration 2. Investigations 3. Findings	Doses (PFU/dose) Duration of Dosing
4648-00029 (GLP)	Mouse/ BALB/c 12M/12F	1. Subcutaneous 2. Clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis, immunochemistry, necropsy, histopathology, organ weight 3. No deaths reported. No effects of OncoVEX^{GM-CSF} or OncoVEX$^{mouseGM-CSF}$ observed on clinical signs, overall body weight gain, food consumption, haematology, clinical chemistry, or urinalysis parameters. At the day 14 interim necropsy, spleens were enlarged and spleen weights were significantly increased in mice in all high dose groups, except OncoVEX^{GM-CSF} (Process B). At terminal necropsy, this effect was reversed and there were no other macroscopic findings. Microscopically, there was cellulitis at the injection site (all groups), marginally higher level of haematopoiesis in the splenic red pulp, lymphoid hyperplasia in the splenic white pulp and minimal to mild increased haematopoiesis in the femoral and sternal marrow (all high-dose groups). In general,	Control: 0 OncoVEX^{GM-CSF} (Process B): 1 x 10^5, 1 x 10^7 OncoVEX^{GM-CSF} (Process C): 1 x 10^5, 1 x 10^7 OncoVEX$^{mouseGM-CSF}$ (Process B): 1 x 10^7 OncoVEX$^{mouseGM-CSF}$ (Process C): 1 x 10^5 and 1 x 10^7 5 doses (on days 1, 4, 7, 10, 13) 24-hour or 28-day observation period

		all effects were reversible at terminal necropsy.	
4648-00026 (GLP)	Mouse/ BALB/c 12M/12F + 9M/9F in high dose group for biodistribution	1. Subcutaneous 2. Clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis, immunochemistry, necropsy, histopathology, organ weight, and collection of tissues, blood and urine for qPCR biodistribution 3. Because of technical issues, this study was considered as failed, and therefore repeated as study 4648-00027.	OncoVEX^{GM-CSF}: 0, 10^5, 10^6, or 0.8 x 10^7 5 doses (on days 1, 4, 7, 10, 13) 1-, 28-, 30- or 54-day observation period
4648-00027 (GLP)	Mouse/ BALB/c 12M/12F + 9M/9F in high dose group for biodistribution	1. Subcutaneous 2. Clinical signs, body weight, food consumption, haematology, clinical chemistry, urinalysis, immunochemistry, necropsy, histopathology, organ weight, and collection of tissues, blood and urine for qPCR biodistribution 3. All mice in the mid and high dose groups developed a dose related antibody responses against HSV. Antibodies were detectable at 14 days after start of dosing, and a robust response had occurred by 42 days. No treatment-related adverse clinical signs, effects on body weight, food consumption, urinalysis, or clinical chemistry were observed. At day 14, necropsy findings in the high dose group indicated local irritation (increased fasciitis and other inflammatory lesions at the injection sites) and minor increases in haematopoiesis and lymphoid hyperplasia in the spleen. At day 42, only occasional minor focal inflammatory lesions in high dose males were seen, indicating reversibility. One high dose male had a focal encephalopathy in the cerebral cortex but was assessed as not to be related to HSV-1 infection.	OncoVEX^{GM-CSF}: 0, 10^5, 10^6, or 10^7 5 doses (on days 1, 4, 7, 10, 13) 1-, 28- or 56 day observation period
4648-00028 (GLP)	Mouse/ BALB/c 18M/18F + 15M/15F in control and high dose group for	1. Subcutaneous 2. Clinical signs, body weight, food consumption, haematology, clinical bone marrow smears, chemistry, urinalysis, immunochemistry, necropsy, histopathology,	OncoVEX^{GM-CSF}: 0, 10^5, 10^6, or 10^7 Once weekly, 12 weeks Once weekly, 5

	biodistribution	organ weight, and collection of tissues, blood and urine for qPCR biodistribution 3. All treated mice at week 16 after start of dosing and most at week 24, had developed detectable antibody responses against HSV-1. No deaths were recorded. There were no OncoVEX^{GM-CSF}-related effects on clinical observations, bodyweight, food consumption, clinical chemistry parameters, bone marrow smears, urinalysis parameters or organ weights. There was an increase in lymphocyte and neutrophil counts in females in the mid- high dose groups. There were no OncoVEXGM-CSF-related macroscopic findings.	weeks for biodistribution 1-, 28- or 84-day observation period

Genotoxicity

No genotoxicity studies have been conducted (see non-clinical discussion).

Carcinogenicity

No carcinogenicity studies have been conducted (see non-clinical discussion). However, the applicant provided a review of published literature of epidemiology studies evaluating the potential of an association of HSV-1 and human cancers.

Epidemiology of HSV-1 infection and cancer risk in human populations

Searches of PubMed (US National Library of Medicine, National Institutes of Health), most recently updated during the week of November 2, 2013, conducted using the search terms "HSV-1" or "herpes simplex virus", "cancer", and "epidemiology" identified 24 articles. These articles were reviewed to establish their relevance and to identify any additional studies that may describe the cancer risk in humans from HSV-1 infection. The resulting relevant literature is summarized in Table 12.

Table 12: Epidemiology Studies Evaluating HSV-1 Infection and Cancer Risk

Citation: Study Design	Result	Comment
(Schildt *et al*. 1998): Case control study of 410 cases with oral cancer with 410 matched controls in Sweden. Exposure assessment based on patient recollection of symptoms.	History of oral infections were a risk factor (odds ratio [OR] = 3.8, 95% CI of 2.1 - 6.9) for oral carcinoma. Among individuals with a high certainty of HSV-1, risk factor status was less clear OR = 1.9 (95% CI: 0.7 - 4.5) for oral carcinoma. Univariate odds ratio of 3.3 (95% CI: 1.6 - 6.5) for individuals with high certainty and probable HSV-1.	HSV-1 exposure based on self-reported history of recurrent oral infection, but did not identify cause of oral infection, including HPV, which is an identified risk factor for oral carcinoma.
(Starr *et al*. 2001): Case control study of 260 oral carcinoma cases and 445 matched controls. Exposure assessment based on serologic evidence.	The OR of HSV-1 antibody positive and oral carcinoma risk was 1.3 (95% CI 0.9-2.0) after adjustment for sex, cigarette smoking, alcohol consumption, age, and income. There was suggestive evidence that HSV-1 increased the oral carcinoma risk among current smokers (OR = 4.2 (95% CI 2.4 -	Serology used to distinguish HSV-1, HSV-2, and HPV-16 exposure. Age, tobacco, income, and alcohol use were considered as co-factors.

	7.1).	
(Maden *et al.* 1992): Case control study of 131 oral carcinoma cases and 136 controls in US. Exposure assessment based on serologic evidence.	History of HSV-1 was not a risk factor (OR = 0.8, 95% CI of 0.3 - 1.7) for oral carcinoma after statistical adjustment for age, smoking, alcohol consumption, and number of sex partners.	Serology used to distinguish HPV strains; survey used to document oral HSV infection. Age, tobacco, income, alcohol use, sexual practices and number of partners were considered as co-factors.
(Parker *et al.* 2006): Case control study of 164 head and neck cancer patients with 295 matched controls in US	History of HSV-1 was not a risk factor (OR = 0.7 (95% CI of 0.4 - 1.1) for head and neck cancer risk after adjustment for age, smoking, drinking, and number of sex partners. In contrast, history of HPV-16 was a strong risk factor (OR = 16.7; 95% CI of 4.4 - 63.5) for head and neck cancer.	Serology used to distinguish HSV-1 and HSV-2. Age, tobacco, alcohol use, HPV-16 exposure, and number of sexual partners considered as co-factors.

Reproduction and developmental toxicity

The potential for reproductive or developmental toxicity of talimogene laherparepvec was evaluated in an embryo-foetal toxicity study conducted in the mouse.

The applicant did not submit prenatal and postnatal development studies or in juvenile animals (see non-clinical discussion).

Embryo-foetal development

Talimogene Laherparepvec: Intravenous Embryo-Foetal Development Study in the BALB/cAnNCrI Mouse (Study 117250)

This GLP-compliant embryo-foetal development study was conducted to evaluate the effect of talimogene laherparepvec on embryo-foetal development in mice, and to assess the placental transfer of talimogene laherparepvec. Pregnant mice (N=35/group) received control article, $1x10^5$, $1x10^6$ and $1x10^7$ PFU/mouse talimogene laherparepvec intravenously on Gestation Days (GD) 6, 9, 12, and 15. Additional satellite animals (N=6/group) were used for assessment of viral DNA content in maternal and foetal blood by qPCR.

There were no talimogene laherparepvec-related mortalities at any dose. All mice survived to scheduled euthanasia, with the exception of two mice treated with 10^6 PFU/mouse (GD9 and GD11), and one mouse treated with 10^7 PFU/dose (GD15), who died as a result of a suspected dosing error or accidental injury. There were no talimogene laherparepvec-related maternal clinical signs or macroscopic observations at any dose. No effects on maternal body weight were observed among mice treated with 10^5 PFU/mouse or 10^6 PFU/mouse. Among mice treated with 10^7 PFU/mouse, a transient decrease in maternal body weight was found on GD6 to 7 and GD9 to 10, resulting in statistically decreased body weight compared to controls on GD7, 8 and 10. Body weights quickly recovered after the first two doses, and no differences in body weights were identified in the high dose group through the rest of the study.

There were no effects on maternal food consumption or gravid uterine weights at any dose.

Pregnancy was confirmed in 21, 15, 18 and 15 mice of the control, 10^5, 10^6 and 10^7 PFU/mouse groups, respectively. There were no talimogene laherparepvec-related effects on ovarian or uterine parameters. The litter averages for corpora lutea, implantations, the percentage of preimplantation loss, litter sizes, live fetuses, early and late resorptions, foetal body weights, the percentage of

postimplantation loss, the percentage of resorbed conceptuses, and the percentage of live male fetuses were comparable among all groups.

Talimogene laherparepvec did not increase the incidence of foetal external, visceral or skeletal malformations or variations.

Placental transfer

Study 117250 was conducted to evaluate the effects of talimogene laherparepvec on pregnancy and embryo-foetal development in BALB/c AnNCrl mice and to assess placental transfer of talimogene laherparepvec. Pregnant BALB/c mice were treated with control, $1x10^5$ PFU/dose, $1x10^6$ PFU/dose, or $1x10^7$ PFU/dose talimogene laherparepvec via lateral tail vein injection on gestation days 6, 9, 12, and 15. Maternal and pooled foetal blood samples were collected on gestation day 18.

Viral DNA was detected in the blood of all dams treated with talimogene laherparepvec, and a dose-dependent increase in mean viral DNA concentrations was observed across treatment groups (~$7.2 x10^4$, $6.5x10^5$ and $4.7x10^6$ viral copies/µg genomic DNA in the $1x10^5$, $1x10^6$ and $1x10^7$ PFU/mouse dose groups, respectively).

Viral DNA concentrations were below the assay limit of detection in pooled foetal blood samples from the $1x10^5$ and $1x10^6$ PFU/mouse dose groups, and in 3/4 samples from the $1x10^7$ PFU/mouse dose group. Viral DNA was found in one pooled foetal blood sample from the high dose group ($1x10^7$ PFU/mouse) at very low concentrations (~44 viral copies/µg genomic DNA), representing less than 0.001% of the concurrent maternal blood viral DNA concentration (~$5.4x10^6$ viral copies/µg genomic DNA).

Other toxicity studies

Immunogenicity

No studies evaluated the immunogenicity of human GM-CSF encoded by talimogene laherparepvec (see non-clinical discussion).

Immunotoxicity

No studies evaluated the immunotoxicity of talimogene laherparepvec (see non-clinical discussion).

The Effect of Acyclovir on Replication of OncoVEX^{GM-CSF} (Study 4648-00024)

The sensitivity of talimogene laherparepvec and its parental strain, JS1, to acyclovir, a standard-of-care anti-viral therapeutic used to treat HSV-1 infection was assessed in an *in vitro* plaque reduction assay using Vero cells. Talimogene laherparepvec and JS1 parental strain had similar sensitivity towards acyclovir, with an average concentration of drug required to produce 50% inhibition of viral cytopathic effect or plaque formation (IC_{50}) of 0.24 and 0.31 µg/mL, respectively. The *in vitro* sensitivity of wild-type HSV-1 viruses towards acyclovir has been reported to range from 0.02 to 0.7 µg/mL, and is lower than the plasma levels achieved clinically after a 1 hour infusion of 10 mg/kg acyclovir (range from 14.1 to 44.1 µg/mL).

Talimogene Laherparepvec: Tolerability and Anti-Tumour Effects on Human Colorectal Carcinoma (HT-29) Tumours in CB17 SCID and BALB/c Nude Mice (Study 118737)

This study evaluated the tolerability and anti-tumour activity of talimogene laherparepvec following repeated intratumoral injection in HT-29 tumours implanted into CB17 SCID (lacking both T and B cells) and BALB/c nude mice (athymic mice).

HT-29 human colorectal carcinomas were initiated in 30 female CB17 SCID mice and 18 female BALB/c nude mice by SC injection of $5x10^6$ cells into the right flank of each animal. After tumour volumes reached approximately 100 mm^3 talimogene laherparepvec ($5x10^6$ PFU) was administered as three intratumoral injections every third day to BALB/c nude mice and SCID mice (9-10/group). Mice were monitored for clinical signs and body weight. Select animals underwent necropsy and collected tissues were examined microscopically.

Intratumoral injection of talimogene laherparepvec resulted in regression of HT-29 human colorectal carcinomas implanted in both CB17 SCID and BALB/c nude mice. In CB17 SCID mice treated with talimogene laherparepvec there were adverse clinical signs, including body weight loss, hypoactivity, and poor response to stimuli on day 17. Between days 18 and 21, all SCID mice treated with talimogene laherparepvec were found dead or euthanized.

Macroscopic observations of the talimogene laherparepvec-treated SCID mice were thin, flaccid, fluid-distended intestines, principally involving the ileum, cecum and large bowel. Several mice had ulcerated skin overlying the flank tumours. There was minimal to marked myenteric neuron necrosis and/or intranuclear viral inclusion bodies, presumed to be HSV-1, in the distal small and large intestines (5/6 mice). The viral inclusion bodies and necrosis in enteric neurons in the distal small and large intestines was presumed to have led to myenteric nervous system dysfunction and impaired peristalsis, consistent with weight loss and the appearance of flaccid/fluid filled gut loops. Moderate to marked necrosis with intranuclear inclusion bodies were observed in the skin overlying the tumour in 4/5 mice and this correlated with the presence of skin ulcers observed at necropsy. Mild skin ulcers with intranuclear inclusion bodies were also observed in the dorsal skin of 3/5 mice and perineal skin of 2/3 mice. Additional lesions included mild, focal neuronal intranuclear inclusion bodies in the brain (1/7 mice); moderate necrosis and intranuclear inclusion bodies in the pineal gland (1/7 mice); mild to marked foci of necrosis with intranuclear inclusion bodies in the adrenal gland (5/5 mice); minimal to mild foci of necrosis with intranuclear inclusion bodies in pancreatic Islet of Langerhans (2/5 mice); and minimal to moderate foci of retinal necrosis with intranuclear inclusion bodies and mild to moderate endophthalmitis (2/4 mice). No intranuclear inclusion bodies were found in other organs examined. These histopathology findings were attributed to treatment with talimogene laherparepvec.

BALB/c nude mice tolerated treatment with talimogene laherparepvec, with no evidence of adverse clinical signs or altered body weight changes, and were euthanized on day 32; mice from this cohort were not submitted for necropsy.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment was performed in accordance with Annex II to Directive 2001/18/EC on the deliberate release into environment of genetically modified organisms (GMOs) and following the precautionary principle using the methodology set down in Commission Decision 2002/623/EC, and EMA guidelines on environmental risk assessments for medicinal products consisting of, or containing GMOs (EMEA/CHMP/BWP/473191/2006) and on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006).

HSV-1 is a human pathogen, as such the risk for environmental spreading to the other species is considered negligible. The transmission of talimogene laherparepvec to an unintended human recipient and establishment of latency/ re-activation was considered a potential risk. In the worst case scenario, it is assumed that talimogene laherparepvec is able to spread in the environment, infect an unintended human recipient and establishment of latency/ re-activation and may also infect immunocompromised individuals. The tropism and infection capability of talimogene laherparepvec is not considered be

different to the wild type HSV1. However, after the infection the replication capability, neurovirulence potential, pathogenicity and potential to establish latency is attenuated compared to the wild type HSV-1. Talimogene laherparepvec is estimated to be 1:100 – 1:10 000 –fold less neurovirulent and pathogenic than the wild type HSV-1. The modifications facilitate replication in tumours compared to normal cells.

The most likely individuals who may be at risk from inadvertent transmission would be healthcare workers involved in the administration of talimogene laherparepvec and patient care, others involved in caring for the patient, which may include washing affected areas and changing dressings and the close contacts of the treated individual. The likelihood of transmission to occur at the site of talimogene laherparepvec administration. The likelihood of transmission is limited by the use as a prescription only medicine for the treatment of adults with melanoma in accordance with its approved product labelling, administered by a healthcare professional in an oncology treatment setting, which have the appropriate facilities to handle GMO's. Outside the host, talimogene laherparepvec is not surviving long periods of time and is relatively rapidly inactivated. The potential for exposure from the environment at the site of administration is considered negligible.

The most likely mechanism of exposure during administration is estimated to be accidental exposures, such as needle-stick injuries to the healthcare personnel. The potential for exposure from the environment at the site of administration is considered negligible.

The magnitude of consequences and the likelihood for exposure during administration and following administration in immunocompetent individuals is considered low. The magnitude of consequences of talimogene laherparepvec transmission to immune-compromised and pregnant individuals is considered moderate to high.

2.3.6. Discussion on the non-clinical aspects

The pharmacology studies evaluated the anti-tumour response of talimogene laherparepvec in various human and murine tumour cells models *in vitro* and *in vivo* in mouse tumour models carrying subcutaneous tumours of human or of mouse origin. Most of the tumour cells tested were susceptible for talimogene laherparepvec infection, including melanoma cells, which resulted in a potent direct cytotoxic effect *in vitro*. *In vivo,* intratumoural injection of talimogene laherparepvec resulted in a direct, anti-tumour effect i.e. significant tumour regression and clearance of tumours at the injected site as well as a systemic anti-tumour response where regression and clearance of the non-injected contralateral tumours in the immunocompetent mouse was observed. The direct and systemic anti-tumour effects were dose dependent, with the greatest anti-tumour effect seen with the highest dose (three doses of 5×10^6). Tumour regrowth occurred in some of the *in vivo* studies after the delivery of talimogene laherparepvec was ceased. The B16F10- muNectin1 melanoma syngeneic tumour model showed that talimogene laherparepvec delivered the anti-tumour efficiency in a melanoma in vivo model. The enhanced systemic anti-tumour effect was obtained with the addition of the GM-CSF cassette compared to infection of the tumours with a vector lacking the GM-CSF gene.

The nonclinical pharmacokinetic evaluation focused mainly on addressing biodistribution, viral shedding, and replication of talimogene laherparepvec as traditional pharmacokinetic studies are not relevant for oncolytic viruses such as talimogene laherparepvec. Biodistribution of talimogene laherparepvec was evaluated following subcutaneous, intravenous and intratumoural administration in naïve and tumour-bearing mice. The biodistribution was most extensive after intravenous dosing, followed by intratumoural and subcutaneous dosing. Highest contents of viral DNA were detected in the injection site (tumour or subcutaneous site in the flank of the animal), blood and organs and

tissues with high blood perfusion such as heart, liver, lungs, kidneys and spleen. Generally, the viral DNA was cleared rapidly possibly due to an anti-HSV antibody response, but presence of viral DNA was detected in some tissues after a prolonged time up to 84 days after the last dose suggesting persistence and possible replication of virus. Viral DNA was detected in low number of samples in the brain, testes, ovaries, duodenum, liver, lung, lymph node and spleen. The evaluation of viral DNA presence in the brain and in the trigeminal ganglia was performed primarily at early time points, and as a result, no conclusion can be drawn on the possible persistence of talimogene laherparepvec in the nervous system. Although no evidence of the presence of viral DNA in the brain has been shown in clinical studies, this is considered a potential safety concern (symptomatic talimogene laherparepvec infection in non-tumour tissue in treated patients) and has been included in the RMP. There is a warning that has been included in the SmPC in section 4.4. Furthermore, a post-authorisation prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterise the risk of herpetic illness among patients, close contacts, and healthcare providers will be conducted. The risk will also be monitored through routine pharmacovigilance. In addition, viral DNA was also detected in lumbar and cervical spinal cord after injection of talimogene laherparepvec in the prostate in dogs. These results indicate that even though ICP34.5 has been removed from the viral genome, the virus still has some affinity for nervous system tissue.

At doses up to 4 x 10^8 PFU/kg or 10^7 PFU/dose (60-fold over the highest proposed clinical dose), single or repeated doses of talimogene laherparepvec administered by SC, IV, or intratumoural injection were well tolerated in immunocompetent mice, rats, and dogs. No neuropathology or adverse neurological effects were observed. In an *in vivo* study of intracerebral injection, talimogene laherparepvec was 10,000-fold less neurovirulent as compared to the wild-type HSV-1 dose that results in death 50% of the time in mice (smPC section 5.3).

Biodistribution of talimogene laherparepvec after intratumoral administration was evaluated in A20 tumour-bearing BALB/c mice following three doses of $1x10^5$ PFU, or $5x10^5$ PFU. Viral DNA was detected in 90% and 100% of tumour samples collected at 24 hours post dose in the low and high dose groups, respectively. The number of tumour samples positive for viral DNA declined at subsequent sampling time points. Viral DNA was not detectable in any samples collected between 50 and 70 days post last dose, while coming up again at 84 days post last dose in approximately 15% and 25% of tumour samples from the low and high dose groups, respectively.

Viral shedding was addressed by evaluation of talimogene laherparepvec excretion to urine and faeces, and to the shedding tissues lachrymal gland, salivary gland and nasal mucosa. The data suggest that viral excretion to urine or faeces is very low, and likewise, viral shedding to lachrymal glands, nasal mucosa and salivary glands is low. One salivary gland sample tested positive at 28-42 days time point. Collectively, these data support the conclusion that the risk of shedding and transmission to third parties is small.

Pharmacokinetic drug-drug interaction studies were not conducted. This is acceptable considering the mode of action for talimogene laherparepvec.

The toxicology program included evaluation of safety of talimogene laherparepvec following repeated subcutaneous dosing for up to 12 weeks in the BALB/c mouse, tolerability of talimogene laherparepvec in tumour bearing mice, and embryo-foetal developmental toxicity in the BALB/c mice. One study (4648-00026) was considered a failed study and it was subsequently repeated (4648-00027). Pivotal repeat-dose toxicology, biodistribution, and embryo-foetal development studies were performed in accordance with the GLP regulations. The toxicity data were collected following a single and repeated subcutaneous and intratumoural administrations of talimogene laherparepvec to naïve or tumour-bearing mice. Talimogene laherparepvec was well tolerated after intratumoral injection up to a dose

level of $5x10^6$ PFU in tumour-bearing animals under conditions allowing viral replication as anticipated in patients, as well as after subcutaneous administration in tumour-free mice up to a dose level of 10^7 PFU. Signs of systemic toxicity were not observed. Generally, the findings that were observed were reversible. Deaths of mice that were reported in the toxicology studies were determined not to be related to treatment with talimogene laherparepvec.

In accordance with ICH S6(R1) guideline, genotoxicity studies were not conducted. Talimogene laherparepvec is a genetically-modified HSV-1 virus, which is an enveloped, double-stranded DNA virus that forms stable, circular episomes and does not integrate with host DNA. Review of the published literature showed no evidence that HSV-1 viruses interact with host DNA or cause genotoxicity or mutagenesis. The genotoxic potential of talimogene laherparepvec has not been evaluated in long-term animal or human studies. Because wild-type HSV-1 does not integrate into the host genome, the risk of insertional mutagenesis with talimogene laherparepvec is negligible (SmPC section 5.3).

In accordance with the ICH S9 guideline, no carcinogenicity studies have been conducted. The carcinogenic potential for an HSV-1-based therapy was evaluated by review of the available epidemiological data. In addition, because talimogene laherparepvec is genetically modified so as to reduce efficient replication in normal cells, any inherent risk of carcinogenesis associated with treatment is anticipated to be reduced as compared to wild-type HSV-1. Given the extensive human exposure to HSV-1, and in view of the mechanism of action of talimogene laherparepvec, it is considered highly unlikely that talimogene laherparepvec will induce tumour development or proliferation. The carcinogenic potential of talimogene laherparepvec has not been evaluated in long-term animal or human studies. However, available data for talimogene laherparepvec and wild-type HSV-1 do not indicate a carcinogenic risk in humans (SmPC section 5.3).

No significant adverse effects on maternal functions or on the foetus were observed in the embryo-foetal developmental toxicity study conducted in mice. Viral DNA was detected in foetal blood representing less than 0.001% of the concurrent maternal blood viral DNA concentration suggesting that talimogene laherparepvec is capable of crossing the placental barrier. Placental transfer was evaluated in an embryo-foetal developmental toxicity study. Viral DNA was detected in one pooled foetal blood sample from the high dose group ($1x10^7$ PFU) at low concentrations representing less than 0.001% of the concurrent maternal blood viral DNA concentration. These data suggest that talimogene laherparepvec is capable of crossing the placental barrier. A warning on the risk of placental transfer in pregnant women has been included in section 4.6 of the SmPC.

There were no impacts to male or female reproductive tissues following treatment of adult mice at doses up to 4×10^8 PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). No effects on embryo-foetal development were observed when talimogene laherparepvec was administered during organogenesis to pregnant mice at doses up to 4×10^8 (400 million) PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). Negligible amounts (< 0.001% of maternal blood levels) of talimogene laherparepvec DNA were found in foetal blood (SmPC section 5.3).

Various local injection site reactions consistent with local irritation and development of an immune response from the repeated subcutaneous injections, such as cellulitis and inflammation, fasciitis and fibrosis, dermatitis and myositis/myopathy were observed. Across these studies, local injection site reactions were either absent at the end of the recovery period, or demonstrated resolution or healing.

The tolerability of repeated intratumoral injections of talimogene laherparepvec was evaluated in two immunocompromised mice strains, the BALB/c nude mice and the SCID mice. Talimogene laherparepvec was injected into various xenograft tumours at doses up to 2×10^8 PFU/kg (30-fold over

the highest proposed clinical dose) in immunodeficient mice (nude and SCID). Lethal systemic viral infection was observed in up to 20% of nude mice (primarily deficient in T lymphocyte function) and 100% of SCID mice (devoid of both T and B lymphocytes). Across studies, fatal disseminated viral infection was observed in 14% of nude mice following treatment with talimogene laherparepvec at doses that are 10 to 100-fold higher than those that result in 100% lethality with wild-type HSV-1 (SmPC section 5.3). Talimogene laherparepvec infected cells were sensitive to acyclovir treatment. Based on the non-clinical data, disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) has been identified as an important identified risk in the RMP. Severely immunocompromised patients are contraindicated in the SmPC (SmPC section 4.3).

The assessment of the ERA concluded that the most likely mechanism of exposure of talimogene laherparepvec in the environment would be accidental exposures, such as needle-stick injuries to the healthcare personnel, during the administration of the product. The transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) has been identified as an important potential risk. The proposed Summary of Product Characteristics (SmPC) will communicate the risks of shedding and transmission to the prescribing physicians (section 4.4, 4.8 and 6.6). In addition, there will also be educational materials to communicate risk and precautions to HCP and patients as part of the RMP. The handling of the product is also adequately described in the SmPC (section 6.6) where there is a recommendation to follow local institutional guidelines for handling and administration, personal protective equipment, accidental spills and waste disposal.

- To wear protective gown or laboratory coat, safety glasses or face shield and gloves while preparing or administering Imlygic. Cover any exposed wounds before administering. Avoid contact with skin, eyes or mucous membranes.
- After administration, change gloves prior to applying occlusive dressings to injected lesions. Wipe the exterior of occlusive dressing with an alcohol wipe. It is recommended to keep injection sites covered with airtight and watertight dressings at all times, if possible. To minimize the risk of viral transmission, patients should keep their injection site covered for at least 8 days from the last treatment or longer if the injection site is weeping or oozing. Advise patients to apply dressing as instructed by the healthcare professional and to replace the dressing if it falls off.
- To dispose of all materials that have come in contact with Imlygic (e.g. vial, syringe, needle, any cotton or gauze) in accordance with local institutional procedures.

<u>Accidental exposure</u>

- In the event of an accidental occupational exposure to Imlygic (e.g. through a splash to the eyes or mucous membranes) during preparation or administration, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the affected area thoroughly with soap and water and/or disinfectant.
- To treat all Imlygic spills with a virucidal agent and absorbent materials.
- To advise patients to place used dressings and cleaning materials in a sealed plastic bag as they may be potentially contaminated, and to dispose of the bag in household waste.

This medicine contains genetically modified organisms. Unused medicine must be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

The potential for exposure from the environment at the site of administration is considered negligible. Thus, the overall risk posed by talimogene laherparepvec for human health (to the unintended recipient) and for the environment is considered low.

The CHMP endorse the CAT discussion on the non clinical aspects as described above.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for talimogene laherparepvec, were considered adequate and acceptable for the assessment of non-clinical aspects.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

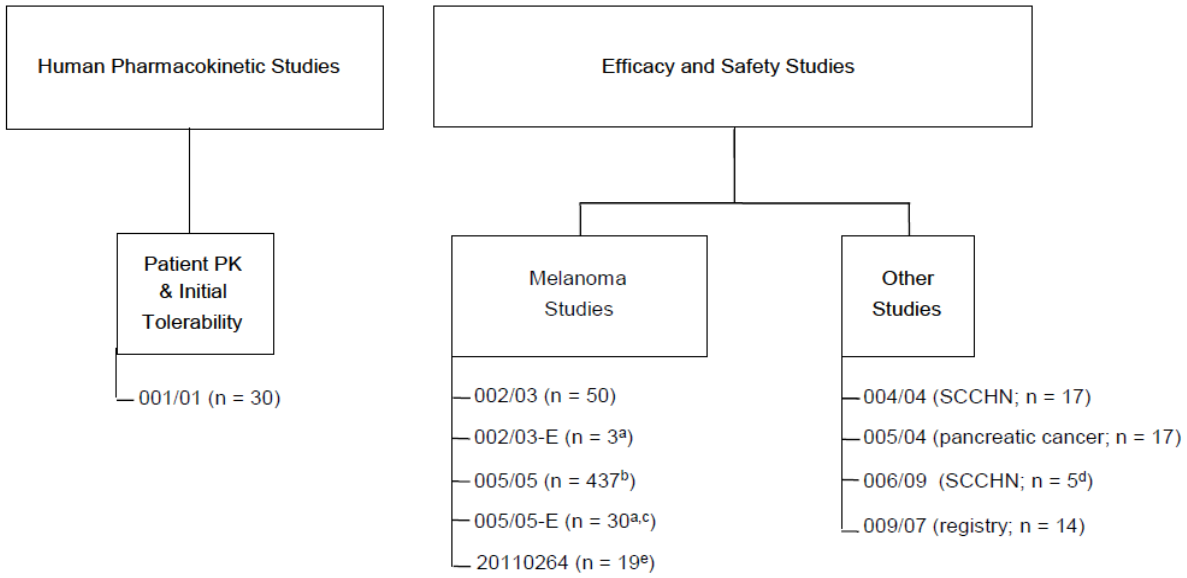
- Tabular overview of clinical studies

Table 13: Tabular overview of efficacy studies

Study Number	Study Design	Study Population	Primary and Secondary Efficacy Endpoints	Region	Number of Subjects	Duration of Treatment
005/05	Phase 3, randomized, open-label, GM-CSF controlled	Unresectable stage IIIB, IIIC, or IV melanoma	Durable response rate[a] Overall survival Best overall response and disease burden Response onset Time to treatment failure Duration of response Response interval	US, Canada, South Africa, and UK	436 (ITT)[b]; 295 talimogene laherparepvec 141 GM-CSF	12 months (or 18 months if the subject was receiving clinical benefit)
005/05-E	Phase 3, open-label extension	Unresectable stage IIIB, IIIC, or IV melanoma	Overall response rate Durable response rate	US, Canada, South Africa, and UK	30; 27 talimogene laherparepvec 3 GM-CSF	12 additional months (or until disease progression if the subject was receiving clinical benefit)
002/03	Phase 2, open-label, single-arm	Unresectable stage IIIC or IV melanoma	Overall response rate[a] Time to tumor response Time to disease progression Overall survival	US and UK	50	Up to 47 weeks
002/03-E	Phase 2, open-label, single-arm extension	Unresectable stage IIIC or IV melanoma	Overall response rate Overall survival	US and UK	3	Up to 24 additional doses or 12 months of additional treatment, whichever was longer

[a]Primary endpoint
[b]A total of 437 subjects were randomized; 1 subject who was randomized 3 times at 3 different study centers was excluded from the ITT population.

Figure 8: Tabular overview of studies with PK endpoints



PK = pharmacokinetics; SCCHN = squamous cell carcinoma of the head and neck
[a] Reflects a subset of subjects enrolled in the principal study
[b] Talimogene laherparepvec: n = 296; granulocyte macrophage colony-stimulating factor: n = 141. Includes one subject who was randomized 3 times (at 3 different sites). The subject ultimately received talimogene laherparepvec and was included in the safety analyses, but excluded from the intent-to-treat analyses.
[c] Talimogene laherparepvec: n = 27; granulocyte macrophage colony-stimulating factor: n = 3.
[d] Talimogene laherparepvec + chemoradiation: n = 2; chemoradiation only: n = 3
[e] Reflects enrollment at data cutoff. Data from nine subjects in Ph 1b portion are summarized separately.

2.4.2. Pharmacokinetics

No traditional pharmacokinetic studies were performed with talimogene laherparepvec. The clinical pharmacology program was focused on the assessment of the viral clearance of talimogene laherparepvec by analysing the biodistribution in the blood and urine, and viral shedding of the infectious virus (from the surface of injected tumour(s) and the exterior occlusive dressing).

Absorption

The applicant did not submit absorption studies (see clinical pharmacology discussion).

Distribution

The biodistribution in the blood and urine was studied in clinical studies 001/01 (as one of the primary objectives), 002/03 (one of the secondary objective), 005/04 (one of the primary safety objective) and in additional supportive clinical studies in patients with other cancer than melanoma (Study 004/04 and 005/04). The viral shedding from the surface of the injected tumours and dressings were assessed in clinical studies 001/01, 004/04 and 002/03 (changed during the study by the amendment that only herpetic lesions were swabbed). The "reactive" swabs (from herpes labialis or other non-injected lesions that arose during treatment, that were suspected to be herpetic in origin, and from injected

tumours that were oozing and weeping) were collected (in addition the above-mentioned studies) in the clinical study 005/05.

Study 001/01

This study was a first-in-human (FIH), 2-part, open-label evaluation of three dose levels of talimogene laherparepvec in subjects with at least one cutaneous or subcutaneous tumour of histologically proven breast adenocarcinoma, melanoma of the skin, or epithelial cancer of the head and neck, gastrointestinal (including pancreatic) cancer and vulval tumours refractory to conventional chemotherapy or for which no better therapy existed (N=30). The assessment of the biodistribution of the virus was one of the primary objectives.

In part 1, talimogene laherparepvec DNA was present in the blood and urine samples as follows: 3 (2.6%) of 117 blood samples were positive for talimogene laherparepvec DNA. Two seronegative subjects had blood samples positive at 1 or more time points and 2 different seronegative subjects had urine samples positive for virus DNA. Virus DNA was detected in the blood/urine samples between 8 hours and 1 week after administration. The number of virus genome copies was low in positive blood and urine samples; < 6.4 to 310 copies/0.1 µg DNA from blood, and < 6.4 to 47 copies/5 µl extracted urine. In part 2, talimogene laherparepvec DNA was only detected in blood samples after the higher doses (i.e. after 2nd and 3rd dose at dose level of 10^8 PFU/ml). Sixteen (i.e. 4.7%) of 340 blood samples were positive. Seven subjects had positive blood samples at 1 or more timepoints. The number of virus genome copies varied from 15 to 310 copies/0.1 µg DNA. No virus DNA was detected after 8 hours from administration indicating that the virus was cleared from the blood quickly. No talimogene laherparepvec DNA was found in the urine.

Study 002/03

This was a phase 2, open-label study to evaluate the efficacy, safety, and biodistribution of talimogene laherparepvec in patients with histologically proven Stage IIIC or IV melanoma that was not eligible for curative surgery. Of the 50 enrolled subjects, 46 and 49 subjects had samples collected for the detection of viral DNA in the blood and urine, respectively. 13 of 46 (28.3%) subjects had any positive blood samples and 10 of 49 (20.4%) subjects had positive urine samples.

Positive qPCR samples in pre dose samples.
Five subjects (12%; all seropositive) had positive blood samples and 2 of these had detectable viral levels above the limit of quantitation (ALQ > 51.2 copies/1 µg DNA; 141 and 182 copies/1 µg DNA, respectively). Six subjects had positive urine samples (13%; 56, 106, 87, 53, 80, and 94 copies/reaction). Three of the subjects were seronegative and 3 subjects were seropositive at baseline.

Positive qPCR samples after the 1st injection
Four subjects had 1 positive blood sample (one had viral DNA 1197 copies/1 µg DNA at 48 hours and 3 had viral DNA levels < 51.2 copies/1 µg = BLQ) collected between 1 and 48 hours after the 1st injection. One of these subjects was seronegative at baseline. One subject had positive urine sample at 24 h after the first injection. One subject had positive blood sample at 4 hours post dose and positive urine samples at pre dose (80 copies/reaction), 1, 4, 24, and 48 h post dose. Only the pre dose sample was ALQ. Three seropositive subjects had multiple positive blood samples. Only 1 pre dose sample was

ALQ (182 copies/ 1 µg DNA), all other had viral DNA levels BLQ. Three (2 seropositive and 1 seronegative) had multiple positive urine samples. One subject had 106 copies/reaction at pre dose, 129 copies/reaction at 24 h and 51.36 copies/reaction at 48 h after the 1st injection. Another subject had 6 positive samples; 4 of them having viral DNA ALQ (at pre dose: 87 copies/reaction, at 1 h: 62 copies/reaction, at 4 h: 82 copies/reaction, and at 48 h: 117 copies/reaction) after the 1st injection. The 2 positive samples were BLQ. One subject had 53 copies/reaction at pre dose and 1 positive sample BLQ at 48 h after the 1st injection. Two seropositive subjects had both positive blood and urine samples at multiple timepoints. One subject had positive blood samples at pre dose (BLQ), at 1 h (338 copies/1 µg DNA), at 4 h (124 copies/1 µg DNA), at 6 h (233 copies/1 µg DNA), at 24 h (BLQ) and at 48 h (114 copies/1 µg DNA) after the first injection. This subject had also positive urine samples at pre dose (56 copies/reaction), at 1 h (250 copies/reaction), at 4 h (2702 copies/reaction), at 6 h (203 copies/reaction), at 24 h (BLQ), and at 48 h (BLQ) after the first injection. Another subject had positive blood samples at pre dose (141 copies/1 µg DNA), at 1 h (BLQ), at 24 h (BLQ), and at 48 h (225 copies/1 µg DNA) and positive urine samples at 1 h (BLQ), and at 24 h (59 copies/reaction) after the first injection.

Positive qPCR samples after the 1st and subsequent injections
Two subjects had positive blood and urine samples after the 1st and after subsequent injections
One subject who received 10^8 PFU/ml instead of 10^6 PFU/ml as the first dose had the positive samples as follows:

- 1st injection- positive blood samples at 4 h (BLQ), at 6 h (BLQ), and at 48 h (75 copies/1 µg DNA) and one positive urine sample between 1 and 48 hours (76 copies/reaction).
- 2nd injection- positive blood samples at 1 h (268 copies/1 µg DNA), at 4 h (BLQ), and at 6 h (BLQ).
- 3rd injection- positive blood samples at 1 h (BLQ), at 4 h (BLQ), and at 6 h (BLQ).
- 4th injection- positive blood samples at 1 h (BLQ) and positive urine samples at pre dose (55 copies/reaction), at 4 h (BLQ) and at 24 h (BLQ).

Another subject had the following positive samples:

- 1st injection- positive urine samples at 1 h (BLQ) and at 48 h (BLQ).
- 2nd injection- positive blood samples at pre dose (BLQ), at 1 h (111 copies/1 µg DNA), at 4 h (81 copies/1 µg DNA), and 6 h (BLQ) and positive urine sample at 1 h (BLQ).
- 3rd injection- positive urine sample (186 copies/reaction) taken at the timepoint which was not recorded and it was not known if this was before or after dose 3.

Positive qPCR samples after subsequent doses only
One seropositive subject had 2 positive blood samples at 1 h (173 copies/1 µg DNA) and at 4 h (86 copies/1 µg DNA) after the 2nd injection and at 1 hour (88 copies/1 µg DNA) after the 3rd injection.

Positive samples at injections with no subsequent testing
Six subjects had positive qPCR samples after the 1st injection and subsequent testing was not done since these subjects were dosed after the Amendment 4 (subsequent testing was removed).
Eleven subjects did not have subsequent testing dose even though positive results were found at the previous injection (after the 1st injection for all, with the exception of 1 subject).

Study 005/04 (supportive study in patients with unresectable pancreatic cancer)
Seventeen subjects provided 130 blood samples and 16 subjects provided 111 urine samples. 5 subjects (29%) had positive blood samples and 7 subjects (44%) had positive urine samples. No

samples were positive before the first injection of talimogene laherparepvec. On week 0 (after the 1st administration), 4 of 17 subjects had positive blood sample results and 2 of 16 subjects had positive urine sample results. Three subjects had blood sample positive at 2 hours after the injection (< 12.8 copies/0.1 µg DNA, < 20.5 copies/0.1 µg DNA and < 25.6 copies/0.1 µg DNA) and 1 subject had blood sample positive at 24 hours after the injection (<14.6 copies/DNA). Two subjects had 2 positive urine samples each (2 and 24 hours [< 51.2 copies/reaction at both timepoints] and 12 and 24 hours [52.7 copies/reaction and < 51.2 copies/reaction], respectively). The positive blood and urine samples were observed after doses of 10^5 or 10^6 PFU/ml. On week 3 (after the 2nd administration), 1 of 11 subjects had a positive blood sample 2 hours after the injection (dose 10^6 PFU/ml; < 11.4 copies/0.1 µg DNA) and 2 of 11 subjects had positive urine samples 2 hours after the injection (a dose of 10^6 PFU/ml for one subject and 10^7 PFU/ml for another subject, < 51.2 copies/reaction for both subjects). On weeks 6 and 9, no positive blood or urine samples were determined. One subject who received extended treatment had positive urine samples after 5th and 6th injections (weeks 12 and 15, respectively). The amount of virus detected was < 51.2 copies/0.1 µg DNA for both urine samples.

Shedding

Study 001/01

Altogether 4 (13%)/30 subjects had swabs that were positive for the virus at the tumour site. One subject (in part 1, seronegative at baseline, first dose 10^7 PFU/ml) tested positive for the virus on 6 occasions between week 1: day 4 and week 2: day 6. The highest level of virus detected was > 600 PFU/swab at week 2: day 4. Another subject (in part 1, seronegative at baseline, first dose 10^7 PFU/ml) had virus detected in tumour swabs on 7 occasions between week 1: day 4 and week 2: day 3. The highest level of virus detected was > 600 PFU/swab at week 1: day 4 and 5. In addition, one subject in part 1 (seropositive at baseline, first dose 10^8 PFU/ml) and one subject in part 2 (seronegative at baseline, first dose 10^6 PFU/ml) had 1 occasion each. For the subject in part 1, the tumour swab at week 2: day 1 contained approx. 24 PFU/swab of virus and for the subject in part 2, the virus swab contained approx. 7.5 PFU/swab and the swab taken vesicle above the infected lesion contained approx. 2.5 PFU/swab. The positive samples were further tested to distinguish between talimogene laherparepvec and WT HSV. The virus detected in 3 of swab samples was talimogene laherparepvec. The identity of the 4th sample could not be confirmed due to the low levels of virus in the original swab. None of the swabs taken from the exterior of the dressing tested positive for live virus. No subject who had a starting dose of 10^6 PFU/ml had virus detected on the surface of tumours and viral shedding was not detected from any subject more than 2 weeks after dosing.

In the swabs taken for 4 subjects from other sites that the injected tumour (i.e. from an ulcer/tumour on the lower lip, from above sternum and left of injection site, from a cold score on the lip and on the cheek and a sample of breast aspirate) no virus was detected. Six subjects had non-injected lesions that were suspected to be herpetic. The swabs were taken from the lesions and analysed to determine if talimogene laherparepvec was present: five subjects had negative results and one subject, who had a lesion above the injected tumour, had positive result. Additional swabs were taken of this lesion and all swabs were negative for the presence of the virus.

Study 002/03

Only one subject had a positive viral plaque assay 24 hours after the first dose, but not at subsequent time points. A swab that was taken from a cold sore in a subject with oral herpes showed that the causative agent was WT HSV-1, not talimogene laherparepvec.

Three subjects had lesions that were suspected to be herpetic. Swabs of the lesions from 2 subjects were negative for virus. For the third subject (a history of developing cold sores) the swab taking of the cold sore indicated that the virus was WT HSV, not talimogene laherparepvec.

Study 004/04 (supportive study in patients with locally advanced epithelial cancer of the head and neck)
Three (18%) of 17 subjects had virus detected by swab analysis of the injection site following talimogene laherparepvec administration: One subject in cohort 2 at visit 0 (24 and 96 h post-injection), one subject in cohort 4 at visit 6 (48 hours post-injection) and end of study (24 hours post injection) and one subject in cohort 4 at visit 3 (24 hours post injection). Swabs taken from the dressings were negative for the presence of virus for all subjects at all timepoints.

Study 005/05
A total of 18 reactive swabs in 12 subjects were collected. Eleven of swabs were taken from a tumour that had been previously injected with talimogene laherparepvec, 4 swabs were taken from uninjected melanoma lesions, and 3 swabs were taken on other sites or site was unknown. All 18 samples tested were negative for live HSV in a plaque assay.

Ongoing clinical study in patients with melanoma (20120324)

The clinical study (20120324) in melanoma subjects is ongoing. Preliminary data (n =20 subjects) showed that talimogene laherparepvec DNA was detected in 36% samples of blood and 2% samples of urine. The proportion of samples with detectable talimogene laherparepvec DNA in blood and urine was highest during the second cycle. 17% of samples from occlusive dressing tested positive for talimogene laherparepvec DNA but none tested positive for presence of infective virus. Among samples of oral mucosa, only one sample had detectable talimogene laherparepvec DNA however the test for infectious virus was negative.

hGM-CSF

In 001/01 Study the hGM-CSF expression was measurable in the FNAs of injected tumours from 11 of the 13 samples tested. The level of hGM-CSF mRNA at the dose level of 10^7 PFU/ml was approx. > 1000-fold higher than that at the dose level of 10^6 PFU/ml. The amount of hGM-CSF mRNA at the dose levels of 10^7 PFU/ml and 10^8 PFU/Ml was similar. Seronegative subjects expressed hGM-CSF more than seropositive subjects. The hGM-CSF levels were below the limit of detection (15.4 pg/ml) of the ELISA assay in all serum samples. Three samples could not be analysed due to insufficient plasma sample availability.

Elimination

The applicant did not submit elimination studies (see clinical pharmacology discussion).

Dose proportionality and time dependencies

The applicant did not submit dose proportionality studies and time dependencies studies (see clinical pharmacology discussion).

Special populations

The applicant did not submit studies in special populations (see clinical pharmacology).

Pharmacokinetic interaction studies

The applicant did not submit pharmacokinetic interaction studies (see clinical pharmacology discussion).

Pharmacokinetics using human biomaterials

The applicant did not submit pharmacokinetics studies using human biomaterials (see clinical pharmacology discussion).

2.4.3. Pharmacodynamics

Mechanism of action

The applicant did not submit clinical studies on the mechanism of action (see clinical pharmacology discussion).

Primary and Secondary pharmacology

The applicant did not submit clinical studies on primary and secondary pharmacology (see clinical pharmacology discussion).

2.4.4. Discussion on clinical pharmacology

Talimogene laherparepvec is a genetically modified and replication-competent HSV-1 virus. Therefore, its pharmacokinetics and biodistribution are driven by the site of intralesional injection, tumour-selective replication and release from tumour tissue (SmPC section 5.2). Therefore, it is acceptable that no pharmacokinetic studies using talimogene laherparepvec have been conducted in the overall patient population and in special populations. No clinical studies have been conducted to evaluate the effect of hepatic or renal impairment on the pharmacokinetics of talimogene laherparepvec. However, no adjustment in dosage is necessary for patients with hepatic or renal impairment (SmPC section 4.2).

Cellular uptake of talimogene laherparepvec occurs through HSV-1 receptors on tumours and non-tumour cells following local injection into tumours. As talimogene laherparepvec is injected and replicates intratumourally, bioavailability and systemic concentration of talimogene laherparepvec are not predictive of drug substance activity and therefore have not been evaluated (SmPC section 5.2).

Talimogene laherparepvec is cleared through general host-defence mechanisms (e.g. autophagy, adaptive immune responses). Talimogene laherparepvec is degraded by typical endogenous protein and DNA catabolic pathways. As with other wild-type HSV-1 infections, a latent pool of talimogene laherparepvec DNA may persist in neuronal cell bodies innervating the injection sites; therefore, the occurrence of latent infection with talimogene laherparepvec cannot be excluded (SmPC section 5.2).

Biodistribution, viral replication and viral shedding were studied for the PK analyses. The studied doses of talimogene laherparepvec varied from 10^4 to 10^8 PFU/ml in the clinical studies and maximum total volumes/intratumoural injections/each administration were from 4 ml to 8 ml. No adjustment of the dose is required in patients ≥ 65 years old (SmPC section 5.1). The method of administration is described in the SmPC section 4.2.

Talimogene laherparepvec DNA was quantified with a highly sensitive and specific qPCR assay which may not correlate with viral infectivity risk. Talimogene laherparepvec was also quantified in selected patient samples in clinical studies using viral infectivity assays at the injection sites and in some cases of potential herpetic lesions (SmPC section 5.2).

There were low copy numbers of the viral DNA detected in blood (30% of subjects) and urine (20% of subjects) samples across the studies from 1 h to 1 week after intralesional injection. Blood and urine samples were negative by 2 weeks post-injection in those subjects for whom additional samples were available. Some evidence of a relationship between the detection of viral DNA in the blood and urine and HSV-1 serostatus was found in studies 001/01 and 005/04.The seronegative subjects who received doses higher than 10^6 PFU/ml were more likely to have viral DNA in the blood and urine than the seropositive subjects. The hGM-CSF mRNA expression was greater with the higher doses of talimogene laherparepvec i.e. 10^7 PFU/ml and 10^8 PFU/ml than with the dose of 10^6 PFU/ml. In addition, seronegative subjects appeared to express hGM-CSF more than seropositive subjects. Few patients had swabs that were positive for viral DNA at the tumour site and all swabs taken from the exterior of the dressing were negative across all studies. The longest time that talimogene laherparepvec DNA was detected in the injection site swabs was 2 weeks post-injection. Very limited data exist on shedding and biodistribution for talimogene laherparepvec after the intratumoural injection with the highest dose (i.e. 10^8 PFU/ml) and maximum volume (i.e. 4 ml/tumour). Thus, it was not possible to assess the correlation between distribution and virus shedding on the basis of the available data. Therefore, a post-authorisation study 20120324, which is a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma will provide further data and

has been included in the RMP as missing information (see RMP). The biodistribution and shedding of intralesionally administered talimogene laherparepvec are being investigated in a melanoma study. Interim results from 30 patients show that talimogene laherparepvec DNA was detected at transient and low concentrations in blood in 90% of patients and in urine in 20% of patients in the study. The proportion of patients with detectable talimogene laherparepvec DNA in blood and urine was highest during the second cycle. Talimogene laherparepvec DNA was detected in samples from injected lesions in approximately 90% of patients. However, only 14% of patients tested positive for infective virus by $TCID_{50}$ assay, all within 1 week after treatment administration. Live virus has not been detected from the exterior of occlusive dressing or in samples obtained from oro-labial region (SmPC section 5.3).

In the phase 3 melanoma clinical study, adverse events in the HSV infection category were reported in 5.5% (n=16) patients in the talimogene laherparepvec group in the phase 3 melanoma clinical study versus 1.6% (n = 2) in the GM-CSF group. 14 cases were reported as oral herpes and 1 case each was reported as herpes simplex and herpetic keratitis in the talimogene laherparepvec group. The symptomatic talimogene laherparepvec infection in non-tumour tissue has been included as an important potential risk in the RMP.

Symptomatic herpetic infection could also occur due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients. Clinical data investigating whether talimogene laherparepvec after being injected intratumorally could also distribute to the site of natural HSV-1 infection (mucosal tissues and neuronal sensory ganglia that innervate the infected dermatome) and

establish infection, latency and reactivation has been included as an important potential risk. The long term safety will be investigated as part of study 20120139, a registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec. Co-infection with talimogene laherparepvec and wild-type HSV-1 could potentially occur in patients; infection by talimogene laherparepvec or a febrile response due to talimogene laherparepvec infection could also stimulate the reactivation of latent HSV-1 in patients.

Since GM-CSF is being expressed at relative high levels in the context of an ongoing HSV-1 infection, the risk of braking tolerance to GM-CSF should be considered. As there are a rather large sequence homology between GM-CSF and G-CSF there is even a hypothetical (albeit unlikely) risk of cross-reactivity of anti GM-CSF antibodies with G-CSF should they arise. Patients treated with talimogene laherparepvec may use GM-CSF or G-CSF therapy at some later stage. Neutralizing GM-CSF antibodies have been described following GM-CSF therapy with Sargramostim or Molgramostim and may reduce effect such treatment. Talimogene Laherparepvec-mediated anti-GM-CSF Antibody Response is therefore considered an important potential risk in the RMP based on theoretical concerns as this event has not been reported in clinical trials.

The risk of recombination of talimogene laherparepvec with wild-type HSV-1 is also a theoretical risk which has not been investigated and has been included in the RMP as missing information.

2.4.5. Conclusions on clinical pharmacology

The pharmacology studies for the biodistribution and shedding of talimogene laherparepvec is considered adequate and acceptable for the authorisation of talimogene laherparepvec in the proposed indication in adult patients with melanoma.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5. Clinical efficacy

2.5.1. Dose response study

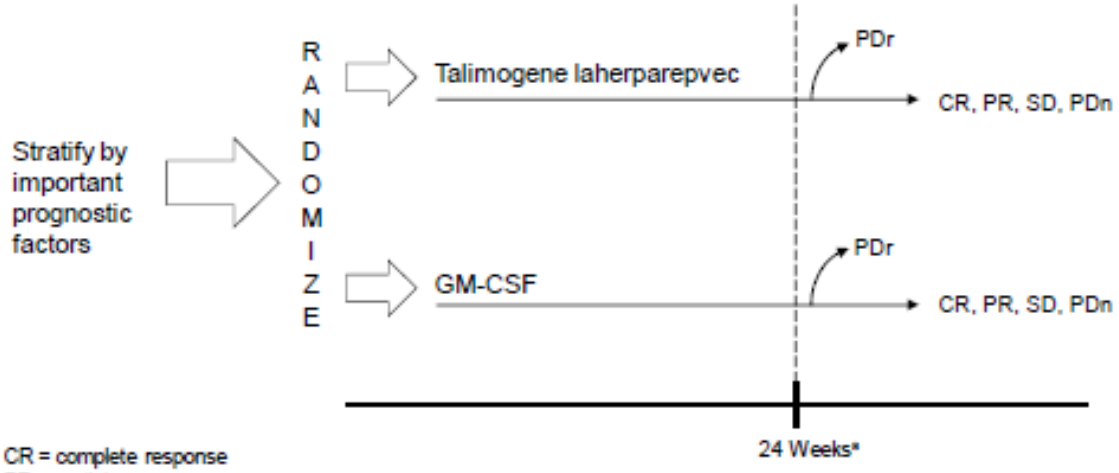
Study 001-01 was a phase 1, open-label, ascending-dose study of talimogene laherparepvec to evaluate single doses of 10^6 PFU/mL, 10^7 PFU/mL, and 10^8 PFU/mL (up to 4 mL) in 30 subjects with various solid tumours, including melanoma (part 1 of the study). Subjects who were HSV seronegative at study entry experienced more adverse events, consisting primarily of flu-like symptoms, than subjects who were HSV seropositive at study entry, particularly if given 10^7 PFU/mL (seronegative subjects were not given a first dose of 10^8 PFU/mL during the study as a result). Overall, all 11 (100%) seronegative subjects experienced an adverse event as did 18/19 (95%) seropositive subjects, with the following percentages for seronegative and seropositive subjects, respectively: pyrexia 10/11 subjects (91%) and 9/19 subjects (47%), anorexia 45% and 11%, vomiting 45% and 5%, injection site reactions 27% and 16%, lethargy 36% and 5%, influenza like illness 27% and 5%, headache and dyspnea 27% and 11%. However, these symptoms were mitigated in part 2 of the study using a dosing regimen that included an initial lower dose of 10^6 PFU/mL in all subjects followed by subsequent doses of 10^8 PFU/mL, regardless of HSV serostatus. Thus, an initial talimogene laherparepvec dose of 10^6 PFU/mL followed by subsequent doses of 10^8 PFU/mL was selected for the phase 2 and 3 studies.

2.5.2. Main study

Study 005/05: A randomized (ratio 2:1), controlled, open-label, multicenter, phase 3 study designed to evaluate the efficacy and safety of treatment with talimogene laherparepvec compared to subcutaneously administered GM-CSF in subjects with unresectable stage IIIB through stage IV M1c melanoma (N=436)

Methods

Figure 9: Study Design and Treatment Schema (Study 005/05)



CR = complete response
PR = partial response
SD = stable disease
PDr = clinically relevant disease progression
PDn = non-clinically relevant disease progression

* Subjects who do not experience PDr at 24 weeks will continue treatment for up to 18 months until response or criterion for withdrawal is met.

Study Participants

Key inclusion criteria

1. Age ≥ 18 years and histologically confirmed diagnosis of malignant melanoma.
2. Stage IIIb, IIIc or stage IV disease that is not surgically resectable.
3. Measurable disease defined as:
    - at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the greatest diameter is ≥ 10 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan for visceral or nodal/soft tissue disease (including lymph nodes) and/or;
    - at least 1 ≥ 10 mm superficial cutaneous melanoma lesion as measured by calipers and/or;
    - at least 1 ≥ 10 mm subcutaneous melanoma lesion and/or;
    - multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm.
4. Injectable disease (i.e. suitable for direct injection or through the use of ultrasound guidance) defined as: at least 1 injectable cutaneous, subcutaneous or nodal melanoma lesion ≥ 10 mm in

longest diameter or; multiple injectable melanoma lesions which in aggregate have a longest diameter of ≥ 10 mm.

5. Serum LDH levels ≤ 1.5 x ULN.
6. ECOG Performance Status of 0 or 1 and live expectancy > 4 months from the date of randomization.
7. Adequate organ function determined within 4 weeks prior to randomization, defined as: Absolute neutrophil count (ANC) ≥ 1500/mm3, Platelet count ≥ 100,000/mm^3, Haemoglobin ≥ 8 g/dL, Serum creatinine ≤ 1.5 x ULN, or 24-hour creatinine clearance ≥ 50 cc/min. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits.), Serum bilirubin ≤ 1.5 x ULN, Aspartate amino transferase (AST) ≤ 2.5 x ULN, Alanine amino transferase (ALT) <2.5 x ULN, Alkaline phosphatase (ALP) ≤ 2.5 x ULN, Serum albumin ≥ 2.5 g/dL, Prothrombin time (PT) ≤ 1.5 x ULN (or INR ≤ 1.3), Partial thromboplastin time (PTT) ≤ 1.5 x ULN (Prolongations in INR, PT, and PTT when the result was from therapeutic anticoagulation treatment were permitted for patients whose injectable lesions were cutaneous and/or subcutaneous such that direct pressure could be applied in the event of excessive bleeding).

Key exclusion criteria

1. Clinically active cerebral or any bone metastases. Patients with up to 3 (neurological performance status of 0) cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, gammaknife therapy, with no evidence of progression, and have not required steroids, for at least two (2) months prior to randomization.
2. Greater than 3 visceral metastases (this does not include lung metastases or nodal metastases associated with visceral organs). For patients with ≤ 3 visceral metastases, no lesion >3 cm, and liver lesions must meet RECIST criteria for SD for at least 1 month prior to randomization.
3. History of second cancer unless disease-free for >5 years. In the case of malignancies that are diagnosed at a stage where a definitive therapy results in near certain cure, a disease free interval of <5 years is permissible. The Medical Monitor must approve such patients.
4. Primary ocular or mucosal melanoma.
5. Evidence of immunosuppression for any reason (HIV, active hepatitis B or hepatitis C infection, chronic oral or systemic steroid medication use at a dose of >10mg/day of prednisone or equivalent, other signs or symptoms of clinical immune system suppression)
6. Baseline prolongation of QT/QTc interval (QTc interval >470 msec).
7. Open herpetic skin lesions.
8. Previous treatment with talimogene laherparepvec or treatment with GM-CSF for active disease (prior adjuvant therapy with GM-CSF is permitted).
9. Require intermittent or chronic treatment with an anti-herpetic drug (e.g., acyclovir), other than intermittent topical use.

Treatments

Subjects were randomized to receive either talimogene laherparepvec or GM-CSF in a 2:1 allocation.

Talimogene laherparepvec

Each treatment cycle of talimogene laherparepvec was defined as a treatment administered on Days 1 and 15 of each 28-day cycle. However, Cycle 1 was a 35-day cycle since the second injection was to occur on Day 22 instead of Day 15. The first dose of talimogene laherparepvec was at a concentration of 10^6 PFU/mL. Subsequent doses were at a concentration of 10^8 PFU/mL. If any injected lesion(s) progressed, the injection frequency was increased to once per week for 4 weeks into the progressing lesion(s) only. Up to three sets of four accelerated injections were given as long as after each set of four accelerated injections clinically relevant disease progression didn't occur and there was still residual tumour to inject.

All reasonably injectable lesions (cutaneous, subcutaneous and nodal disease, injected with or without ultrasound guidance) were injected up to the maximum dosing volume available on an individual dosing occasion, the largest injectable tumour on each dosing occasion being dosed first.

The dose (volume) delivered to the tumour(s) was dependent on the size of the tumour nodule(s) and was determined according to the following algorithm: up to 0.1 mL for tumours up to 0.5 cm longest dimension; up to 0.5 mL for tumours of 0.5 to 1.5 cm longest dimension; up to 1.0 mL for tumours of 1.5 to 2.5 cm longest dimension; up to 2.0 mL for tumours of 2.5 to 5 cm longest dimension; up to 4.0 mL for tumours >5 cm longest diameter. There was no minimum size for a tumour mass to be eligible for injection. In order to enrol patients with lesions larger than 10 cm in longest diameter, or with a total cumulative tumour burden in excess of 20 cm based on the sum of the longest diameters of individual lesions, prior approval was obtained from the Medical Monitor. The maximum volume injected into any individual lesion was 4 mL. The maximum dose on any one treatment day was to be 4 mL.

Previously uninjected lesions were to be injected if the initially injected lesions reduce in size such that there is a residual volume of talimogene laherparepvec available for injection. New lesions, newly measurable lesions and newly documented lesions which appeared during the course of the study which are injectable were also to be injected.

Dosing with talimogene laherparepvec was to be continued until: Complete remission was obtained (disappearance of all disease); all injectable tumours have disappeared; PDr (clinically relevant disease progression) after 24 weeks on study; twelve months on therapy was reached without any response up to that time; intolerable toxicity occurred defined as the need to stop study therapy due to treatment related adverse events; the investigator believed that it was in the best interest of the patient to stop investigational therapy or be given other therapy; the patient withdraws consent.

Patients who were in response at 12 months (PR or CR) should not have had an end of treatment visit until 18 months or PD (PDn, PDr, PDcns), whichever was the earlier. Patients who developed a new injectable lesion(s) within 12 months from the start date of treatment, but after all other injectable lesions have responded such that they were no longer injectable were eligible to restart treatment with talimogene laherparepvec.

No patient was to be dosed on more than 45 injection days, allowing for up to 18 months of dosing and the increased frequency of dosing if injected lesions progress.

<u>GM-CSF</u>

GM-CSF was administered SC at a dose of 125 μg/m^2/day. The first dose was administered at the study centre to monitor for any first-dose reactions (eg, flushing, faintness, dizziness, or weakness). GM-CSF was administered daily for 14 days followed by a 14-day rest period; this constituted one treatment cycle.

The GM-CSF dose was reduced by 50% if the following occurred: ANC exceeded 20,000 cells/mm^3 (if this level persisted despite the 50% dose reduction, GM-CSF was to be discontinued); platelet count exceeded 500,000/mm^3 (if this level persisted despite the 50% dose reduction, GM-CSF was to be discontinued); if these hematologic values decreased to levels below those indicated for 2 consecutive measurements, then the GM-CSF dose could be increased to 25% below the subject's original calculated dose for the remainder of the study.

Dosing with GM-CSF would continue until: PDr after 24 weeks on study (as defined in the protocol); twelve months on therapy is reached without any response up to that time; intolerable toxicity occurs defined as the need to stop study therapy due to treatment related adverse events; the investigator believes that it is in the best interest of the patient to stop investigational therapy or be given other therapy; the patient withdraws consent.

Prior or concomitant Therapies

Supportive therapy for the subject's cancer that was ongoing at the initiation of study treatment was permitted during the study. Other medications or supportive therapies were permitted at the investigator's discretion, except other investigational drugs, concurrent anti-tumour therapies other than radiation therapy required for palliation, oral or systemic steroids (with the exception of those used during treatment for central nervous system disease) and anti-herpetic drugs (other than in topically administered > 20 cm from a talimogene laherparepvec injection site).

Objectives

The objective of this study was to evaluate the efficacy and safety of treatment with talimogene laherparepvec compared to subcutaneously (SC) administered GM-CSF in patients with unresectable stage IIIB, IIIC and IV melanoma.

The primary objective was to evaluate the durable response rate (DRR).

The key secondary objectives included:

- to evaluate OS
- to analyse response onset
- to evaluate time to treatment failure
- to estimate duration of response
- to evaluate best response and disease burden.

The exploratory objectives were: to assess reported Quality of Life; to analyse the impact that having a response to therapy (ie, achieving a CR or PR) and a durable response to therapy (durable response rate, DRR) has on survival; analysis of treatment effects based on BRAF mutation status (if the information would be available).

Outcomes/endpoints

The primary endpoint was the durable response rate (DRR), defined as the rate of objective response (complete or partial response, defined by modified World Health Organization criteria as shown in Table 14 and Table 15) lasting continuously for 6 or more months until clinically relevant decline in PS or subsequent therapy is needed, and beginning at any point within 12 months of initiating therapy. For the first 24 weeks, treatment was to continue despite increases in tumour burden or appearance of

new lesions, unless clinical deterioration or subsequent therapy was required (PDr). An independent Endpoints Assessment Committee (EAC) confirmed response status for the purpose of primary efficacy analysis. The EAC's final conclusions with respect to response prevailed over those of Investigators. Additional analyses were performed using the investigator's assessments.

Table 14: Response assessment for measurable lesions (modified WHO criteria) - Study 005/05

Category	Definition
Complete response (CR)	Disappearance of all clinical evidence of tumour (both measurable and non-measurable but evaluable disease including any new tumours which might have appeared). Any residual cutaneous or sub-cutaneous masses must be documented by representative biopsy to not contain viable tumour.
Partial response (PR)	Achieving a 50% or greater reduction in the sum of the products of the perpendicular diameters of all measurable tumours at the time of assessment as compared to the sum of the products of the perpendicular diameters of all measurable tumours at baseline. If any new tumours have appeared, the sum of products of the perpendicular diameters of these must have reduced by 50% or more from when first documented. Any residual cutaneous or sub-cutaneous masses which must be tumour free for the patient to meet the criteria for PR must be documented as such by representative biopsy.
Stable disease (SD)	Neither sufficient overall tumour shrinkage to qualify for response (PR or CR) nor sufficient tumour increase to qualify for PD.
Progressive disease (PD)	A >25% increase in the sum of the products of the perpendicular diameters of all measurable tumours since baseline, or the unequivocal appearance of a new tumour since the last response assessment time point. There are three types of PD defined in this protocol: **Non-clinically relevant progressive disease (PDn):** PD in patients who do not suffer a decline in performance status and/or in the opinion of the investigator do not require alternative therapy. Patients showing PDn will be allowed to continue study treatment. **Clinically relevant progressive disease (PDr):** PD that is associated with a decline in performance status and/or in the opinion of the investigator the patient requires alternative therapy. Patients with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted. **CNS progressive disease (PDcns):** Progression in the central nervous system (brain)

Table 15: Response Assessment for Non-Measurable but Evaluable Disease - Study 005/05

Category	Definition
Complete Response (CR)	• Disappearance of all non-measurable but evaluable tumours.
Incomplete Response/Stable Disease (SD)	• Persistence of one or more non-measurable but evaluable tumour(s).
Progressive Disease (PD)	• Unequivocal appearance of one or more non-measurable but evaluable tumour.

The key secondary endpoints included the following:

- overall survival (OS), defined as the time from the date of randomization to the date of death from any cause (subjects were to be followed for OS for at least 36 months from the date the last patient was randomized or until the last study subject had died, whichever was earlier);
- objective response rate (ORR), defined as the best overall response observed across all time points (complete and partial response, defined by modified World Health Organization criteria);
- time to response defined as the time from the date of randomization to the date of the first documented evidence of response;
- duration of response, defined as the longest individual period from entering response (PR or CR) to the first documented evidence of the subject no longer meeting the criteria for being in response (progressive disease PDr) or the subject's death, whichever is earlier;
- time to treatment failure (TTF), calculated from baseline until the first PDr (ie, progressive disease associated with a reduction in performance status) where there was no response achieved after the PDr.

Exploratory endpoints included: the Quality of Life assessed with a standardized instrument, the Functional Assessment of Cancer Therapy - biologic response modifier (FACT-BRM, subjects were required to complete the questionnaire on Day 1 of each treatment cycle and at the EOT visit before they undergo any treatment-related study procedures including administration of investigational product); impact of durable response on survival; influence of *BRAF* mutation status.

Sample size

The study was multi-national and initially planned to be conducted in approximately 85 clinical study centres and was expected to randomize approximately 430 patients to provide 360 evaluable patients (240 talimogene laherparepvec, 120 GM-CSF).

It was assumed that the DRR in the control arm would be <10%. Using the intended sample size of 360 evaluable patients randomized 2:1 (talimogene laherparepvec: control), if a 3% response rate was achieved for the control arm, an increase to 13% in the talimogene laherparepvec arm would be able to be detected, and if an 8% response rate was achieved for the control arm, an increase to 21% in the talimogene laherparepvec arm would be able to be detected. These are both at 90% power for a two-sided test with 5% Type I error.

Randomisation

The randomization was a 2:1 allocation for talimogene laherparepvec versus GM-CSF, accordingly. Prior to randomization, patients were stratified on the basis of known prognostic factors: site of first recurrence (in transit vs. lymph node vs. visceral); liver metastases (yes vs. no); stage of disease (stage IIIB/C vs. stage IV M1a vs. stage IV M1b vs. stage IV M1c); prior nonsurgical melanoma treatment other than adjuvant therapy (no vs. yes and recurrence <1 year from primary diagnosis vs. yes and recurrence >1 year from primary diagnosis).

The Stage IV M1c patients were stratified and balanced across the two treatments groups and capped such that the percentage of Stage IV M1c patients in each treatment arm was to be no more than 40% of the total in that arm.

Blinding (masking)

Study 005/05 was an open-label study.

Statistical methods

The primary analysis of the primary endpoint and all response-based endpoints was to occur when no further subjects had the possibility of meeting the criteria for durable response or all subjects had reached 18 months after their first dose (whichever was earlier). Overall survival was a secondary endpoint, and was to be tested if statistical significance was demonstrated for DRR. The primary analysis of OS was to occur after 290 deaths had occurred, or at the time of the primary analysis of DRR, whichever was later. If less than 290 deaths had occurred at the time of the primary analysis of DRR, an interim analysis of OS was to be performed. A non-inferential analysis of OS at 3 years from the last subject's randomization was also to be performed.

Comparisons between treatment arms were performed using the intent-to-treat (ITT) population for the primary analysis (Table 16). Comparisons using the per-protocol population (or other clinically meaningful populations as noted) were performed as a sensitivity analysis.

Table 16: Analysis sets - Study 005/05

Analysis Set	Definition
Screened Population	All subjects who signed informed consent and participated in screening procedures at the investigative site to assess eligibility
Randomized Population/ Intent-to-treat Population	All subjects who were randomized once to study treatment
Safety Population	All randomized and treated subjects (subjects were excluded if they did not receive at least 1 dose of study treatment)
Per-protocol Population	All subjects who were randomized, eligible and treated, received at least 2 cycles of therapy and completed the assessment after 8 weeks (and at other time of termination for those who stay on study past 8 weeks), unless taken off therapy due to progression or due to safety issues before two cycles have been received

The primary analysis of the primary endpoint was performed using a two-sided unadjusted Fisher Exact test to determine whether talimogene laherparepvec improves the DRR relative to Control. The multivariate statistical analyses (secondary analyses including a logistic regression model) were tested for treatment effect while controlling for the potentially important prognostic factors (see results).

Study success was defined as the rejection of the null hypothesis of no difference when comparing talimogene laherparepvec vs. control at the interim or at the primary DRR analysis using the two-sided Fisher's Exact test for which the p-value is ≤ 0.0488 (0.05-0.0001*2-0.0005*2).

Two formal interim analyses were planned to assess aspects of both efficacy and safety. A Bonferroni alpha allocation was used for significance testing, for an overall 1-sided test of alpha = 0.025.

The first formal interim analysis was planned after the first 75 subjects had been on study for 9 months. This analysis assessed efficacy on the basis of both response rate (CR and PR) and DRR (CR and/or PR maintained for at least 6 months). This analysis also assessed safety. Interim data were

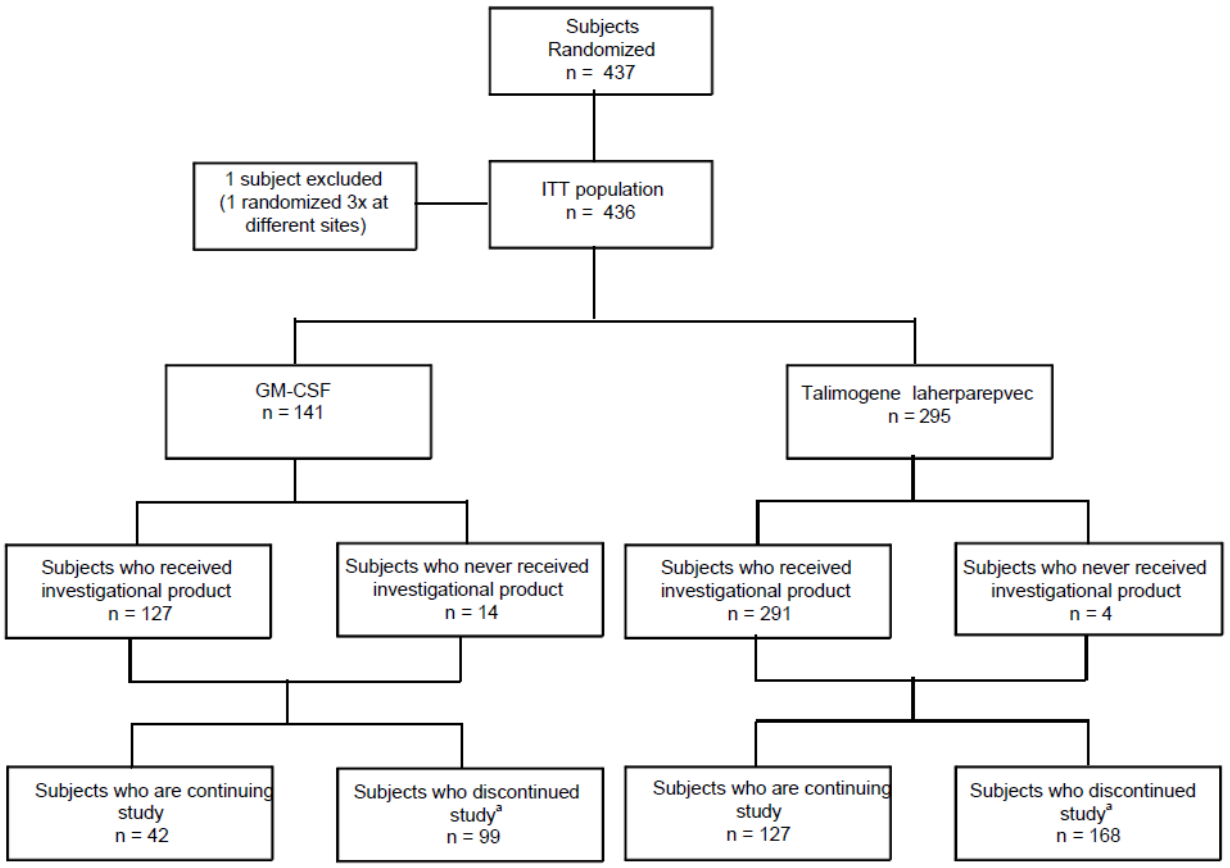
tabulated as of 10 September 2010. The DMC recommended that the study be allowed to continue since no safety concerns were raised, and the futility boundaries had not been crossed.

The second formal interim analysis was planned after all subjects were randomized and had been on study for at least 9 months from randomization. In addition, at least 42 durable responders were to have been identified by the EAC. Because a sufficient number of EAC assessments were not completed until less than 1 month before the cutoff date for the primary analysis, and the safety data had been recently reviewed, the DMC agreed to remove the second interim analysis. The SAP was amended to remove this interim analysis.

In addition, a planned interim safety analysis was performed by the DMC after the first 20 subjects who received 8 doses of talimogene laherparepvec in the phase 3 melanoma study to compare the safety profile of talimogene laherparepvec administered in Study 005/05 with that administered in Study 002/03. The DMC conducted a review of the treatment-emergent adverse events from these studies and in March 2010 concluded that the safety profile was generally similar to that observed in Study 002/03. The DMC recommended for the study to continue under the current protocol.

Results

Participant flow



Recruitment

The first subject was enrolled on 29th April 2009 and the last one on 08th June 2011. The patients were recruited from 64 centres in the US (382 subjects), Canada (7 subjects), South Africa (14 subjects), and United Kingdom (33 subjects).

Conduct of the study

The protocol for Study 005/05 was amended five times. A summary of the major changes for each amendment is provided in Table 17.

Table 17: Summary of Protocol Amendments - Study 005/05

Amendment	Major Changes
Original Protocol 02 October 2008 (0 subjects enrolled between this date and the date of the first amendment)	–
Amendment 1 15 October 2008 (61 subjects randomized between this date and the date of the next amendment)	• Measurable disease was further defined.
Amendment 2 17 November 2009 (35 subjects randomized between this date and the date of the next amendment)	• Subjects with previously untreated melanoma were allowed to enroll. • Permitted medications were updated to allow for oral and systemic steroid use. • Baseline brain MRI was included as a measure to assess disease status. • The use of liquid GM-CSF was added.
Amendment 2.01 04 February 2010 (114 subjects randomized between this date and the date of the next amendment)	• Preparation instructions for talimogene laherparepvec were updated for consistency with stability data.
Amendment 3 08 July 2010 (227 subjects randomized between this date and the date of the next amendment)	• Survival follow-up was increased from 2 years to 3 years from the time of randomization. • Subjects were allowed to continue to receive study treatment during corticosteroid therapy following stereotactic radiotherapy providing that the total daily dose did not exceed the equivalent of 10 mg prednisone. • Exclusion criteria were updated to allow subjects with a second cancer to enroll if they were diagnosed at a stage where definitive therapy results in near certain cure (with Medical Monitor approval). • Subjects with a total cumulative tumor burden in excess of 20 cm were allowed to enroll with Medical Monitor approval. • Injectable local anesthetic was allowed during talimogene laherparepvec administration, and procedures required during the 4-hour period after the first injection were clarified. • GM-CSF dosing modifications were clarified. • A photographic requirement for events of vitiligo was added.

Amendment	Major Changes
Amendment 4 30 November 2011 (all subjects already randomized)	• A secondary endpoint (the probability of being in response) was deemed to be of minimal benefit and was removed. • The ability to conduct an exploratory analysis of treatment effects based on BRAF status was added. • A window for the scheduling of scans and ultrasounds was added. • Response criteria were clarified. • Additional details were added regarding the statistical analyses.
Amendment 5 04 January 2013 (all subjects already randomized)	• The follow-up for survival was corrected for consistency between protocol sections. • The second formal interim analysis was removed due to the timing of the EAC reading process. • The timing of the primary analysis of the primary endpoint was clarified.

The SAP was originally approved on 28 September 2008 and amended on 30 November 2009, 21 June 2010, 30 November 2011 and 4 January 2013. All the four amendments were done prior to the primary analysis.

Baseline data

Baseline demographic and disease characteristics are summarised in Table 18 and Table 19, respectively.

Table 18: Key Baseline Demographics (ITT Population) - Study 005/05

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
Sex - n (%)			
Male	77 (54.6)	173 (58.6)	250 (57.3)
Female	64 (45.4)	122 (41.4)	186 (42.7)
Ethnicity - n (%)			
Hispanic or Latino	1 (0.7)	9 (3.1)	10 (2.3)
Not Hispanic or Latino	139 (98.6)	285 (96.6)	424 (97.2)
Missing	1 (0.7)	1 (0.3)	2 (0.5)
Race - n (%)			
White	138 (97.9)	289 (98.0)	427 (97.9)
Black	2 (1.4)	1 (0.3)	3 (0.7)
Asian	0 (0.0)	1 (0.3)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)	1 (0.2)
Other	1 (0.7)	3 (1.0)	4 (0.9)
Age (years)			
n	141	295	436
Mean	62.92	63.14	63.07
SD	14.13	13.67	13.80
Median	64.00	63.00	63.00
Q1, Q3	54.00, 74.00	54.00, 74.00	54.00, 74.00
Min, Max	26.0, 91.0	22.0, 94.0	22.0, 94.0
Age Group - n (%)			
< 55 years	36 (25.5)	80 (27.1)	116 (26.6)
≥ 55 years	105 (74.5)	215 (72.9)	320 (73.4)
< 65 years	72 (51.1)	152 (51.5)	224 (51.4)
≥ 65 years	69 (48.9)	143 (48.5)	212 (48.6)
< 75 years	109 (77.3)	229 (77.6)	338 (77.5)
≥ 75 years	32 (22.7)	66 (22.4)	98 (22.5)

	GM-CSF (N=141)	Imlygic (N = 295)	Total
US	122 (86.5%)	260 (88.1%)	382
Rest of world	19 (13.5%)	35 (11.9)	54

N = Number of subjects in the analysis set; SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile. Intent to treatment population includes all subjects that have been randomized. Subjects will be analysed using the randomized treatment.

Table 19: Key Baseline Disease Characteristics (ITT Population) - Study 005/05

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
ECOG performance status - n(%)			
0	97 (68.8)	209 (70.8)	306 (70.2)
1	32 (22.7)	82 (27.8)	114 (26.1)
Missing	12 (8.5)	4 (1.4)	16 (3.7)
Histogenetic classification at orginal diagnosis			
Histogenetic subtype - n(%)			
Superficial spreading melanoma	39 (27.7)	72 (24.4)	111 (25.5)
Lentigo maligna melanoma	3 (2.1)	11 (3.7)	14 (3.2)
Acral lentiginous melanoma	6 (4.3)	17 (5.8)	23 (5.3)
Nodular melanoma	39 (27.7)	76 (25.8)	115 (26.4)
Desmoplastic	1 (0.7)	10 (3.4)	11 (2.5)
Unclassifiable	38 (27.0)	99 (33.6)	137 (31.4)
Missing	15 (10.6)	10 (3.4)	25 (5.7)
Disease stage from CRF - n(%)			
Stage IIIb	12 (8.5)	22 (7.5)	34 (7.8)
Stage IIIc	31 (22.0)	66 (22.4)	97 (22.2)
Stage IV M1a	43 (30.5)	75 (25.4)	118 (27.1)
Stage IV M1b	26 (18.4)	64 (21.7)	90 (20.6)
Stage IV M1c	29 (20.6)	67 (22.7)	96 (22.0)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
LDH			
≤ ULN	124 (87.9)	266 (90.2)	390 (89.4)
>ULN	5 (3.5)	15 (5.1)	20 (4.6)
BRAF status			
Mutation	23 (16.3)	46 (15.6)	69 (15.8)
Wild-type	23 (16.3)	45 (15.3)	68 (15.6)
Unknown	5 (3.5)	9 (3.1)	14 (3.2)
Missing	90 (63.8)	195 (66.1)	285 (65.4)
HSV-1 status			
Negative	45 (31.9)	97 (32.9)	142 (32.6)
Positive	78 (55.3)	175 (59.3)	253 (58.0)
Unknown	18 (12.8)	23 (7.8)	41 (9.4)
Prior non-surgical procedures (CRF)			
Yes	89 (63.1)	202 (68.5)	291 (66.7)
No	36 (25.5)	80 (27.1)	116 (26.6)
Unknown	16 (11.3)	13 (4.4)	29 (6.7)
Line of therapy per IVRS			
First line	65 (46.1)	138 (46.8)	203 (46.6)
≥ Second line	76 (53.9)	157 (53.2)	233 (53.4)
Anatomic location of original disease[b] – n(%)			
Scalp, face, neck	26 (18.4)	59 (20.0)	85 (19.5)
Chest, back, abdomen, pelvis	34 (24.1)	72 (24.4)	106 (24.3)
Hand, arm	23 (16.3)	35 (11.9)	58 (13.3)
Leg, foot	43 (30.5)	107 (36.3)	150 (34.4)
Plantar	3 (2.1)	5 (1.7)	8 (1.8)

Subungual	0 (0.0)	0 (0.0)	0 (0.0)
Other	6 (4.3)	21 (7.1)	27 (6.2)
Unknown	2 (1.4)	6 (2.0)	8 (1.8)
Missing	10 (7.1)	3 (1.0)	13 (3.0)
Nodal status at original diagnosis - n(%)			
Uninvolved	49 (34.8)	118 (40.0)	167 (38.3)
Involved, single regional node	26 (18.4)	65 (22.0)	91 (20.9)
Involved, 2-3 regional nodes	14 (9.9)	32 (10.8)	46 (10.6)
Involved, ≥ 4 regional nodes	5 (3.5)	12 (4.1)	17 (3.9)
Unknown	37 (26.2)	65 (22.0)	102 (23.4)
Missing	10 (7.1)	3 (1.0)	13 (3.0)
Mitototic rate/mm^2 - n(%)			
≥ 5	28 (19.9)	65 (22.0)	93 (21.3)
< 5	35 (24.8)	69 (23.4)	104 (23.9)
Unknown	66 (46.8)	158 (53.6)	224 (51.4)
Missing	12 (8.5)	3 (1.0)	15 (3.4)
Breslow thickness - n(%)			
< 0.76mm	11 (7.8)	15 (5.1)	26 (6.0)
≥ 0.76mm and ≤ 1.5mm	31 (22.0)	58 (19.7)	89 (20.4)
> 1.5mm and ≤ 4mm	63 (44.7)	156 (52.9)	219 (50.2)
Unknown	24 (17.0)	63 (21.4)	87 (20.0)
Missing	12 (8.5)	3 (1.0)	15 (3.4)
Ulceration - n(%)			
Yes	39 (27.7)	99 (33.6)	138 (31.7)
No	55 (39.0)	110 (37.3)	165 (37.8)
Unknown	36 (25.5)	83 (28.1)	119 (27.3)
Missing	11 (7.8)	3 (1.0)	14 (3.2)
Time from initial diagnosis to first recurrence (years)			
n	107	229	336
Mean	1.95	2.12	2.07
SD	2.25	3.32	3.01
Median	1.10	0.87	0.91
Q1, Q3	0.46, 2.55	0.42, 2.24	0.43, 2.41
Min, Max	0.0, 11.4	0.0, 20.8	0.0, 20.8
Anatomic location of first recurrence[bc] – n(%)			
Surgical scar (local)	26 (18.4)	59 (20.0)	85 (19.5)
In-Transit/satellitosis	43 (30.5)	108 (36.6)	151 (34.6)
Regional lymph node(s)	31 (22.0)	85 (28.8)	116 (26.6)
Distant skin site	26 (18.4)	26 (8.8)	52 (11.9)
Distant lymph node(s)	7 (5.0)	20 (6.8)	27 (6.2)
Visceral	8 (5.7)	22 (7.5)	30 (6.9)
Other	10 (7.1)	27 (9.2)	37 (8.5)
Missing	14 (9.9)	16 (5.4)	30 (6.9)

Sites of disease[bd] - n(%)			
Skin	74 (52.5)	176 (59.7)	250 (57.3)
Brain	0 (0.0)	4 (1.4)	4 (0.9)
Lymph nodes	60 (42.6)	158 (53.6)	218 (50.0)
Lung	33 (23.4)	81 (27.5)	114 (26.1)
Liver	2 (1.4)	16 (5.4)	18 (4.1)
Soft tissue	66 (46.8)	151 (51.2)	217 (49.8)
Other visceral metastases	9 (6.4)	27 (9.2)	36 (8.3)
Other	31 (22.0)	58 (19.7)	89 (20.4)
Missing	11 (7.8)	3 (1.0)	14 (3.2)

[a] BMI = (weight in kg)/((height in cm/100)^2)
[b] The categories are not mutually exclusive.
[c] Not all subjects have recurrent disease.
[d] For the current sites of disease grouping: Skin = Skin; Brain = Brain; “Lymph Nodes” = Axillary Lymph Nodes, Cervical Lymph Nodes, Thoracic Lymph Nodes, Intra-Abdominal Lymph Nodes, and Inguinal Lymph Nodes; Lung = Lung; Liver = Liver; “Soft tissue” = Soft tissue of Arm, Soft Tissue of Leg, and Soft Tissue of Trunk/Back; “Other visceral metastases” = thyroid gland, heart/pericardium, gastrointestinal tract, pancreas, gallbladder, kidney, uterus, ovary, adrenal gland, and peritoneum; Other = "pleural effusion, ascites, Other".
Intent to treatment population includes all subjects that have been randomized. Subjects will be analyzed using the randomized treatment.
N = Number of subjects; SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile.
CRF=case report forms; ECOG=Eastern Cooperative Oncology group; GM-CSF=granulocyte macrophage colony-stimulating factor; HSV=herpes simplex type 1 virus; ITT=intention-to-treat; IVRS=interactive voice response system; LDH=lactate dehydrogenase; ULN=upper limit of the normal range

Table 20: Reasons for discontinuation of treatment - Study 005/05

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
Investigational product accounting			
Subjects who never received study treatment	14 (9.9)	4 (1.4)	18 (4.1)
Subjects who received study treatment	127 (90.1)	291 (98.6)	418 (95.9)
Subjects continuing study treatment[a]	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who discontinued study treatment[a]	127 (90.1)	291 (98.6)	418 (95.9)
Maximum allowed dose without PR/CR	9 (7.1)	26 (8.9)	35 (8.4)
PR or CR for at least 6 continuous months	0 (0.0)	42 (14.4)	42 (10.0)
Progressive disease	95 (74.8)	191 (65.6)	286 (68.4)
Adverse event	3 (2.4)	11 (3.8)	14 (3.3)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	3 (2.4)	5 (1.7)	8 (1.9)
Consent withdrawn	12 (9.4)	10 (3.4)	22 (5.3)
Physician decision	5 (3.9)	6 (2.1)	11 (2.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Study completion accounting			
Subjects continuing study	42 (29.8)	127 (43.1)	169 (38.8)
Subjects who discontinued study	99 (70.2)	168 (56.9)	267 (61.2)
Lost to follow-up	1 (1.0)	0 (0.0)	1 (0.4)
Deaths	86 (86.9)	164 (97.6)	250 (93.6)
Consent withdrawn	11 (11.1)	3 (1.8)	14 (5.2)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.0)	1 (0.6)	2 (0.7)

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
Actual follow -up time (months)[b]			
n	141	295	436
Mean	18.59	20.28	19.73
SD	11.09	10.83	10.93
Median	18.53	20.57	19.93
Q1, Q3	8.74, 26.84	10.91, 28.42	10.18, 28.22
Min, Max	0.0, 43.0	0.0, 44.3	0.0, 44.3

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[a] Subjects who discontinued/ continuing treatment from the protocol (005/05).
[b] Actual follow-up time for a subject is calculated from the randomization date to the death date if a subject has died or last known to be alive date if subject is alive.

Numbers analysed

Patient populations of the Study 005/05 are reported in Table 21.

Table 21: Analysis Sets - Study 005/05

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 296)	Total (N = 437)
Number of subjects randomized [a]	141	296	437
Intent to Treat (ITT) Population	141	295	436
EAC Evaluable Subjects	19	124	143
Safety Population	127	292	419
Per protocol Population	110	262	372

Page 1 of 1

[a] One subject was randomized three times. This subject is decided to be removed from ITT population and per protocol population. This subject will be included in the safety population based on the treatment received.
ITT population includes all subjects who have been randomized to receive study treatment.
EAC Evaluable Subjects includes all subjects who have been reviewed by EAC. These subjects have responded (PR/CR) or have been on therapy for 9 months without response according to investigators' judgment. Subjects are analyzed according to the treatment arms they were randomized.
Safety Population is defined as randomized subjects who have received at least one dose of study treatment.
The per protocol population is defined as all subjects who are randomized, eligible and treated, received at least 2 cycles of therapy and completed the assessment after 8 weeks, unless taken off therapy due to progression or due to safety issues before twocycles have been received. subjects with major protocol deviation will be excluded from this population.

Outcomes and estimation

Primary Efficacy Endpoint: Durable Response Rate (DRR)

Results in term of DRR per EAC (primary endpoint) and Investigator assessment are shown in Table 22. The minimum follow-up time, calculated from the date of the last randomization to the data cut-off date (21 Dec 2012), was 17.1 months.

Table 22: Summary of Durable Response Rate - Study 005/05

	EAC				Investigator			
	GM-CSF n (%)	Talimogene Laherparepvec n (%)	Unadjusted odds ratio[a] (95% CI), p-value[b]	p-value	GM-CSF n (%)	Talimogene Laherparepvec n (%)	Unadjusted odds ratio[a] (95% CI), p-value[b]	p-value
ITT population	3 (2.1)	48 (16.3)	8.9 (2.7, 29.2)	< 0.0001	2 (1.4)	56 (19.0)	16.3 (3.9, 67.8),	< 0.0001
Per-protocol population	2 (1.8)	44 (16.8)	10.9 (2.6, 45.8)	<0.0001	1 (0.9)	51 (19.5)	26.3 (3.6, 192.9)	<0.0001
Sensitivity analysis[c]	3 (2.1)	49 (16.6)	9.2 (2.8, 29.9)	<0.0001	-	-	-	-

CI = confidence interval; EAC = Endpoint Assessment Committee; GM-CSF = granulocyte macrophage colony-stimulating factor
[a] An odds ratio >1.0 indicates a higher durable response rate for talimogene laherparepvec relative to GM-CSF.
[b] Based on Fisher's exact test.
[c] The sensitivity analysis includes all available EAC data.

Key Secondary Efficacy Endpoints

The results of key secondary endpoints, including Overall survival (at the time of the primary OS analysis data cut-off: 31 March 2014), ORR, duration of response, response onset, and time to treatment failure are reported in Table 23.

Table 23: Summary of Key Secondary Efficacy Results (ITT Population) - Study 005/05

	GM-CSF (n = 141)	Talimogene laherparepvec (n = 295)
Overall response rate[a]		
% (95%, CI)	5.7 (1.9, 9.5)	26.4 (21.4, 31.5)
p-value[b]	< 0.0001	
CR, n (%)	1 (0.7)	32 (10.8)
PR, n (%)	7 (5.0)	46 (15.6)
Best tumor area ratio[c,d]		
Mean rank (Wilcoxon rank sum test)	164.61	141.69
p-value[b]	0.0351	
Duration of response (responders only)[a]		
Median, Months (95% CI)	2.8 (1.2, NE)	NE (NE)
Unstratified HR[e] (95% CI); p-value[b]	0.40 (0.14, 1.18); 0.087	
Kaplan-Meier estimate[f] - % (95% CI)		
At Month 3	46.9 (12.0, 76.3)	86.7 (76.7, 92.6)
At Month 6	46.9 (12.0, 76.3)	80.6 (69.3, 88.0)
At Month 9	46.9 (12.0, 76.3)	68.0 (54.9, 78.0)
At Month 12	46.9 (12.0, 76.3)	65.0 (51.1, 75.9)
Response onset (responders only)[a]		
Median, Months (95% CI)	3.7 (1.9, 5.6)	4.1 (3.8, 5.4)
Time to treatment failure[c]		
Median, months (95%CI)	2.9 (2.8, 4.0)	8.2 (6.5, 9.9)
HR[g] (95% CI); p-value[b]	0.42 (0.32, 0.54); < 0.0001	
Response Interval[c] (responders only)		
Median, months (95% CI)	7.5 (1.9, NE)	NE (NE)
HR[h] (95% CI); p-value[b]	0.30 (0.13, 0.73); 0.005	
OS		
Median OS, Months (95% CI)	18.9 (16.0, 23.7)	23.3 (19.5, 29.6)
HR[i] (95% CI); p-value[j]	0.79 (0.62, 1.00); p = 0.0511	
Kaplan-Meier estimate - % (95% CI)		
At month 12	69.1 (60.6, 76.2)	73.7 (68.3, 78.4)
At month 24	40.3 (32.0, 48.4)	49.8 (44.0, 55.4)
At month 36	30.1 (22.5, 38.0)	38.6 (33.0, 44.2)
At month 48	21.3 (13.7, 30.0)	32.6 (26.6, 38.7)

Overall survival

The Kaplan-Meier plot of the Overall Survival in provided on Figure 10.

Figure 10: Kaplan-Meier Plot for Primary Analysis of Overall Survival (ITT Population) - Study 005/05

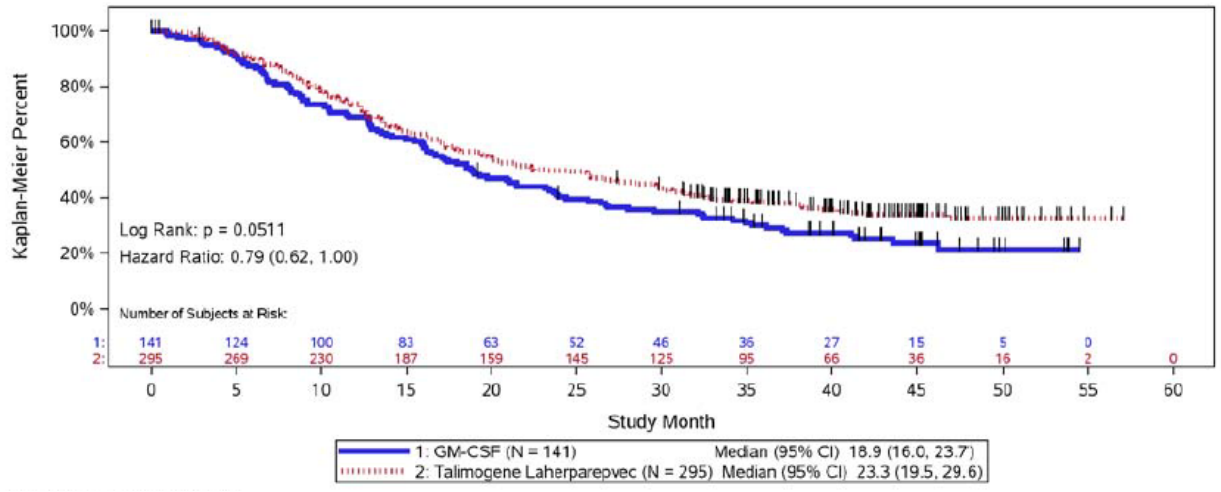


Table 24: Overall survival (primary and final analyses – ITT population) - Study 005/05

	Primary Analysis		Final Analysis	
	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)
Subject Status				
Deaths - n (%)	101 (71.6)	189 (64.1)	101 (71.6)	190 (64.4)
Censored[a] - n (%)	40 (28.4)	106 (35.9)	40 (28.4)	105 (35.6)
Time to Deaths (KM) (Months)[b]				
Median	18.9	23.3	18.9	23.3
95% CI (Median)	(16.0, 23.7)	(19.5, 29.6)	(16.0, 23.7)	(19.5, 29.6)
Unstratified log-rank test				
p-value	0.0511		0.0494	
Unstratified Hazard Ratio[c]	0.79		0.79	
(95% CI)	(0.62, 1.00)		(0.62, 1.00)	

Additional analyses on OS were performed by imputing the 5 patients with potential informative censoring. An updated analysis showed a HR=0.82 (95%CI 0.65, 1.05, p=0.1158) in the ITT population and a HR=0.61 (95%CI 0.43, 0.86, p=0.0039) for the subgroup of patients with stage IIIB, IIIC and IVM1a.

Further analyses showed that for the ITT population, the HR=0.85 (95% CI 0.66, 1.08, p=0.1780) was shown for inputing on the date that patients were censored and HR=0.85 (95% CI 0.67, 1.09, p=0.1999) for inputing when the censoring time was moved to the data cut-off date (31st March 2014). For the patients in stage IIIB,IIIC and IVM1a, a HR=0.63 (95%CI 0.45, 0.88, p=0.0070) and HR=0.64 (95%CI 0.45, 0.89, p=0.0086) was observed, respectively. A similar trend was observed for ≥2 lines vs 1st line.

Table 25: OS Sensitivity Analysis Imputing 5 Patients with Potential Informative Censoring Either as Having an Event at Censoring or Moving Their Censoring to the Data Cut-off after Vital Status Updates for 5 Other Patients

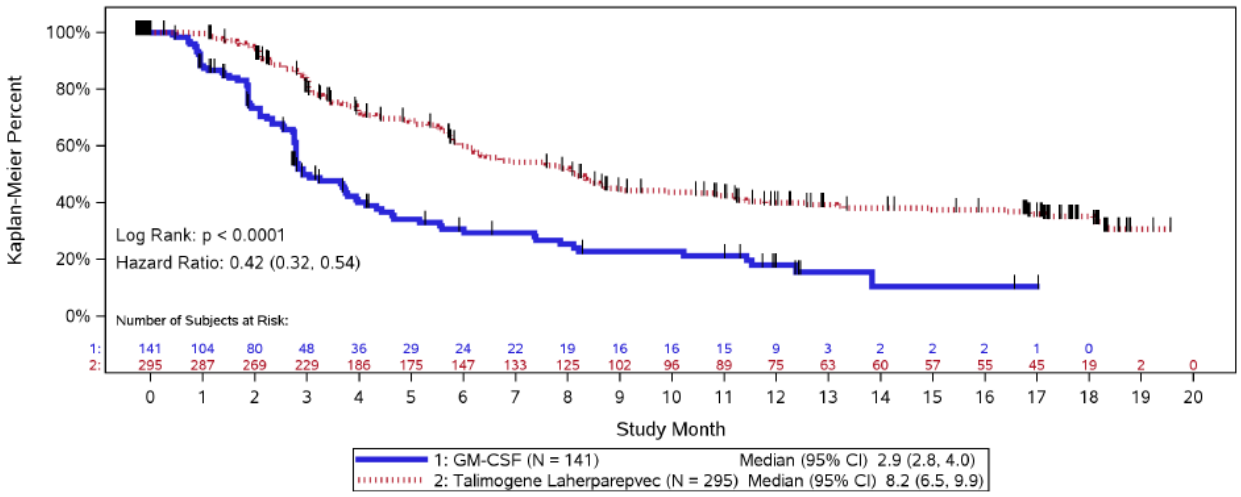
	Unadjusted Hazard Ratio (95% CI) log-rank P-value		
Population	Analysis with 5 Updates[a]	Event Imputed at Censoring[b]	Censoring Moved to DCO[c]
ITT	0.82 (0.65, 1.05) 0.1158	0.85 (0.66, 1.08) 0.1780	0.85 (0.67, 1.09) 0.1999
Stage IIIB-IVM1a	0.61 (0.43, 0.86) 0.0039	0.63 (0.45, 0.88) 0.0070	0.64 (0.45, 0.89) 0.0086
Stage IVM1b-c	1.07 (0.75, 1.52) 0.7094	1.09 (0.77, 1.55) 0.6341	1.11 (0.78, 1.57) 0.5703
1st-line	0.54 (0.38, 0.78) 0.0008	0.57 (0.39, 0.82) 0.0023	0.57 (0.39, 0.82) 0.0021
≥ 2nd-line	1.17 (0.84, 1.61) 0.3569	1.17 (0.85, 1.62) 0.3334	1.19 (0.86, 1.65) 0.2880

DCO, data cut-off date (31-Mar-2014). A Includes all patients, include the remaining 5 with potential informative censoring. One of the 5 updates included an event prior to the analysis data cut-off, therefore there are 291 events in the ITT population. B All 5 patients had an event imputed on the date they were censored, resulting in 296 event in the ITT population. Prior to analysis, events and censoring times after the 290th event were censored on the date of the 290th event to be consistent with the planned primary analysis after 290 events. C All 5 patients had their censoring time moved to the DCO date. Prior to analysis, events and censoring times after the 290th event were censored on the date of the 290th event.

Time to treatment failure

The time to treatment failure was calculated from randomisation until the first clinically relevant disease progression (PDr) where there was no response achieved after the progression, or until death if no such progression occurs. Subjects who did not have clinically relevant progression or did not die were censored at the time of their last tumour assessment. Subjects who withdrew from treatment due to a clinically unacceptable toxicity were not considered as an event in the analysis. In the ITT population, 59.6% patients in the GM-GSF group and 55.3% of subjects in the talimogene laherparepvec group experienced treatment failure. The Kaplan-Meier plot of the time to treatment failure is provided on Figure 11.

Figure 11: K-M plot for the time to treatment failure per investigator (ITT) - Study 005/05



Exploratory Analysis: Patient-reported Outcomes

The treatment estimate (95% CI) of the average change on trial outcome index (TOI) across all time points was -2.43 (-3.98, -0.87); p = 0.002. The difference was to be considered clinically meaningful if a decrease or increase of at least 5 points in TOI from baseline would be reported.

Exploratory Analysis: association between response and Overall Survival

Analyses were performed to explore the association between durable response and OS among subjects randomized to each separate treatment arm. Results are reported in Table 26.

Table 26: Overall Survival by Durable Response per Endpoint Assessment Committee, Talimogene Laherparepvec Arm (ITT Population) - Study 005/05

	Durable Responder (Yes)	Durable Responder (No)	Comparison (Yes vs. No)
Landmark analysis at 9 month			
Subject Status			
Deaths - n (%)	1 (5.0)	102 (47.7)	
Censored [a] - n (%)	19 (95.0)	112 (52.3)	
Unstratified log-rank test			
p-value			0.0011
Unstratified Hazard Ratio [b]			0.08
(95% CI)			(0.01, 0.56)
Landmark analysis at 12 month			
Subject Status			
Deaths - n (%)	1 (3.0)	77 (43.8)	
Censored [a] - n (%)	32 (97.0)	99 (56.3)	
Unstratified log-rank test			
p-value			<0.0001
Unstratified Hazard Ratio [b]			0.05
(95% CI)			(0.01, 0.39)
Landmark analysis at 18 month			
Subject Status			
Deaths - n (%)	2 (4.3)	32 (27.1)	
Censored [a] - n (%)	45 (95.7)	86 (72.9)	
Unstratified log-rank test			
p-value			0.0009
Unstratified Hazard Ratio [b]			0.13
(95% CI)			(0.03, 0.54)
Durable response as a time-dependent covariate in cox model			
Hazard Ratio			0.09
(95% CI)			(0.03, 0.29)

[a] Subjects that have not been recorded as dead are included as censored.
[b] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average death rate and a longer overall survival for durable responders. 95% CI Calculated from Cox regression model.
CI: Confidence Interval.
For time-dependent covariate cox model: Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause.
For landmark analysis : OS is defined as the time from the landmark time to the date of death from any cause.
ITT population includes all subjects who have been randomized to receive study treatment. Subjects will be analyzed using the randomized treatment.
Durable responders are defined as subjects with complete response (CR) or partial response (PR) maintained continuously for at least 6 months (183 days) from when an objective response was first observed and initiating at any point within 12 months of starting therapy.
Subjects who are off study before the fixed time are excluded from the analysis.

Similar analyses were conducted for the association between overall objective response and OS and results were generally similar to those for durable response (data not shown).

Exploratory Analysis: Incidence of Lesion Response

Among 2116 evaluable baseline or new individual lesions directly injected with talimogene laherparepvec, 1361 (64.3%) decreased in size by ≥ 50% and 995 (47.0%) completely resolved. A similar pattern was observed separately for baseline and new non-injected lesions (non-visceral and visceral).

Of 981 evaluable non-injected non-visceral lesions 331 (33.7%) decreased in size by ≥ 50%, the majority of which (212 [21.6%]) completely resolved. Of 177 evaluable visceral lesions, 27 (15.3%) decreased in size by ≥ 50%, the majority of which (16 [9.0%]) completely resolved.

There were 50 subjects in the Systemic Effects Analysis Set with 471 evaluable lesions that met the criteria for DR per investigator assessment, including 55 non-injected non-visceral lesions in 13 subjects.

Within this response category, 47 (85.5%) non-injected non-visceral lesions existing prior to the onset of DR decreased in size by ≥ 50%, including 45 lesions (81.8%) that completely resolved. All visceral lesions (n = 4 lesions in 3 subjects) existing prior to the onset of durable response in these subjects completely resolved. Similarly, there were 72 subjects with 745 evaluable lesions who met the criteria for OR per investigator assessment, including 65 non-injected, non-visceral lesions in 18 subjects.

Within this response category, 54 (83.1%) non-injected non-visceral lesions existing prior to the onset of OR decreased in size by ≥ 50%, including 50 lesions (76.9%) that completely resolved. Among 7 visceral lesions existing prior to the onset of OR in 6 subjects, 6 lesions (85.7%) completely resolved.

A reduction in size of ≥ 50% in at least 1 injected lesion, at least 1 non-injected / non visceral lesion, and at least 1 visceral lesion was seen in 75%, 52%, and 27% of subjects, respectively. For subjects in the DR and OR response subgroups as defined in the 005/05 Primary Analysis CSR, the proportion of subjects who experienced reductions in size of at least 1 evaluable lesion of each type was higher than the "All Subjects" group; more than 75% of subjects experienced a decrease of ≥ 50% in size of at least 1 evaluable lesion of any type, including visceral lesions.

There were 220 subjects evaluable for overall lesion-type burden including 56 (25.5%) who met the criteria for DR per investigator, and 85 (38.6%) who met the criteria for OR per investigator. Of these 220 subjects, 78 subjects (35.5%) had a ≥ 50% reduction in the total burden of all lesions.

Of the 79 subjects evaluable for overall lesion-type burden who had non-injected non-visceral disease, 27 subjects (34.2%) had a ≥ 50% reduction in the total burden of those non-injected non-visceral lesions. Of the 71 subjects evaluable for overall lesion-type burden who had with baseline or new visceral disease, there were 11 subjects (15.5%) with an OR, (including 2 subjects with CR and 6 subjects [8.5%] who met the criteria for DR). Eight subjects (11.3%) had a ≥ 50% reduction in the total burden of visceral lesions, of whom 6 had visceral disease at baseline.

Of the 56 subjects evaluable for overall lesion-type burden who had a durable response per investigator, 13 subjects (16.7%) had at least 1 non-injected non-visceral lesion at baseline and 5 subjects (7.9%) had at least 1 visceral lesion at baseline. Of the 85 subjects evaluable for overall lesion-type burden who had an objective response per investigator, 20 subjects (25.6%) had non-injected non-visceral lesions at baseline and 9 subjects (14.3%) had visceral lesions at baseline.

Ancillary analyses

The results of DRR (per EAC) in key subgroups are summarized in Table 27 and Figure 12.

Table 27: Summary of Key Subgroup Analyses for Durable Response Rate per Endpoint Assessment Committee (ITT Population) - Study 005/05

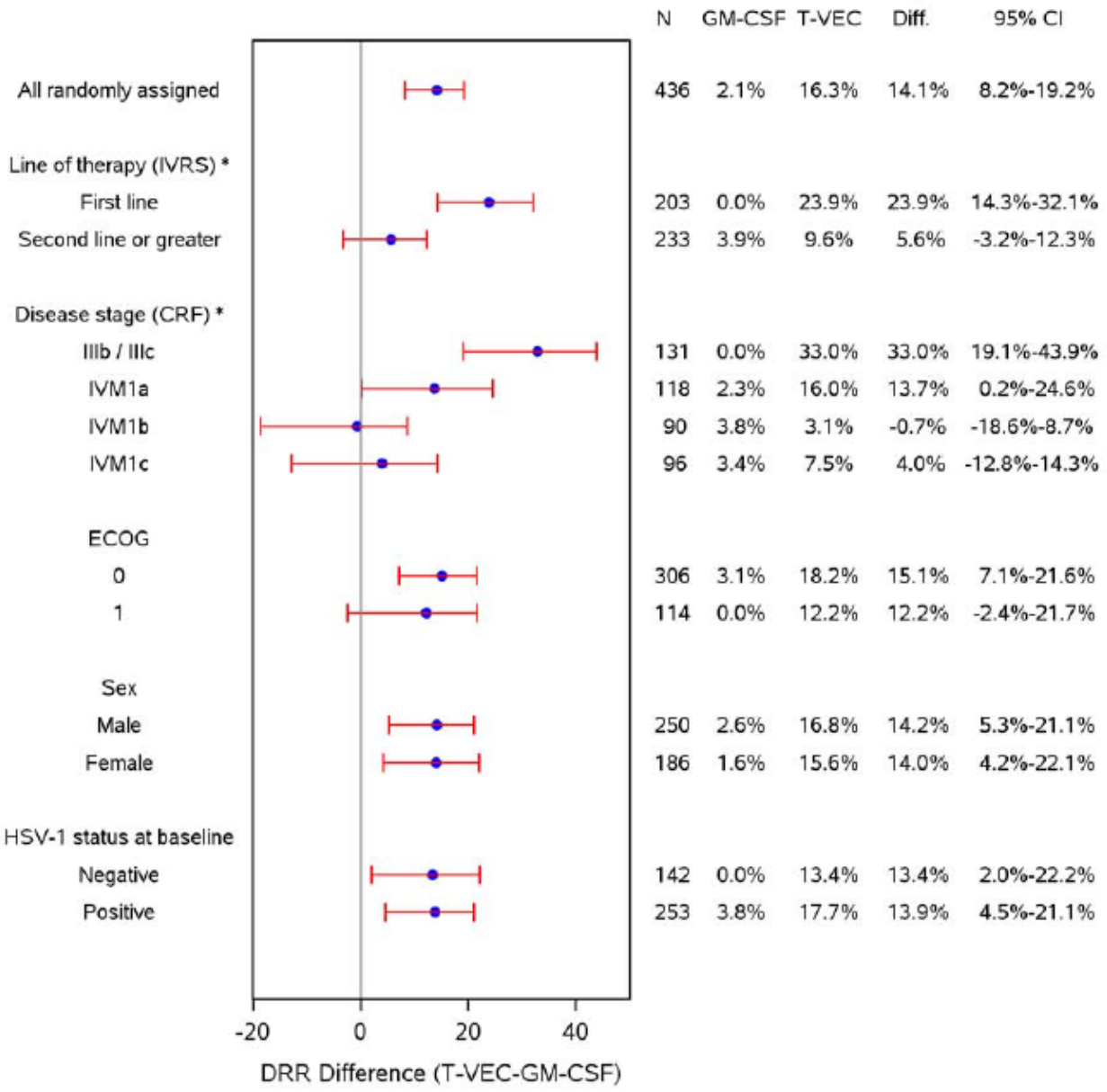
	GM-CSF (N=141) Events/ Subjects (%)	Talimogene Laherparepvec (N=295) Events/ Subjects (%)	Talimogene Laherparepvec/ GM-CSF Odds Ratio[a] (95% CI)	p-value
Line of therapy (IVRS)[b]				
First line	0/65 (0.0)	33/138 (23.9)	NE	<0.0001
Second line or greater	3/76 (3.9)	15/157 (9.6)	2.57 (0.72, 9.16)	0.1908
LDH				
≤ ULN	3/124 (2.4)	44/266 (16.5)	7.99 (2.43, 26.27)	<0.0001
>ULN	0/5 (0.0)	0/15 (0.0)	NE	NE
Disease stage (CRF)				
IIIb / IIIc	0/43 (0.0)	29/88 (33.0)	NE	<0.0001
IVM1a	1/43 (2.3)	12/75 (16.0)	8.00 (1.00, 63.82)	0.0299
IVM1b	1/26 (3.8)	2/64 (3.1)	0.81 (0.07, 9.30)	1.0000
IVM1c	1/29 (3.4)	5/67 (7.5)	2.26 (0.25, 20.23)	0.6643
Sex				
Male	2/77 (2.6)	29/173 (16.8)	7.55 (1.75, 32.50)	0.0014
Female	1/64 (1.6)	19/122 (15.6)	11.62 (1.52, 88.94)	0.0023
Age				
<50	1/22 (4.5)	5/45 (11.1)	2.62 (0.29, 23.95)	0.6551
≥ 50	2/119 (1.7)	43/250 (17.2)	12.15 (2.89, 51.07)	<0.0001
HSV-1 status at baseline				
Negative	0/45 (0.0)	13/97 (13.4)	NE	0.0095
Positive	3/78 (3.8)	31/175 (17.7)	5.38 (1.59, 18.18)	0.0023
Unknown	0/18 (0.0)	4/23 (17.4)	NE	0.1177

CI = confidence interval; EAC = Endpoint Assessment Committee; GM-CSF = granulocyte macrophage colony-stimulating factor; HSV-1 = herpes simplex virus, type 1; ITT = intent-to-treat; IVRS = interactive voice response system; LDH = lactate dehydrogenase; NE = not estimable ULN = upper limit of the normal range

[a] An odds ratio >1.0 indicates a higher durable response rate for Talimogene Laherparepvec relative to GM-CSF.

[b] randomization factors

Figure 12: Durable Response Rate per Endpoint Assessment Committee Key Stratification Factors and Covariates (ITT Population) - Study 005/05

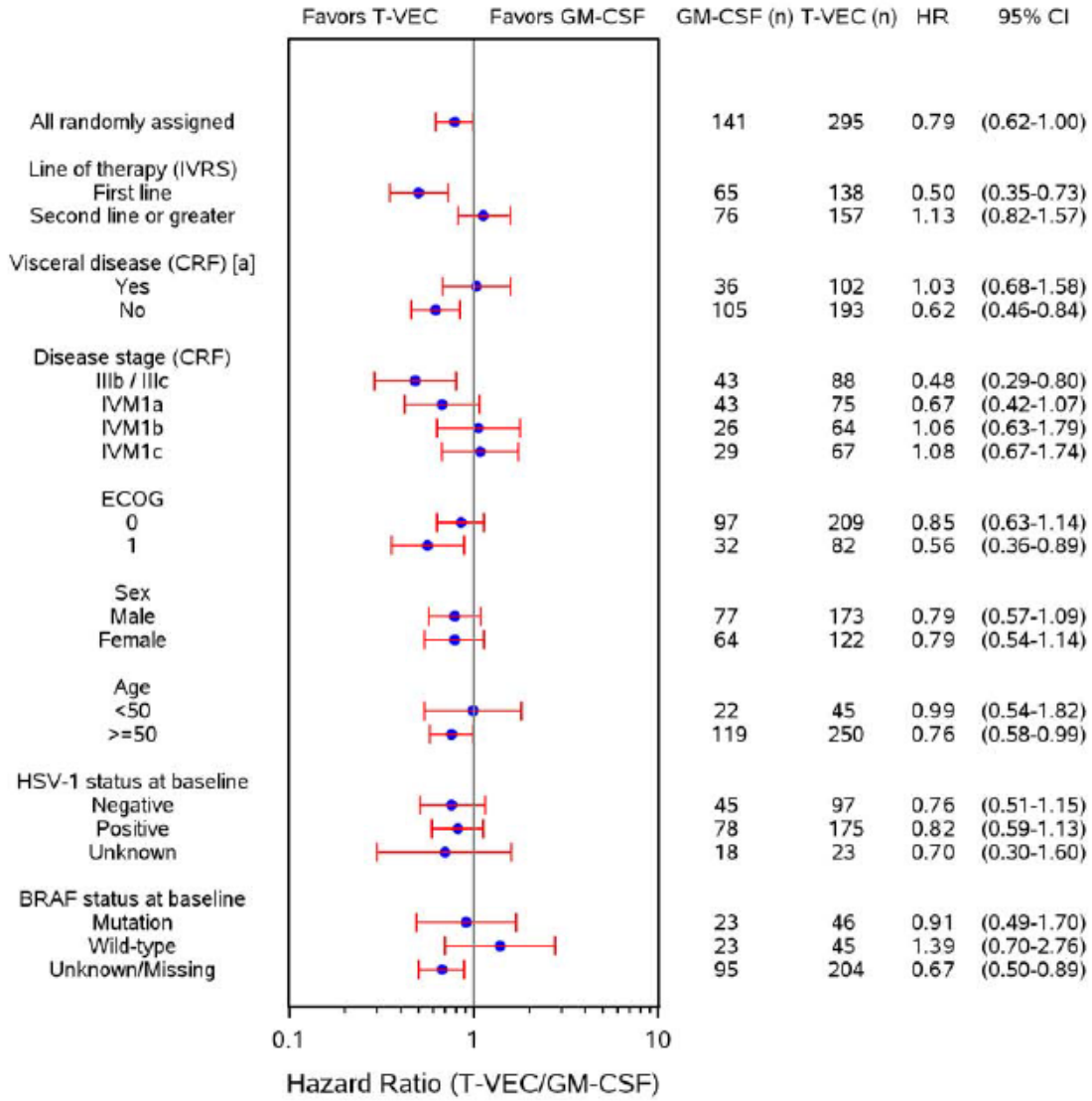


* Gail & Simon quantitative treatment by covariate interaction test P-value <= 0.05.
T-VEC=Talimogene Laherparepvec
ITT population includes all subjects who have been randomized to receive study treatment. Subjects will be analyzed using the randomized treatment.
Durable response rate (DRR) is defined as the percent of subjects with complete response (CR) or partial response (PR) maintained continuously for at least 6 months (183 days) from when an objective response was first observed and initiating at any point within 12 months of starting therapy. This reflects all new sites of disease as well as all disease sites identified at baseline. NE = not estimable.
The confidence interval is calculated using Wilson's score method with continuity correction.

In exploratory quantitative interaction tests, the magnitude of the estimated treatment effect on durable response was statistically significantly different across the 4 disease stage categories ($p < 0.0001$) or between the 2 grouped stage categories ($p < 0.0001$). The difference in effect on durable response was also statistically significantly different by line of therapy ($p = 0.0002$).

Treatment effect heterogeneity was examined using qualitative and quantitative treatment-by-covariate interaction tests. In an exploratory analysis, OS was analyzed for the ITT population at the time of the OS primary analysis within subgroups defined by randomization stratification factors and key covariates (clinically relevant subgroups defined by prognostic covariates displayed in Figure 13).

Figure 13: Hazard Ratio Plot with Log Scale - Overall Survival Hazard Ratio Key Stratification Factors and Covariates (ITT Population - Study 005/05



[a] If current sites of disease =brain/lung/liver/other visceral metastases , then visceral disease=Y. Otherwise visceral disease =N.
T-VEC=Talimogene Laherparepvec
Subjects that have not been recorded as dead are included as censored.
ITT population includes all subjects who have been randomized to receive study treatment. Subjects will be analyzed using the randomized treatment.
Overall survival is calculated as the number of months from randomization date to death date or last known to be alive date. One month = 365.25/12 days.

Although line of therapy was predictive, there was a strong correlation between line of therapy and disease stage, with a lower proportion of patients with stage IVM1b-c disease (33%) in the first-line population compared to the second-line or greater population (52%) (Chi-square $p < 0.0001$). Line of therapy was not retained as an independent predictor for durable response in a multivariate analysis considering disease stage ($p = 0.0763$). In addition, in an analysis of subjects with earlier stage disease (stage IIIB/C and stage IVM1a) receiving ≥ second-line therapy, talimogene laherparepvec was associated with an improvement in DRR (17% vs 2%) and objective response (28% vs 2%) relative to GM-CSF.

In an additional post-hoc landmark analysis, an association was observed between the achievement of a durable response and improvement in quality of life based on the Functional Assessment of Cancer Therapy – Biologic Response Modifier [FACT-BRM]), including the Trial Outcome Index (a composite of FACT-BRM subscale endpoints). In subjects with stage IIIB/C and stage IVM1a disease, achievement of a durable response per EAC was also associated with an improvement in the Trial Outcome Index (odds ratio 2.763; 95% CI: 1.018,7.797).

A further analysis was conducted to evaluate clinical outcomes in subjects who had a durable response per EAC. Of the 51 subjects with a durable response, all had a CR or PR per EAC ongoing at the time of the primary analysis. In addition, most subjects were still alive at the time of the most recent contact date (49 subjects were still alive after 3 years) and did not require subsequent systemic anti-cancer therapy during the follow-up period. In addition, long-term benefit was observed for subjects with a complete response in Study 005/05. In post-hoc landmark analyses of subjects receiving talimogene laherparepvec who had a complete response per investigator assessment, the probability of still being in complete response was 84% at 12 months, 75% at 24 months, and 72% at 36 months.

Post-hoc Analyses

Time to Subsequent Anticancer Therapy Use

When the analysis was limited to ipilimumab, vemurafenib, dabrafenib, or trametinib (Figure 14) or ipilimumab only (Figure 15), the median time to subsequent therapy was shorter in the GM-CSF arm in subjects with earlier stages of disease, no prior treatment, and lower than the median amount of total tumour burden.

Figure 14: Subsequent ipilimumab, vemurafenib, dabrafenib or trametinib – Study 005/05

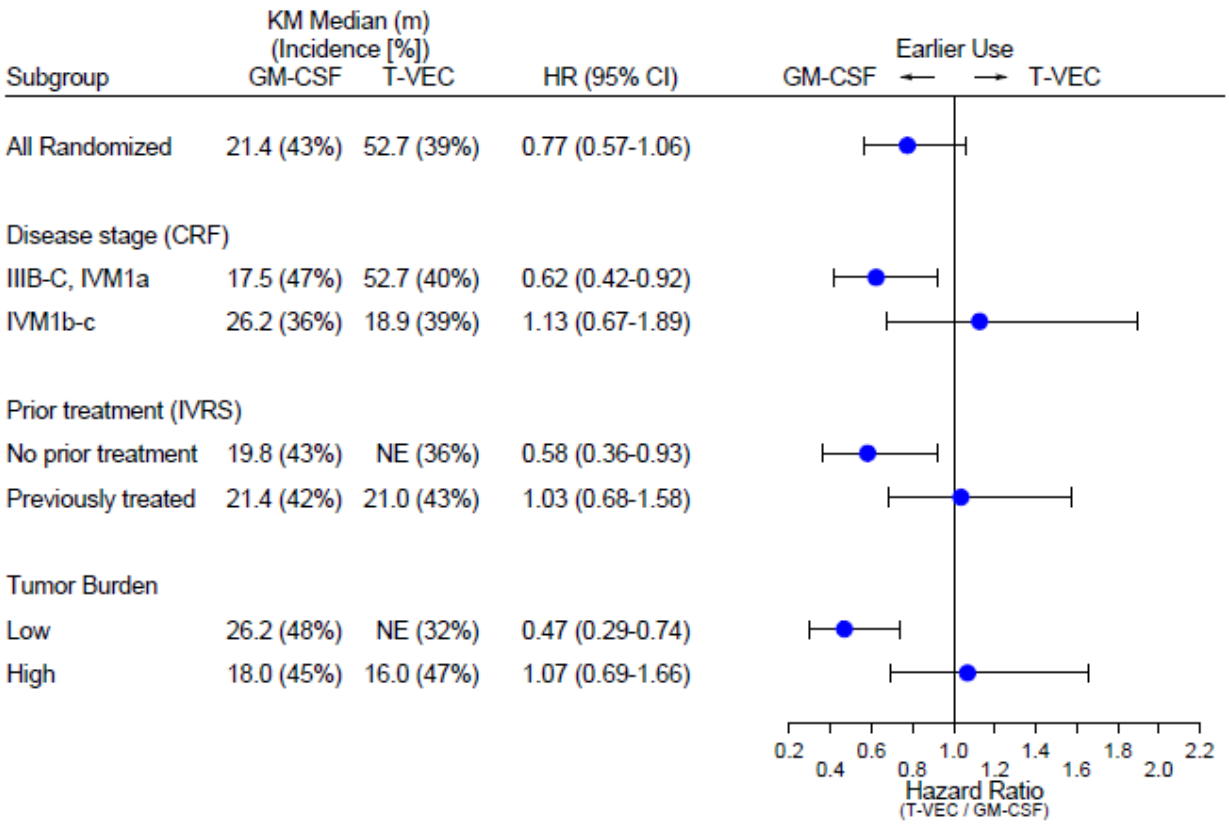
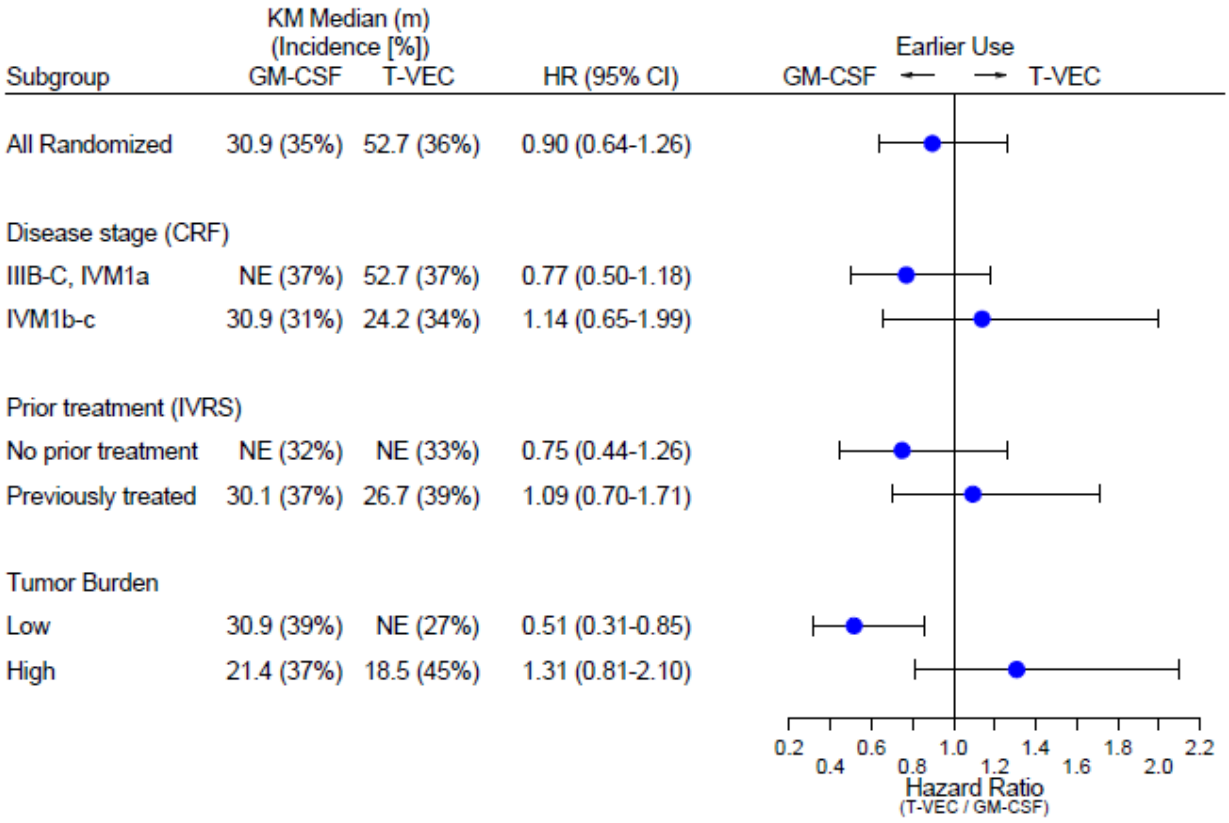


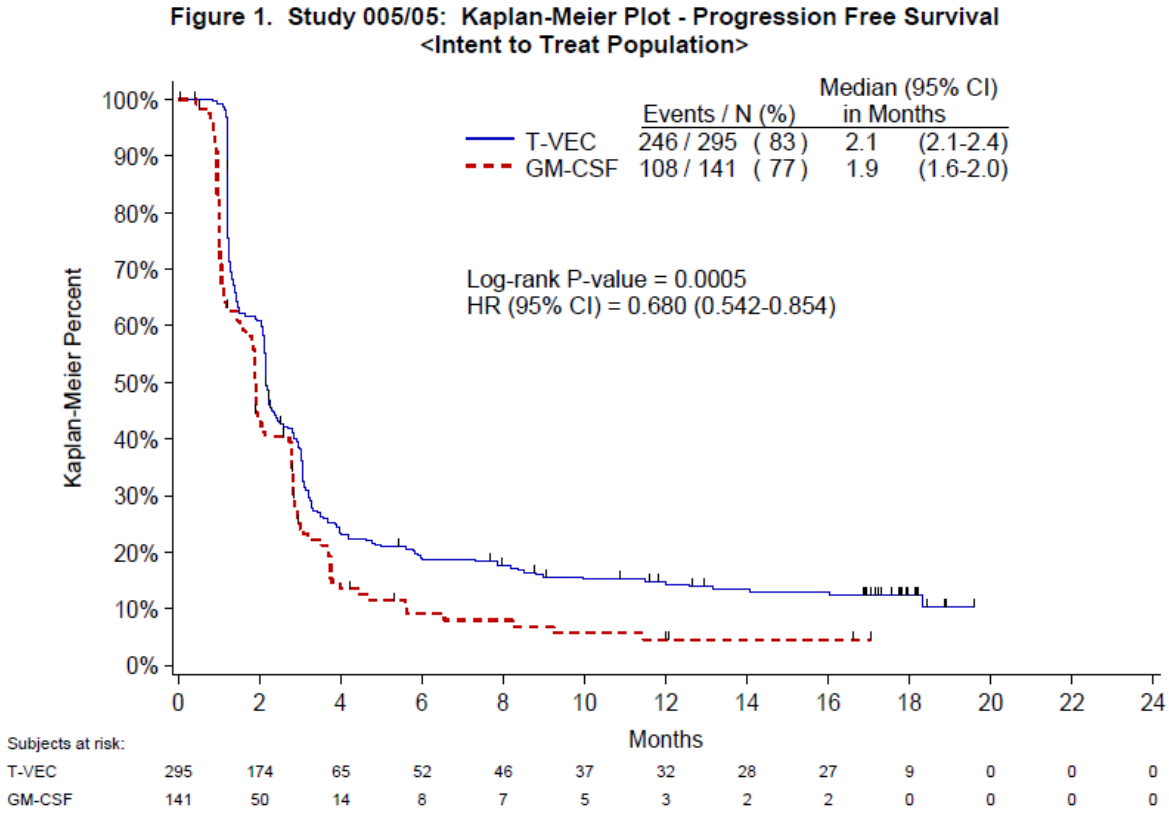
Figure 15: Subsequent ipilimumab treatment only – Study 005/05



Progression free survival (PFS)

A post-hoc analysis of progression-free survival (PFS) was performed using the intent-to-treat (ITT) population. In this analysis, PFS was defined as the time from randomization until first progressive disease (PD) per investigator assessment (using modified World Health Organization [WHO] criteria) or death, whichever was earlier. As PD was not assessed by the Endpoint Assessment Committee (EAC) for all subjects, PFS per EAC could not be derived for the ITT population.

Figure 16: K-M plot for PFS (ITT population) - Study 005/05



A similar analysis was conducted in the subgroups of subjects with non-visceral disease (stage IIIB-C/IVM1a) (Figure 17) and visceral disease (stage IVM1b-c) (Figure 18).

Figure 17: K-M plot for PFS for patients with stage IIIB-C/M1a (ITT population) – Study 005/05

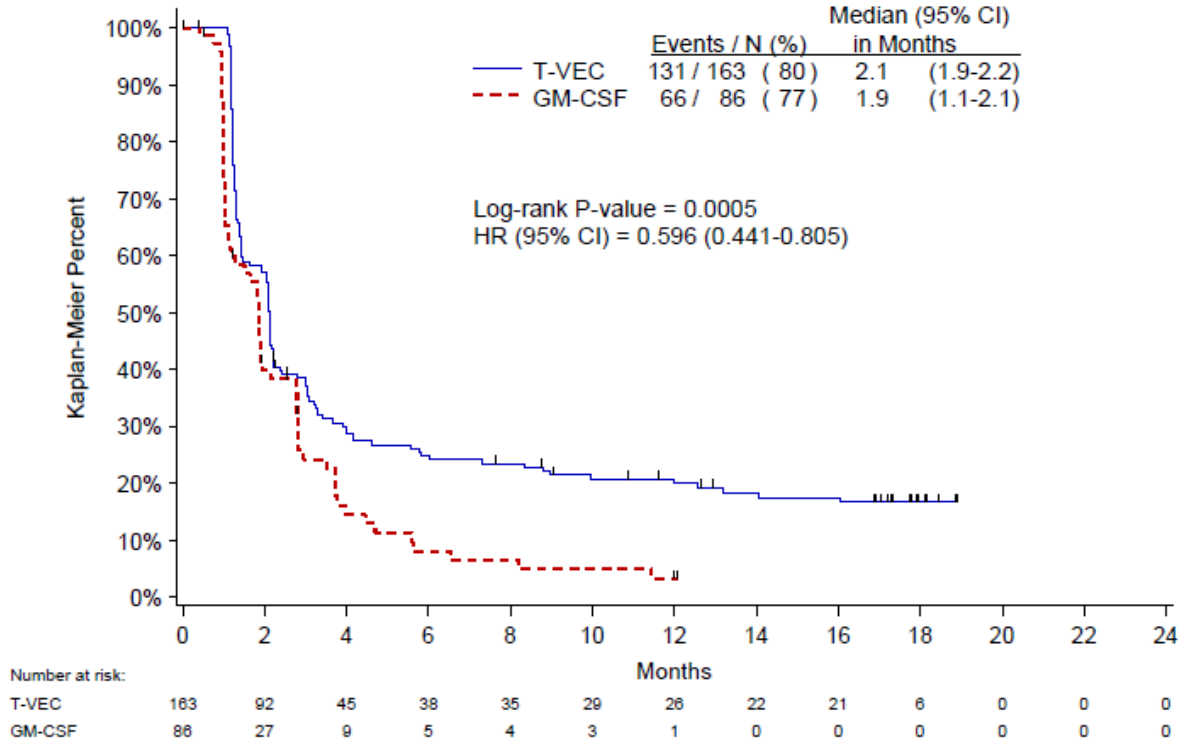
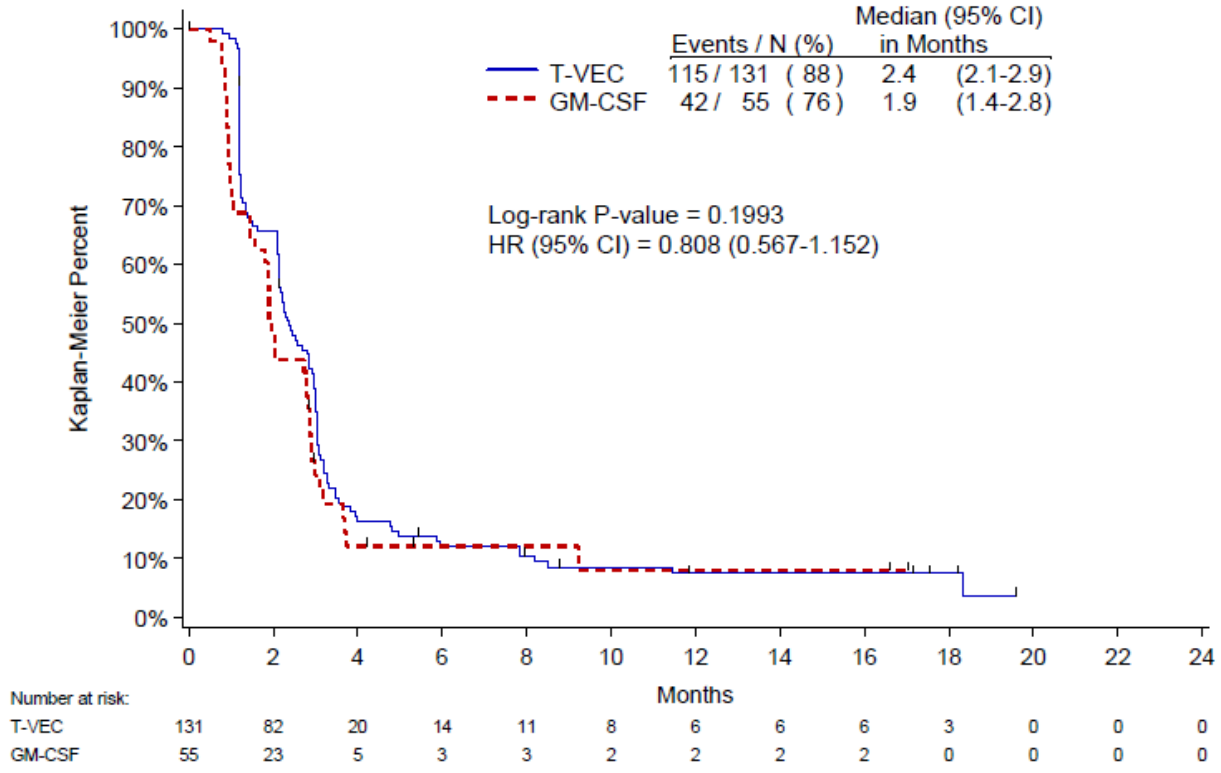


Figure 18: K-M plot for PFS for patients in stage IVMb-c (ITT population) – Study 005/05



Overall Survival (OS)

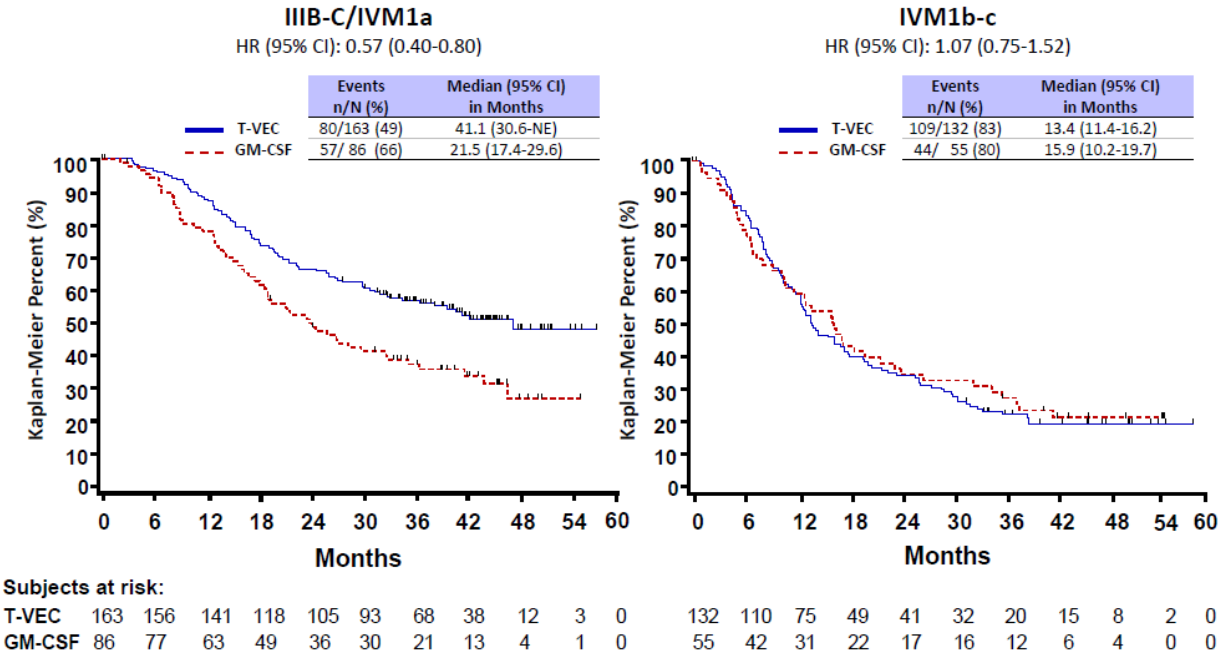
Analyses show an improvement with talimogene laherparepvec compared to GM-CSF for patients without visceral disease (stage IIIB-B, IVM1a) of 24% in DRR, 38% in ORR (Table 28) , and a HR for OS of 0.57 (95% CI: 0.40, 0.80) in subjects with stage IIIB/C and IVM1a disease and 1.07 (0.75, 1.52) in subjects with IVM1b-c disease (Figure 19).

Table 28: Consistency of substage effects between durable response and overall survival – Study 005/05

		DRR		Odds Ratio (95% CI)	Interaction Test P-value	
Disease Stage	N	GM-CSF	T-VEC		Quantitative	Qualitative
IIIB/IIIC/IVM1a	249	1.2%	25.2%	28.6 (18.5,211.5)	<0.0001	0.500
IVM1b/IVM1c	186	3.6%	5.3%	1.5 (0.3, 7.4)		

		Median OS (months)		OS Hazard Ratio (95% CI)	Interaction Test P-value	
Disease Stage	N	GM-CSF	T-VEC		Quantitative	Qualitative
IIIB/IIIC/IVM1a	249	21.5	41.1	0.57 (0.40, 0.80)	0.011	0.354
IVM1b/IVM1c	186	15.9	13.4	1.07 (0.75, 1.52)		

Figure 19: Overall Survival by disease substage



Sensitivity analyses

To evaluate potential bias in DRR arising from differences in early treatment discontinuation, a post-hoc sensitivity analysis was conducted. In this analysis, the number of durable responses for subjects who discontinued early was imputed based on the DRR for those subjects who did not discontinue early. A subgroup of subjects not reviewed by the EAC was defined as potentially having "discontinued early" (DE); these subjects ended the treatment phase without evidence of clinically relevant disease progression as shown in Table 29 and 30.

Table 29: Subjects who potentially "discontinued early" (ITT) – Study 005/05

Reason	GM-CSF (N=141) n (%)	Talimogene laherparepvec (N=295) n (%)
Any early discontinuation	58 (41)	73 (25)
Treatment ended due to investigator decision or consent withdrawn without clinically relevant disease progression	10 (7)	3 (1)
Treatment ended due to disease progression		
Response missing or reported as clinically relevant progression without evidence of performance status decline or new treatment in 60 days	22 (16)	35 (12)
Response reported as not clinically relevant progression or stable disease	11 (8)	32 (11)
Treatment ended for other reasons (excluding adverse event or death) with no response reported	15 (11)	3(1)

Table 30: Sensitivity analyses of durable response rate with imputation for early discontinuations

	GM-CSF (N = 141)	Talimogene laherparepvec (N = 295)	p-value
DE, n (%)	58 (41)	73 (25)	-
ITT DRR primary analysis, n (%)	3 (2)	48 (16)	<0.0001
ITT DRR imputation both arms, n (%)	6 (4)	63 (21)	< 0.0001
ITT DRR imputation GM-CSF only, n (%)	6 (4)	48 (16)	0.0003

Talimogene laherparepvec systemic effect on new visceral metastases

The talimogene laherparepvec systemic effects on prevention or delay of micrometastasis to develop into new metastases was investigated. This was achieved by exploring whether talimogene laherparepvec decreased the risk of developing new visceral (including brain and bone) metastases in subjects without visceral disease at baseline (ie subjects with Stages IIIB, IIIC and IVM1a melanoma at baseline) in Study 005/05 by comparing visceral metastasis-free survival (VMFS) in subjects treated with talimogene laherparepvec (n=152) vs subjects treated with GM-CSF (n=73). VMFS was calculated from the date of randomization to the date of the appearance of first visceral lesion(s).

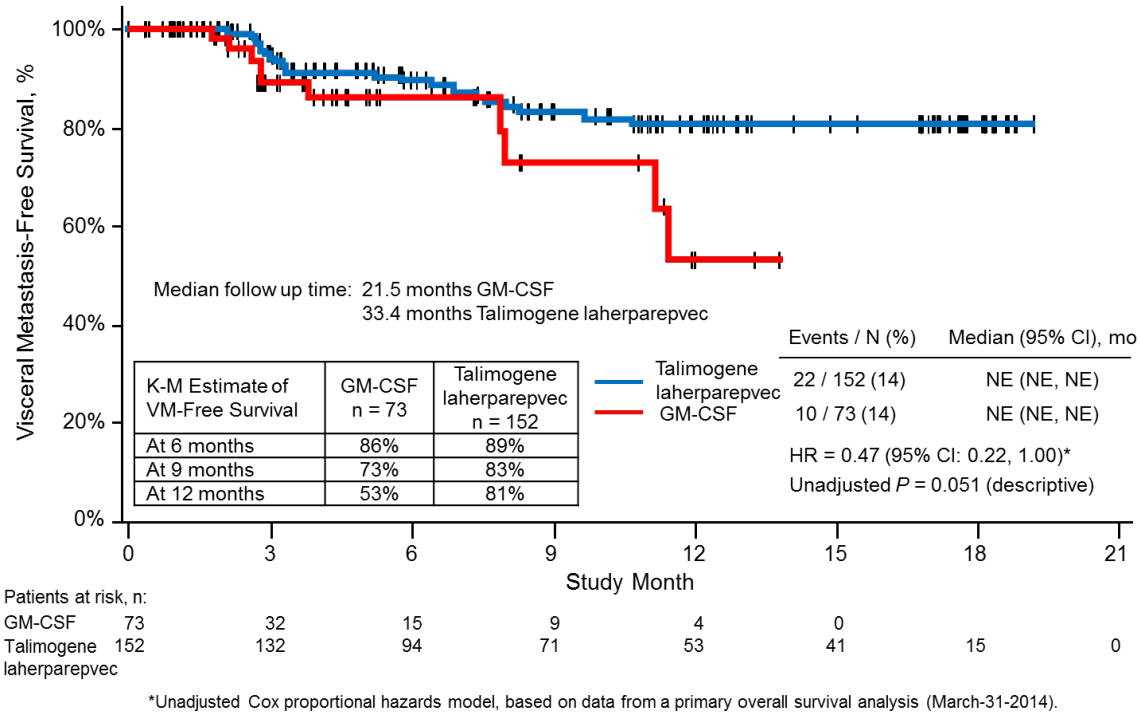
Among subjects without visceral lesions at baseline approximately 14% in both groups developed visceral metastases at disease progression during tumour response assessments in Study 005/05 (Table 31), although median follow up for subjects treated with talimogene laherparepvec was 55% longer than subjects treated with GM-CSF: 33.4 (interquartile range, 17.6, 41.9) months vs 21.5 (12.7, 38.7) months (P=0.0052, Wilcoxon rank sum test).

Table 31: Visceral Metastases in Subjects without Visceral Metastases at Baseline - Study 005/05

	GM-CSF N = 73	Talimogene laherparepvec N = 152
Number of events of first visceral metastasis, n (%)	10 (13.7)	22 (14.5)
Location of first visceral metastasis, n (%)		
Adrenal glands	1 (10)	1 (5)
Bone	1 (10)	2 (9)
Brain	2 (20)	2 (9)
Heart/Pericardium	-	1 (5)
Gastrointestinal tract	1 (10)	-
Kidney	-	2 (9)
Liver	1 (10)	4 (18)
Lung	4 (40)	9 (41)
Spleen	-	1 (5)

The Kaplan-Meier plots of VMFS and Cox proportional hazards model that were used to estimate the effect of talimogene laherparepvec vs GM-CSF on VMFS are shown in Figure 20. Subjects who did not develop visceral lesions were censored at the date of their last tumour response assessment. The unadjusted HR for VMFS of subjects treated with talimogene laherparepvec vs GM-CSF was 0.47 (0.22, 1.00), *P* = 0.051 (descriptive).

Figure 20: Kaplan-Meier plots of VMFS and Cox proportional hazards model that were used to estimate the effect of talimogene laherparepvec vs GM-CSF on VMFS - Study 005/05



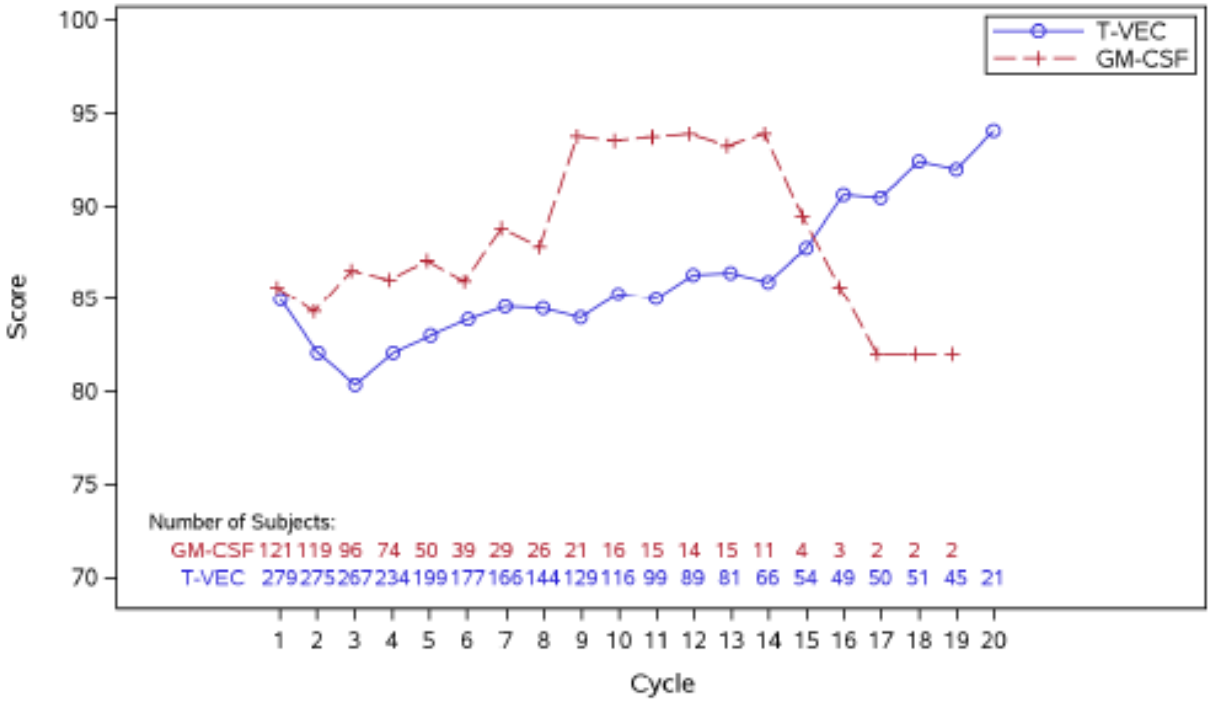
K-M – Kaplan-Meier; NE – not estimable; HR – hazard ratio; VMFS – visceral metastases free survival

Quality of Life

The quality of life was assessed by the FACT-BRM questionnaire. The TOI is a 27-item measure that is the sum of the domains for physical and functional well-being and the BRM subscale scores of the FACT-BRM.

A summary of the mean TOI by treatment arm and by cycle is described below (Figure 21).

Figure 21: Summary of mean trial outcome index (ITT population)



T-VEC=Talimogene Laherparepvec

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of Efficacy for Study 005/05

Title: A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc, and IV Disease		
Study identifier	005/05	
Design	international, open-label, controlled, randomized (2:1), multicenter, prospective phase III study	
	Duration of main phase:	24 weeks or CR. After 24 weeks, subjects were to remain on study until clinically relevant disease progression up to 12 months. Subjects in response at 12 months were to continue treatment for up to an additional 6 months or disease progression, whichever was earlier.
	Duration of follow-up phase:	Subjects were followed for response duration for at least 12 months after randomization. Subjects were to be followed for OS for at least 36 months from the date the last patient is randomized or until the last study subject had died, whichever was earlier.

Hypothesis	Superiority		
Treatments groups	talimogene laherparepvec		talimogene laherparepvec 10^6 PFU/mL, injected into 1 or more skin, nodal, or sc tumours (up to 4 mL total). Subsequent doses at least 3 weeks after the first dose, talimogene laherparepvec 10^8 PFU/mL (up to 4 mL total) every 2 weeks for 24 weeks unless other therapy for melanoma was required (N=295)
	GM-CSF		GM-CSF 125 µg/m^2/day SC for 14 days, followed by a 14-day rest period. Subjects were to receive treatment until week 24, unless other therapy for melanoma was required (N=141)
Endpoints and definitions	Primary endpoint	Durable Response Rate (DRR)	rate of objective response (CR or PR) lasting continuously for 6 or more months and beginning at any point within 12 months of initiating therapy (per EAC assessment)
	Secondary endpoint	Overall Survival (OS)	Time from the date of randomization to the date of death from any cause
	Secondary endpoint	Objective Response Rate (ORR)	Best overall response observed across all time points (CR+PR)
	Secondary endpoint	Time to Response	Time from the date of randomization to the date of the first documented evidence of response (response onset)
	Secondary endpoint	Duration of Response	Longest individual period from entering response (PR or CR) to the first documented evidence of the subject no longer meeting the criteria for being in response or the subject's death, whichever is earlier (responders only)
	Secondary endpoint	Time to Treatment Failure	Time from randomization until the first clinically relevant disease progression where there is no response achieved after the progression, or until death if no such progression occurs
Database lock	31 March 2014 OS primary analysis; 21 Dec 2012 DR primary analysis		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	talimogene laherparepvec	GM-CSF
	Number of subject	295	141
	DRR (%)	16.3	2.1
	95% CI	(12.1, 20.5)	(0.0, 4.5)
	Median OS (months)	23.3	18.9
	95% CI	(19.5, 29.6)	(16.0, 23.7)

	ORR (%)	26.4	5.7
	95% CI	(21.4, 31.5)	(1.9, 9.5)
	Median Time to response (months)	4.1	3.7
	95% CI	(3.8, 5.4)	(1.9, 5.6)
	Median Duration of response (months)	NE	2.8
	95% CI	(NE)	(1.2, NE)
	Median Time to treatment failure (months)	8.2	2.9
	95% CI	(6.5, 9.9)	(2.8, 4.0)
Effect estimate per comparison	Primary endpoint (DRR)	Comparison groups	talimogene laherparepvec vs GM-CSF
		OR (unadjusted)	8.9
		95% CI	(2.7 - 29.2)
		P-value (Fischer's test)	<0.0001
	Secondary endpoint (OS)	Comparison groups	talimogene laherparepvec vs GM-CSF
		HR	0.79
		95% CI	(0.62 – 1.00)
		P-value (unstratified log-rank test)	0.0511
	Secondary endpoint (ORR)	Comparison groups	talimogene laherparepvec vs GM-CSF
		Treatment arm difference	20.8%
		95% CI	(14.4 - 27.1)
		P-value (descriptive)	< 0.0001
	Secondary endpoint (Time to response)	Comparison groups	talimogene laherparepvec vs GM-CSF
		Treatment arm difference	0.4 months
		P-value (unstratified log-rank test)	0.2020
	Secondary endpoint (Duration of response)	Comparison groups	talimogene laherparepvec vs GM-CSF
		HR (Unstratified)	0.40
		95% CI	(0.14 - 1.18)
		P-value (descriptive)	0.087
	Secondary endpoint (Time to treatment failure)	Comparison groups	talimogene laherparepvec vs GM-CSF
		HR	0.42
		95% CI	(0.32 - 0.54)
		P-value (descriptive)	< 0.0001

Notes	Stratification factors: site of first recurrence (in transit vs. lymph node vs. visceral); liver metastases (yes vs. no); stage of disease (stage IIIB/C vs. stage IV M1a vs. stage IV M1b vs. stage IV M1c); prior nonsurgical melanoma treatment other than adjuvant therapy (no vs. yes and recurrence <1 year from primary diagnosis vs. yes and recurrence >1 year from primary diagnosis)

Analysis performed across trials (pooled analyses and meta-analysis)

An analysis was performed to compare the substage covariate chosen for the randomisation of the phase III 005/05 study. The result of the post-hoc analysis is shown in Table 33.

Table 33: Substage effects are replicated across studies 002/03 (phase II) and 005/05 (phase III)

Study	Imlygic N	ORR (%)	DRR (%)	CR (%)
Phase 2				
ITT	50	28	12	16
III-IVM1a	23	39	13	26
IVM1b/c	25	16	8	4
Phase 3				
ITT	295	26	16	11
III-IVM1a	163	41	25	17
IVM1b/c	131	9	5	4

The age distribution of patients in the clinical trials is presented in Table 34.

Table 34: Age distribution of geriatric subjects in completed clinical trials

	Age 65-74 (Older subjects number /total number)		Age 75-84 (Older subjects number /total number)		Age 85+ (Older subjects number /total number)	
	T-VEC	GM-CSF	T-VEC	GM-CSF	T-VEC	GM-CSF
Controlled Trials[a]	76/292	35/127	51/292	25/127	15/292	6/127
Non Controlled Trials[b]	12/114	N/A	14/114	N/A	3/114	N/A

[a] Includes study 005/05
[b] Include studies 001/01, 002/03, 004/04, 005/04

Supportive studies

Study 002/03

This was a phase 2, open label, single arm study in 50 subjects with unresectable stage IIIC or stage IV melanoma. The primary objective of the study was to assess the clinical efficacy of talimogene laherparepvec in terms of tumour response rates (primary endpoint: overall response rate). Secondary efficacy objectives were to assess the efficacy of talimogene laherparepvec in terms of time to response, median survival time (OS), and time to progression.

Subjects received 8 doses of talimogene laherparepvec over a 15-week period. Talimogene laherparepvec was administered at an initial dose of 10^6 plaque-forming units (PFU)/mL, injected into 1 or more skin or subcutaneous tumours (up to 4 mL total). Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec 10^8 PFU/mL (up to 4 mL total) every 2 weeks. If indications of biological activity were observed after the initial 8 doses (stable disease or better, inflammatory response in an uninjected tumour, and/or injection site reaction), treatment could be continued for an additional 16 doses unless the investigator determined that another therapy was appropriate. Treatment continued until 1 of the following occurred: complete response (CR), disappearance of all injectable tumours, symptomatic disease progression requiring alternative therapy, or the maximum treatment period was achieved.

Per investigator assessment, the best overall response rate (best response observed across all time points) was 28%, including 8 subjects (16%) with a CR and 6 subjects (12%) with a partial response (PR).. Eight subjects (16%) had stable disease per investigator assessment at the time they discontinued from the study.

Median overall survival (defined as the number of months from the date of the first dose to the date of death or the date that the subject was last known to be alive) was 14.7 months (95% CI: 10.3, NE). The percentage of subjects still alive was 57% at month 12 and 41% at months 24 and 36.

Study 005/05-E

This was an extension protocol (Study 005/05) to evaluate the efficacy and safety of extended use treatment with talimogene laherparepvec or GM-CSF for eligible melanoma patients. Subjects enrolled in Study 005/05 who did not have clinically relevant disease progression at the end of the study, who had received the maximum number of injections of talimogene laherparepvec or GM-CSF allowed under the protocol (up to 18 months of treatment), and in whom further treatment was warranted (in the opinion of the investigator and the Sponsor's medical monitor), or those for whom new lesion(s) appeared within 12 months after previous resolution of all disease while on Study 005/05, had the option to be enrolled into extension Study 005/05-E. In Study 005/05-E, talimogene laherparepvec or GM-CSF administration and disease assessments continued according to the Study 005/05 protocol guidelines for an additional 12 months.

Total of 30 subjects (3 in the GM-CSF group and 27 in the talimogene laherparepvec group) received treatment through Study 005/05-E. As of the cut-off date (29 March 2013) 3 subjects (all receiving talimogene laherparepvec) were continuing to receive treatment, 10 subjects (2 GM-CSF, 8 talimogene laherparepvec) completed the maximum duration allowed in this study without PR or CR, 6 subjects (all talimogene laherparepvec) discontinued after no injectable disease, 6 subjects (1 GM-CSF, 5 talimogene laherparepvec) discontinued after progressive disease, 2 subjects (both talimogene laherparepvec) died, 1 subject (talimogene laherparepvec) discontinued due to an adverse event, 1 subject (talimogene laherparepvec) withdrew consent, and 1 subject (talimogene laherparepvec) was withdrawn by the treating physician’s decision.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant submitted an application for the indication of treatment of adults with melanoma that is regionally or distantly metastatic. To support the indication, the applicant submitted study 005/05, a randomized (ratio 2:1), controlled, open-label, multicenter, phase 3 study designed which compared treatment with talimogene laherparepvec to subcutaneously administered GM-CSF in subjects with unresectable stage IIIB through stage IV M1c melanoma. In general, the study was well conducted and no major issues were raised as to the conduct or the validity of the data. The treatment arms were well-balanced in terms of baseline characteristics.

The CAT expressed some concerns over the comparator, GM-CSF, that it may not have been the most appropriate comparator for this patient population with advanced disease. However, the CAT, in line with the Scientific Advice Working Party (SAWP), acknowledged that at the time the study was initiated, the number of possible and available active treatment options was limited where dacarbazine and high dose IL-2 were the main treatments of choice. The proposed comparator was accepted as part of the scientific advice before the study was initiated. In addition, as talimogene laherparepvec contains the GM-CSF gene insert, this arm would serve as an important control to investigate whether GM-CSF could be responsible for the efficacy observed. Taking into account these arguments, the CAT was of the opinion that the trial had been designed appropriately given the context in which it was being conducted. Thus the use of GM-CSF as the comparator in the Study 005/05 is considered acceptable.

The CAT discussed the validity of using DRR as the primary endpoint for the pivotal trials as opposed to using other more robust endpoints such as PFS or OS, as proposed by the CHMP in their Scientific Advice in 2008 and 2013. The CAT expressed concerns that using a new non-validated endpoint, there could be potential sources of bias that could have been introduced during the conduct or the analyses of the data. Nonetheless CAT concluded that DRR is an acceptable endpoint in this setting as it captures a relevant clinical effect of the treatment. One issue that was raised was that the EAC reviewed data for all subjects with a response per investigator and not all subjects (those without response as per investigator) were reviewed by the EAC. Subjects who could not have achieved a response lasting ≥ 6 months based on their duration of treatment were not required to be reviewed. The applicant provided further analyses that demonstrated that no additional durable responders were identified by the EAC in the talimogene laherparepvec arm and only one patient was identified in the GM-CSF among investigator non-responders. This data was reassuring that no bias was introduced from the EAC review.

Another potential source of bias which concerned the CAT was early treatment discontinuation, which could have potentially disproportionately affected the OS results in favour of the talimogene laherparepvec arm if patients in the GM-CSF arm were to discontinue early. Progressive disease was the most frequently reported reason for treatment discontinuation in both the talimogene laherparepvec arm (78.3%) and the GM-CSF arm (72.3%) during the first 6 months. The applicant submitted a sensitivity analysis which clarified that the patients who discontinued early did not affect the observed treatment difference.

The number of subjects with major protocol deviations was higher in the talimogene laherparepvec group (12.2% vs. 3.5% the GM-CSF group) and with missing confirmatory scans being the most common protocol deviation (6.1% vs. 0.7%, correspondingly). The Applicant has provided an

additional analysis of durable response. The imputation of subjects with major protocol deviations (including missing confirmatory scans) did not have a major effect on DRR.

Efficacy data and additional analyses

The primary efficacy endpoint, DRR, was met in the primary efficacy analysis; talimogene laherparepvec resulted in a statistically significant improvement in DRR compared with GM-CSF (16.3% vs. 2.1%). The magnitude of the effect was considered clinical relevant. Overall survival was a secondary endpoint and the study does not provide enough statistical power to show a statistically significant difference for this endpoint. A trend in increased OS was observed in the talimogene laherparepvec arm, with median OS of 23.3 months in the talimogene laherparepvec treated group and 18.9 months in the GM-CSF treated group (HR 0.79; 95% CI 2.7-29.2; p-value 0.0511).

Overall response rate (PR + CR) was higher in the talimogene laherparepvec group, with 10.8% of subjects reaching CR (0.7% in the GM-CSF group).

The median time to lesion response was shortest for lesions that were directly injected (21.1 weeks), followed by non-injected non-visceral lesions (44.1 weeks) and visceral lesions (110.4 weeks). This finding is consistent with initiation of a delayed regional and systemic anti-tumour immune response to talimogene laherparepvec and supports the proposed mechanism of action in melanoma.

A subgroup analysis of DRR and ORR indicated that the observed efficacy was most pronounced in stage IIIb-c/IVM1a patients, in particular in the untreated patients (first-line setting). There were very little effect observed in stage IVM1b and IVM1c patients. The applicant submitted further post-hoc analyses to show that there was co-linearity in the multivariate analysis for line of therapy and stage of disease. Thus, it was not possible to distinguish whether the clinical benefit observed was derived from patients having had no prior treatment or from the patients in the early stages of the disease. The CAT also highlighted that the current pre-treated melanoma population will be different that the pre-treated population when the study was conducted as new approved therapies are available and the standard of care has evolved since then. Thus, the CAT acknowledged that restricting the indication to only untreated patients would not be justified (See SmPC section 4.4). Therefore, the patient population was restricted based on stage of disease to patients that have unresectable disease and no visceral metastases, hence excluding patients with stage IVM1b and IVM1c advanced metastatic disease. The CAT expressed some concern that the data of post-hoc subgroup analyses in a single study has not been confirmed in a confirmatory study. However, it was acknowledged that the applicant has discussed the credibility of the subgroup analyses and that it followed the EMA guideline (EMA/CHMP/539146/2013 Guideline on the investigation of subgroups in confirmatory clinical trials) with robust statistical analyses based on pre-specification of covariate, replication across studies (study 005/05 and 002/03), consistency across endpoints, statistical significance of treatment-by-covariate interaction and biological plausibility of the observed effect.

Secondary analyses and exploratory subgroup analyses of overall survival indicate differences between the survival distributions of the talimogene laherparepvec group compared to the GM-CSF group, in particular after excluding patients with stage IVM1b and IVM1c. Based on the totality of the data and analyses presented, a trend in OS favouring talimogene laherparepvec was seen supporting a clinical benefit for patients in early stage patients.

The exploratory analyses of overall survival are adequately reflected in the SmPC, section 5.1.

The exploratory data on the incidence of lesion response indicated that talimogene laherparepvec could potentially have a systemic effect and decrease and even prevent micrometastases/new lesions. However, the data presented are still preliminary and not definitive conclusions can be drawn.

The CAT expressed some concern over the potential delay in next-line treatment in patients that were defined as non-responders, given that there are currently other treatments approved for the same patient population eg ipilimumab, pembrolizumab and nivolumab. This has been identified as an important potential risk in the RMP and will be evaluated from current clinical trials that are ongoing (see PhV post-authorisation studies) and the literature. Preliminary results from a study where patients were treated with talimogene laherparepvec prior to receiving ipilimumab showed that response to ipilimumab was not affected by talimogene laherparepvec (data not shown)[17]. Thus, it appears that subsequent therapies should not be affected by treatment with talimogene laherparepvec. The loss of efficacy in patients treated with systemic acyclovir to manage complications has also been identified as an important potential risk which will be managed in the RMP by ongoing clinical trials and the literature. Long-term efficacy has been identified as missing information in the RMP and study 20120139, a registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec.

The safety and efficacy of Imlygic in paediatric patients has not been established. No data are available. The European Medicines Agency has deferred the obligation to submit the results of studies with Imlygic in one or more subsets of the paediatric population in melanoma (SmPC section 5.1, see section 4.2 for information on paediatric use).

Additional expert consultation

Following a CAT request, a Scientific Advisory Group meeting was convened on 10th September 2015 to provide advice on the list of questions adopted by the CAT at its July 2015 meeting. On 9th October 2015 a Scientific Advisory Group was convened to assess the need to revise the answers to the list of questions following receipt of further information on the statistical analysis of the overall survival.

FINAL SAG ANSWERS

An updated survival with additional events has been submitted. In light of this analysis, should any of the answers from the SAG meeting of 10 September be revised?

The SAG considered the updated analysis and agreed that in the light of the data presented (including the updated analysis), there is a need to clarify that although in exploratory subgroup analyses talimogene laherparepvec appeared to be associated with an effect on OS in the stage IIIB-C/IVM1a, this effect was not based on robust statistical evidence and should require collateral confirmation. Accordingly, the answers from the SAG meeting of 10 September have revised as described below.

It would be useful to reflect the overall survival data in the overall population and in the subgroup in the product information (preferably using Kaplan-Meier curves) and to clearly state that the subgroup results are exploratory only and that on the basis of the current evidence, it has not been established that talimogene laherparepvec is associated with an effect on overall survival in the target subgroup.

1. Is the improvement in the primary endpoint, DRR (16.3% vs. 2.1 in the primary analysis population and 25.2% vs. 1.2 in the stage IIIB-C/IVM1a population) of clinical relevance when seen in light of the results of the analysis of OS and the favourable safety profile of the product?

The improvement in the primary endpoint, DRR in the overall population was 16.3% vs 2.1% for talimogene laherparepvec and GM-CSF, respectively. In post-hoc subgroup analyses, stage IIIB, IIIC

[17] Puzanov et al, ASCO 2014, Abstract #9029

and IV M1a population showed an improvement in DRR of 25.2% in talimogene laherparepvec treated patients compared to 1.2% for GM-CSF treat patients.

In the overall population, the overall survival HR (95% C.I) was 0.79 (0.62, 1.00), p=0.051. In the exploratory analysis in the target subgroup of patients with stage IIIB, IIIC and IV M1a, the overall survival HR was: 0.57 (0.40-0.80). In an updated analysis in the overall population (including events that had been censored in earlier analyses for 5 patients), the overall survival HR was 0.82 (0.65,1.05), p=0.116. In the target subgroup (stage IIIB, IIIC and IV M1a), the updated HR was 0.61 (0.43, 0.86).

Many SAG members found the effect clinically relevant for the primary endpoint of DRR, although being an unconventional endpoint. However, if the aim of the study was to achieve loco-regional antitumour response in soft tissue disease, then there were concerns about the suboptimal GM-CSF control arm. Although talimogene laherparepvec was clearly associated with an effect on DRR, it is doubtful that the observed DRR of 16% (or about 25% in exploratory subgroup analyses) is of clinical value considering the available loco-regional treatment options, such as combination chemotherapy (the response rate associated with combination chemotherapy in patients with soft tissue disease is in the range of 30%-40%[18,19,20,21]), or electro-chemotherapy and the new immunotherapies all of which are known to be associated with high and durable response rate in soft tissue disease. There is also uncertainty about the efficacy in terms of neighbouring soft tissue lesions that have not been injected with talimogene laherparepvec (further analyses may help clarify this point), as the there is a limit to the number of lesions that can be treated in terms of total volume administered. This and the complexity of talimogene laherparepvec administration may further reduce the value of talimogene laherparepvec as a possible loco-regional treatment of melanoma.

Although there appeared to be an effect on overall survival in the subgroup of patients with Stage IIIB-IVM1a disease, overall survival was a secondary endpoint and the effect was based on exploratory subgroup analyses, after the analysis in the full analysis set was not statistically significant, and without a pre-specified strategy for multiplicity adjustment. The notable changes in statistical significance based on the inclusion of a few more events (updated analysis) add to the uncertainty of this exploratory finding. Thus, the apparent association between treatment with talimogene laherparepvec and overall survival cannot be considered statistically convincing. Furthermore collateral reproducibility from other studies was lacking and the phase II data did not provide support for this finding. In terms of biological rationale, a decreasing effect for the more advanced stages has been consistently observed with other immunotherapies, and could provide indirect support. However, the claimed mechanism of action in terms of the systemic immunological effect has not been fully elucidated (and the lack of a clear effect in visceral lesions would suggest a modest effect), which adds uncertainty about the validity of the findings of the exploratory subgroup analysis of overall survival.

In summary, considering all evidence, it cannot be concluded that an effect on overall survival has been established for talimogene laherparepvec in the overall population and there still uncertainties in the subgroup including stages IIIB, IIIC and IV M1a. To determine the existence of a relevant effect on overall survival, direct comparison with effective first-line systemic therapy currently available (e.g., anti-PD-1 or ipilimumab) would be necessary. Although talimogene laherparepvec is associated with an effect on DRR, the existence of other therapeutic options with rigorously established effect on overall survival needs to be taken into account when evaluating the best treatment option for patients.

Concerning the line of therapy, there are practically no data about the effect of talimogene laherparepvec after current effective immunotherapy (given as adjuvant treatment or as treatment for metastatic disease). Thus, the efficacy of talimogene laherparepvec in the second-line setting is essentially unknown and cannot easily be assumed based on pharmacological grounds. In the present study, however, the effect in first line revealed a HR of 0.36 (95% COI…) while in second line the HR was 0.93, (95% COI…). Thus no convincing effect was observed for talimogene laherparepvec used as second-line treatment following the standard first line treatments that were conventional at the time

[18] Verschraegen CF, Kleeberg UR, Mulder J, Rumke P, Truchetet F, Czarnetzki B, et al. Combination of cisplatin, vindesine, and dacarbazine in advanced malignant melanoma. A Phase II Study of the EORTC Malignant Melanoma Cooperative Group. Cancer. 1988;62(6):1061-5.
[19] Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer. 1989;64(10):2024-9.
[20] Hill GJ, 2nd, Krementz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. IV. Late results after complete response to chemotherapy (Central Oncology Group protocols 7130, 7131, and 7131A). Cancer. 1984;53(6):1299-305.
[21] Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(9):2745-51.

the study was conducted and the efficacy of talimogene laherparepvec can only be considered established in the first-line treatment of patients with stage IIIB, IIIC and IV M1a melanoma. Further studies will be needed to establish the optimal sequence of new agents in the treatment of advanced melanoma.

In conclusion, talimogene laherparepvec was associated with an effect on DRR; in view of the acceptable toxicity profile, the benefits of talimogene laherparepvec are considered to outweigh its risks in the first-line treatment of patients with stage IIIB, IIIC and IV M1a melanoma. However, given the effective systemic treatment options that have become available, it is difficult to define a priori a patient population for whom talimogene laherparepvec might be the optimal treatment option.

2. The Applicant proposes a restricted indication to only include stage IIIB/C and IVM1a subgroups. The SAG Oncology is asked to discuss whether data as a whole and the subgroup analyses support a restricted indication, and whether additional ways to identify true responders/patients who benefit from talimogene laherparepvec could be identified.

The efficacy of talimogene laherparepvec has only been established in the first-line treatment of patients with stage IIIB, IIIC and IV M1a melanoma (see answer to question No. 1).

Unfortunately, no comprehensive biomarker data have been submitted to allow exploration of important prognostic or predictive biomarkers. A number of studies are being planned aiming to explore a multitude of possible biomarkers, which is encouraged. Concerns were expressed about the size of the studies that are possibly too small to have sufficient power to identify important biomarkers amongst the multitude of possible biomarkers, and the need to be selective about the biomarkers to be explored taking into account state-of-the art knowledge.

3. Are there concerns related to treating certain patients with talimogene laherparepvec monotherapy through the pseudoprogression/progression prior to response, and possible postponement of other available therapies?

There are concerns that using talimogene laherparepvec in first-line therapy of patients with stage IIIB, IIIC and IV M1a melanoma will delay the use of therapies with an established effect on overall survival in terms of preventing metastatic disease, especially visceral or brain disease and result in a detriment in overall survival. In the case of talimogene laherparepvec, the fact that treatment is recommended beyond progression adds to this concern. Direct comparison with effective currently available first-line systemic therapy is lacking.

At present, it is not possible to give clear guidance about patient or disease characteristics that would allow selecting patients for whom Imlygic might be the optimal treatment option (see also answers to questions 1 and 3). In the absence of evidence-based recommendations, the use of talimogene laherparepvec in first-line therapy of patients with stage IIIB, IIIC and IV M1a melanoma will require careful consideration of the available systemic treatment options and their associated benefits, risks and uncertainties, and the risk of delaying systemic therapies with an established survival benefit. From a patient perspective, this in depth discussion about the benefits, risks and uncertainties of different treatments will be critical in order to determine the preferred treatment option.

There is also a risk that in clinical practice, treatment compliance with talimogene laherparepvec after progression will be poor compared to the clinical trial in view of the possibility to switch to other effective treatment options. This could reduce the effectiveness of treatment with Imlygic.

4. The new proposed indication excludes patients with visceral disease. The SAG oncology is asked if there are situations where Imlygic might be beneficial also for these patients despite limited evidence of a systemic effect on visceral disease.

Based on available data, the efficacy in the treatment of patients with stage IV M1b and M1c has not been established (see answer to question No. 1). It is recommended to reflect the target population using the correct AJCC melanoma staging and classification explicitly in the indication avoiding the term "visceral", which does not include other metastatic disease (e.g., to the bone, or brain) that should also be excluded from the target indication.

5. Given other available treatments, and with particular consideration of the potential for "loss of chance" by delaying other therapeutic alternatives, in what situations does the SAG consider that use of Imlygic might be appropriate.

As for any new treatment, there is potential loss of chance in terms of other establish treatments that are indicated for the first-line treatment of melanoma. Comparative data with currently available effective systemic treatments are needed to rule out any detriment (see answers to questions 1 and 3).

2.5.4. Conclusions on the clinical efficacy

The pivotal study 005/05 met its primary endpoint and provided satisfactory evidence that talimogene laherparepvec demonstrated a clinically relevant benefit in patients with unresectable melanoma without visceral disease. The primary endpoint, DRR, was considered appropriate for this type of new agent targeting the tumour as well as the immune system. Therefore, the CAT considered that the efficacy of talimogene laherparepvec in adult patients with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease (see section SmPC 4.4 and 5.1) had been demonstrated.

Without having specific validated biomarkers, the challenge remains in trying to identify the limited number of patients who respond to talimogene laherparepvec with a durable response. In order to further define this population it might be considered relevant to generate further efficacy data in the post-authorisation phase in order to monitor the impact of the intervention on clinical outcome or disease progression. The CAT considers the following measures necessary to address the issues related to efficacy:

- The MAH should submit the preliminary results of Study 20120325 (a phase 2, multicenter, open-label, single-arm trial to evaluate the correlation between objective response rate and baseline intratumoral CD8+T-lymphocyte density in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec), by 31st December 2018.
- To submit the preliminary results from Study 20110266 (a phase 2, multicenter, randomized, open-label trial assessing the efficacy and safety of talimogene laherparepvec neoadjuvant treatment plus surgery vs surgery alone for resectable stage IIIB to IVM1a melanoma).
- To provide preliminary efficacy results from the phase III part of the Study 20110265 (a multicenter trial evaluating the combination of talimogene laherparepvec with pembrolizumab).

The CHMP endorse the CAT conclusion on clinical efficacy as described above.

2.6. Clinical safety

Patient exposure

The clinical safety of talimogene laherparepvec has been addressed with three defined safety sets.

- Primary Melanoma Analysis Set**,** n=419, 1 pivotal, open-label, active-controlled (GM-CSF) phase III trial in unresectable stage IIIB, IIIC, and IV melanoma (Study 005/05): n=292 subjects exposed to talimogene laherparepvec in multiple doses of 10^6 (initial dose only) and 10^8 PFU/mL for a median treatment duration of 23.0 weeks (range: 0.1 to 78.9 weeks); n=127 subjects exposed to GM-CSF for a median treatment duration of for 10 weeks (range 0.6 to 72 weeks) weeks.

  Primary Melanoma Analysis Set was defined as all randomized subjects who received ≥ 1 dose of study treatment whereof 292 subjects received ≥1 dose, 172 patients received a cumulative exposure of 0 to <6 months, 94 patients from 6 to <12 months, 25 from 12 to <18 months and one subject 18 months and longer.

- Supportive Melanoma Analysis Set, n= 342 subjects exposed to talimogene laherparepvec in multiple doses of 10^6 (initial dose only) and 10^8 PFU/mL: Study 005/05, n=292 subjects exposed to talimogene laherparepvec; Study 002/03 (open-label, single-arm, phase II trial in stage IIIC and IV melanoma that was not eligible for curative surgery), n=50 subjects exposed to talimogene laherparepvec in multiple doses of 10^6 (initial dose only) and 10^8 PFU/mL with a median of 6 doses of talimogene laherparepvec (range, 1 to 24); extension study 005/05-E, n=27 subjects exposed to talimogene laherparepvec for a median treatment duration of 34.1 weeks (range: 2.0 to 61.3 weeks) during the extension period; extension study 002/03-E, n=3 subjects exposed to talimogene laherparepvec for a treatment duration of 47.1, 47.3 and 49.4 weeks, respectively.
- Program-Wide Analysis Set, n=408 subjects exposed to ≥ 1 dose of talimogene laherparepvec in multiple doses of 10^4, 10^5, 10^6, 10^7 or 10^8 in melanoma and non-melanoma studies: Study 005/05, n=292 subjects exposed to talimogene laherparepvec; 1 first-in-human, 2-part, open-label phase I PK study (Study 001/01) in breast adenocarcinoma, melanoma of the skin, or epithelial cancer of the head and neck refractory to conventional chemotherapy (as per protocol), n=30 subjects exposed to talimogene laherparepvec; Study 002/03, n=50 subjects exposed to talimogene laherparepvec; 1 open-label, dose-escalation phase I/II study (004/04), in locally advanced epithelial cancer of the head and neck in combination with chemoradiation (cisplatin), n=17 subjects exposed to talimogene laherparepvec; 1 open-label, dose-escalation phase I study (005/04), in unresectable pancreatic cancer, n=17 subjects exposed to talimogene laherparepvec; 1 randomized, open-label, phase III trial (006/09) in locally advanced squamous cell carcinoma of the head and neck in combination with chemoradiation (cisplatin), n=2 subjects exposed to talimogene laherparepvec; 2 extension studies (002/03-E and 005/05-E), n=3+27 subjects exposed to talimogene laherparepvec.

The exposure data at 0 to <6 months, 6 to <12 months, 12 to <18 months and18 months and longer) for the Primary Analysis Set, including patient exposure in the control group to GM-CSF is provided in Table 35.

Table 35: Number of subjects receiving study therapy by duration of cumulative exposure Study 05/05 - Safety Population

	GM-CSF (N = 127)	Talimogene Laherparepvec (N = 292)	Total (N = 419)
Overall total exposure			
≥ 1 dose	127	292	419
< 6 months	106	172	278
6 to < 12 months	18	94	112
12 to < 18 months	3	25	28
18 months and longer	0	1	1

Table 36: Summary of study treatment exposure - Safety population

	GM-CSF (N = 127)	Talimogene Laherparepvec (N = 292)	Total (N = 419)
Treatment Duration (weeks)			
n	127	292	419
Mean	15.76	26.83	23.47
SD	15.79	18.39	18.34
Median	10.00	23.00	17.29
Q1, Q3	6.00, 18.29	11.29, 37.07	10.00, 34.86
Min, Max	0.6, 72.0	0.1, 78.9	0.1, 78.9

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N = Number of subjects in the analysis set; SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile. Treatment duration = last dose date - first dose date +1.
Safety Population is defined as randomized subjects who have received at least one dose of study treatment.

Table 37: Summary of talimogene laherparepvec exposure – Safety population

	Talimogene Laherparepvec (N = 292)
Dose at cycle 1 day 1 (10^6 pfu)	
n	292
Mean	2.80
SD	1.22
Median	3.00
Q1, Q3	2.00, 4.00
Min, Max	0.4, 4.0
Average dose post cycle 1 day 1 (10^6 pfu)	
n	290
Mean	2.83
SD	1.21
Median	3.33
Q1, Q3	1.75, 4.00
Min, Max	0.3, 4.4
Volume at cycle 1 day 1 (ml)	
n	292
Mean	2.80
SD	1.22
Median	3.00
Q1, Q3	2.00, 4.00
Min, Max	0.4, 4.0
Average volume post cycle 1 day 1 (ml)	
n	290
Mean	2.84
SD	1.22
Median	3.33
Q1, Q3	1.75, 4.00
Min, Max	0.3, 4.4

	Talimogene Laherparepvec (N = 292)
Cumulative dose (10^8 pfu)	
n	292
Mean	34.13
SD	28.13
Median	24.03
Q1, Q3	12.81, 47.67
Min, Max	0.0, 152.0
Cumulative volume (ml)	
n	292
Mean	36.93
SD	28.48
Median	27.00
Q1, Q3	16.00, 50.15
Min, Max	1.8, 156.0
Number of injections	
n	292
Mean	14.1
SD	9.1
Median	12.0
Q1, Q3	6.0, 19.0
Min, Max	1, 42

N = Number of subjects in the analysis set. n = non missing values. SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile .
Safety Population is defined as randomized subjects who have received at least one dose of study treatment.

Table 38: Summary of GM-CSF exposure – Safety population

	GM-CSF (N = 127)
Daily prescribed dose per subject (µg)	
n	127
Mean	245.58
SD	49.01
Median	247.50
Q1, Q3	219.17, 269.04
Min, Max	125.0, 515.0
Number of patients with dose reductions[a] - n(%)	
0	121 (95)
1	6 (5)
Number of doses	
n	127
Mean	60.46
SD	54.78
Median	42.00
Q1, Q3	28.00, 70.00
Min, Max	4.0, 252.0

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N = Number of subjects in the analysis set. n = non missing values. SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile .
[a] Dose reduction is defined as 40% decrease of the daily prescribed dose from previous daily prescribed dose.
Safety Population is defined as randomized subjects who have received at least one dose of study treatment.

Adverse events

A treatment-emergent adverse event (AE) was defined as any adverse event that occurred after administration of the first dose of study drug and through 30 days after the last dose of study treatment, or any event that was present at baseline and continued after the first dose of study treatment but worsened in intensity. An overview on the overall subject incidence of treatment emergent AEs for the Primary Melanoma Analysis Set (Study 005/05) is provided in Table 39.

Table 39: Summary of subject incidence of treatment-emergent Adverse Events (primary melanoma analysis set)

	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
All treatment-emergent adverse events	121 (95.3)	290 (99.3)	411 (98.1)

Treatment-emergent adverse events with worst grade of 3	21 (16.5)	82 (28.1)	103 (24.6)
Treatment-emergent adverse events with worst grade of 4	4 (3.1)	13 (4.5)	17 (4.1)
Treatment-emergent serious adverse events	17 (13.4)	75 (25.7)	92 (22.0)
Fatal adverse events on-study	2 (1.6)	10 (3.4)	12 (2.9)
Treatment-related adverse events[a]	101 (79.5)	271 (92.8)	372 (88.8)
Treatment-related adverse events with worst grade of 3[a]	6 (4.7)	30 (10.3)	36 (8.6)
Treatment-related adverse events with worst grade of 4[a]	0 (0.0)	3 (1.0)	3 (0.7)
Treatment-related serious adverse events[a]	0 (0.0)	19 (6.5)	19 (4.5)
Treatment-emergent adverse events leading to permanent discontinuation of study treatment	8 (6.3)	29 (9.9)	37 (8.8)

N = Number of subjects in the analysis set; n = number of subjects with event.

[a] Treatment-related adverse event refers to treatment-emergent adverse events that have possible or probable relation to study treatment as determined by investigator.

The listings of the adverse drug reactions (ADRs) and their frequency estimations in Section 4.8 of the proposed Summary of Product Characteristics are based on the crude incidence data available for treatment-emergent adverse events as indicated above. According to the Guideline on Summary of Product Characteristics (September 2009), the frequency of adverse reactions should represent crude incidence rates (and not differences or relative risks calculated against placebo or other comparator). The methodology for the ADR table below includes the following:

- ADRs are defined as preferred terms (PTs) with ≥ 2% difference in subject incidence in the talimogene laherparepvec arm compared to the granulocyte-macrophage colony-stimulating factor (GM-CSF) arm in Study 005-05, and
- Biological plausibility likely to be related to talimogene laherparepvec.

- Events with < 2% difference were included if terms were similar to other terms defined as ADRs and met biological plausibility criterion.
- Events were excluded if all cases were more likely to be related to an alternative etiology.
- In addition, other adverse events were included in the SmPC (Section 4.8) even if they did not meet the 2% threshold, but based on temporal association, seriousness and possible relatedness (eg, plasmacytoma, airway obstructive disorder, immune mediated adverse event) following medical review.

Treatment Emergent Adverse Events by Preferred Term are reported in Table 40.

Table 40: Adverse Events by preferred term (≥ 5% subject incidence in either treatment group; primary melanoma analysis set)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting treatment emergent adverse events with at least 5% frequency in any treatment group	121 (95.3)	290 (99.3)	411 (98.1)
Fatigue	46 (36.2)	147 (50.3)	193 (46.1)
Chills	11 (8.7)	142 (48.6)	153 (36.5)
Pyrexia	11 (8.7)	125 (42.8)	136 (32.5)
Nausea	25 (19.7)	104 (35.6)	129 (30.8)
Influenza like illness	19 (15.0)	89 (30.5)	108 (25.8)
Injection site pain	8 (6.3)	81 (27.7)	89 (21.2)
Vomiting	12 (9.4)	62 (21.2)	74 (17.7)
Diarrhoea	14 (11.0)	55 (18.8)	69 (16.5)
Headache	12 (9.4)	55 (18.8)	67 (16.0)
Myalgia	7 (5.5)	51 (17.5)	58 (13.8)
Arthralgia	11 (8.7)	50 (17.1)	61 (14.6)
Pain in extremity	12 (9.4)	48 (16.4)	60 (14.3)
Pain	13 (10.2)	47 (16.1)	60 (14.3)
Oedema peripheral	12 (9.4)	35 (12.0)	47 (11.2)
Constipation	8 (6.3)	34 (11.6)	42 (10.0)
Cough	10 (7.9)	31 (10.6)	41 (9.8)
Decreased appetite	14 (11.0)	30 (10.3)	44 (10.5)
Upper respiratory tract infection	8 (6.3)	29 (9.9)	37 (8.8)
Dizziness	4 (3.1)	28 (9.6)	32 (7.6)
Pruritus	19 (15.0)	28 (9.6)	47 (11.2)
Back pain	8 (6.3)	27 (9.2)	35 (8.4)
Abdominal pain	3 (2.4)	26 (8.9)	29 (6.9)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Rash	10 (7.9)	26 (8.9)	36 (8.6)
Hyperhidrosis	9 (7.1)	23 (7.9)	32 (7.6)
Tumour pain	7 (5.5)	22 (7.5)	29 (6.9)
Erythema	9 (7.1)	21 (7.2)	30 (7.2)
Insomnia	6 (4.7)	21 (7.2)	27 (6.4)
Anxiety	2 (1.6)	19 (6.5)	21 (5.0)
Cellulitis	2 (1.6)	17 (5.8)	19 (4.5)
Oropharyngeal pain	1 (0.8)	17 (5.8)	18 (4.3)
Weight decreased	1 (0.8)	17 (5.8)	18 (4.3)
Anaemia	2 (1.6)	15 (5.1)	17 (4.1)
Depression	3 (2.4)	15 (5.1)	18 (4.3)
Dyspepsia	9 (7.1)	15 (5.1)	24 (5.7)
Injection site erythema	33 (26.0)	15 (5.1)	48 (11.5)
Vitiligo	1 (0.8)	15 (5.1)	16 (3.8)
Musculoskeletal pain	7 (5.5)	14 (4.8)	21 (5.0)
Neck pain	7 (5.5)	14 (4.8)	21 (5.0)
Dyspnoea	13 (10.2)	13 (4.5)	26 (6.2)
Muscle spasms	7 (5.5)	13 (4.5)	20 (4.8)
Injection site swelling	8 (6.3)	10 (3.4)	18 (4.3)
Injection site reaction	12 (9.4)	9 (3.1)	21 (5.0)
Injection site pruritus	21 (16.5)	5 (1.7)	26 (6.2)

The majority (70-90%) of the events chills, pyrexia, and influenza-like illness resolved within 72 hours. Most of the AEs were mild to moderate in severity: more specifically, 63% were grade I-II and 36% were grade ≥3 in severity.

The subject incidence of treatment-related adverse events with a worst grade of 3 was 10.3% (n = 30) for the talimogene laherparepvec group and 4.7% (n = 6) for the GM-CSF group. Treatment-related adverse events with a worst grade of 3 that were reported in ≥ 1% of subjects in the talimogene laherparepvec group were fatigue (1.0% [n=3] talimogene laherparepvec, 0% GM-CSF), cellulitis (1.4% [n=4], 0%), and tumour pain (1.0% [n=3], 0%). All these are identified as ADRs associated with the use of talimogene laherparepvec.

The subject incidence of adverse events with a worst grade of 4 was 4.5% (n = 13) for the talimogene laherparepvec group and 3.1% (n = 4) for the GM-CSF group. The subject incidence of treatment-related adverse events with a worst grade of 4 was 1.0% (n = 3) for the talimogene laherparepvec group and 0.0% for GM-CSF group. The grade 4 treatment-related adverse events in the talimogene laherparepvec group were plasmacytoma, glomerulonephritis, and obstructive airways disorder. These events have been identified as ADRs associated with the use of talimogene laherparepvec.

The most commonly reported Grade ≥3 AEs are reported in Table 41.

Table 41: Treatment emergent Grade 3 or Greater Adverse Events by preferred term in descending order of frequency in talimogene laherparepvec arm (primary melanoma analysis set)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting grade 3 or greater adverse events	27 (21.3)	105 (36.0)	132 (31.5)
Disease progression	2 (1.6)	8 (2.7)	10 (2.4)
Cellulitis	1 (0.8)	6 (2.1)	7 (1.7)
Deep vein thrombosis	0 (0.0)	5 (1.7)	5 (1.2)
Dehydration	0 (0.0)	5 (1.7)	5 (1.2)
Fatigue	1 (0.8)	5 (1.7)	6 (1.4)
Tumour pain	0 (0.0)	5 (1.7)	5 (1.2)
Vomiting	0 (0.0)	5 (1.7)	5 (1.2)
Back pain	0 (0.0)	4 (1.4)	4 (1.0)
Hypokalaemia	1 (0.8)	4 (1.4)	5 (1.2)
Hyponatraemia	1 (0.8)	4 (1.4)	5 (1.2)
Pain in extremity	1 (0.8)	4 (1.4)	5 (1.2)
Abdominal pain	0 (0.0)	3 (1.0)	3 (0.7)
Anaemia	1 (0.8)	3 (1.0)	4 (1.0)
Dyspnoea	3 (2.4)	3 (1.0)	6 (1.4)
Hypertension	0 (0.0)	3 (1.0)	3 (0.7)
Infected neoplasm	0 (0.0)	3 (1.0)	3 (0.7)
Injection site pain	0 (0.0)	3 (1.0)	3 (0.7)
Metastases to central nervous system	1 (0.8)	3 (1.0)	4 (1.0)
Pleural effusion	1 (0.8)	3 (1.0)	4 (1.0)
Urinary tract infection	0 (0.0)	3 (1.0)	3 (0.7)
Arthralgia	0 (0.0)	2 (0.7)	2 (0.5)
Asthenia	0 (0.0)	2 (0.7)	2 (0.5)
Atrial fibrillation	1 (0.8)	2 (0.7)	3 (0.7)

Adverse Events of Special Interest

Adverse events of special interest in the context of talimogene laherparepvec administration are shown in Table 42.

Table 42: Subject incidence of Adverse Events of interest by category (primary melanoma analysis set)

Event of Interest Category	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
IMMUNE-MEDIATED EVENTS (AUTOIMMUNE DISORDERS)[a]			
Adverse event	2 (1.6)	5 (1.7)	7 (1.7)
Serious adverse event	0 (0)	1 (0.8)	1 (0.2)
CELLULITIS AT THE INJECTION SITE (BACTERIAL CELLULITIS)			
Adverse event	2 (1.6)	18 (6.2)	20 (4.8)
Serious adverse event	1 (0.8)	7 (2.4)	8 (1.9)
FLU LIKE SYMPTOMS			
Adverse event	83 (65.4)	264 (90.4)	347 (82.8)
Serious adverse event	0 (0.0)	9 (3.1)	9 (2.1)
HERPES SIMPLEX VIRUS (HSV) INFECTIONS			
Adverse event	2 (1.6)	16 (5.5)	18 (4.3)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
HYPERSENSITIVITY			
Adverse event	25 (19.7)	53 (18.2)	78 (18.6)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
INJECTION SITE REACTIONS			
Adverse event	64 (50.4)	122 (41.8)	186 (44.4)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
VITILIGO			
Adverse event	2 (1.6)	15 (5.1)	17 (4.1)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
IMPAIRED WOUND HEALING AT THE INJECTION SITE[a]			
Adverse event	3 (2.4)	16 (5.5)	19 (4.5)
Serious adverse event	1 (0.8)	0 (0.0)	1 (0.2)
OTHER NEOPLASTIC EVENTS (MALIGNANT OR UNSPECIFIED TUMORS)			
Adverse event	3 (2.4)	16 (5.5)	19 (4.5)
Serious adverse event	1 (0.8)	9 (3.1)	10 (2.4)
PLASMACYTOMA			
Adverse event	0 (0.0)	1 (0.3)	1 (0.2)
Serious adverse event	0 (0.0)	1 (0.3)	1 (0.2)

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N = Number of subjects in the analysis set

Primary Melanoma Analysis Set is defined as all randomized subjects who received ≥ 1 dose of study treatment.

[a] The incidence rates in this table reflect only the number of cases/events that were reported with preferred terms using the search strategy (SMQ or Amgen-specified strategy) and do not imply a causal drug event association. The cases/events identified in this table were medically reviewed to determine if they met the case definition in order to provide a true ascertainment of the subject incidence of the event shown.

Six patients in the talimogene laherparepvec-group and two in the GM-CSF-group had immune-mediated events compatible with autoimmune aetiology; included two cases of glomerulonephritis and two cases of vasculitis as well as a pneumonitis and an exacerbation of psoriasis. Hypersensitivity reactions (53 vs. 25 cases) and vitiligo (15 vs 2 cases) were excluded from this analysis. Rash was the most common hypersensitivity in both treatment group, 8.9% in the talimogene laherparepvec-group. One patient in the talimogene laherparepvec-group developed bronchial asthma during the treatment. No cases of anaphylaxis were reported in the Primary Melanoma Analysis Set. The exposure-adjusted subject incidence rates for hypersensitivity were driven by the PT "Rash" and the PT "dermatitis".

Fever, elevated white blood cell count, bacteraemia or sepsis, and hospitalization for intravenous antibiotics were reported in 5 of the 7 cases of cellulitis in the talimogene laherparepvec group. Cellulitis developed after one to multiple doses, and 5 of the events (all in the talimogene laherparepvec group) were considered to be possibly related to study treatment. None of the serious cellulitis events resulted in study treatment discontinuation; study treatment was delayed for one subject.

Serious adverse event/deaths/other significant events

Serious adverse events

An overview of the treatment-emergent serious adverse events with ≥1 % incidence is reported in Table 43. No serious adverse events with at least 5% frequency were reported in either of the treatment groups.

Table 43: Treatment-Emergent Serious Adverse Events by preferred term with ≥1 % subject incidence in either treatment group (primary melanoma analysis set)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting serious treatment-emergent adverse events	17 (13.4)	75 (25.7)	92 (22.0)
Disease progression	2 (1.6)	9 (3.1)	11 (2.6)
Cellulitis	1 (0.8)	7 (2.4)	8 (1.9)
Pyrexia	0 (0.0)	5 (1.7)	5 (1.2)
Tumour pain	0 (0.0)	4 (1.4)	4 (1.0)
Cerebral haemorrhage	0 (0.0)	3 (1.0)	3 (0.7)
Deep vein thrombosis	0 (0.0)	3 (1.0)	3 (0.7)
Gastrointestinal haemorrhage	0 (0.0)	3 (1.0)	3 (0.7)
Infected neoplasm	0 (0.0)	3 (1.0)	3 (0.7)
Metastases to central nervous system	1 (0.8)	3 (1.0)	4 (1.0)

Metastatic malignant melanoma	0 (0.0)	3 (1.0)	3 (0.7)
Pleural effusion	0 (0.0)	3 (1.0)	3 (0.7)

The subject incidence of all treatment-related serious adverse events was 6.5% (n = 19) in the talimogene laherparepvec group and 0% in the GM-CSF group. The 2 most common treatment-related serious adverse events were cellulitis (1.7% [n = 5] talimogene laherparepvec, 0% GM-CSF) and pyrexia (1.4% [n = 4], 0%).

The subject incidence of serious adverse events was 28.0% in the talimogene laherparepvec group for subjects who were seropositive at baseline and 25.5% for subjects who were seronegative at baseline.

Deaths

Fatal adverse events were reported for 23 subjects receiving talimogene laherparepvec during the study treatment periods. There were nine fatal events among subjects receiving talimogene laherparepvec that were classified as disease progression, all from the melanoma studies. From these, seven (7/9) have occurred during the first three months after the first dose of talimogene laherparepvec, and two out of these seven cases (2/7) after the first dose of talimogene laherparepvec. None of the events have been considered to be related to study drug (studies 005/05 and 002/03).

Other significant events - viral shedding and transmission

The most comprehensive set of samples (ie, in terms of the number of time points tested) was obtained from Study 001/01 and the pivotal Study 005/05 did not include any shedding data outside the reactive swabs nor were they collected systematically. In the 20120324 study (A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma), talimogene laherparepvec was not detectable in blood, urine, injected lesion and occlusive dressing at day 30 post treatment (Table 44).

Table 44: Viral DNA concentration in blood by Treatment Cycle - Study 20120324

Sampling Time			Number of Samples with Detectable Talimogene Laherparepvec DNA/ Number of Samples Tested	Mean (min-max) concentration of talimogene laherparepvec DNA in blood (copies of talimogene laherparepvec DNA/µg DNA)[a]
Cycle 1	Day 1	Predose	0 / 20	-
		Hour 1	9 / 20	20.8 (6.7-58.0)
		Hour 4	11 / 20	6.1 (2.0-12.3)
		Hour 8	9 / 20	5.0 (2.6-6.5)
	Day 2		5 / 20	4.0 (1.9-6.2)
	Day 3		6 / 20	12.8 (11.6-14.0)
	Day 8		4 / 20	23.8 (1.8-62.3)
	Day 15		2 / 17	14.1 (4.9-23.3)
Cycle 2	Day 1	Predose	2 / 16	4.7 (4.7-4.7)
		Hour 1	15 / 17	281.6 (2.9-1,650.0)
		Hour 4	11 / 16	56.0 (5.2-159.0)
		Hour 8	13 / 16	50.3 (2.4-126.0)
	Day 2		10 / 16	15.3 (2.5-41.0)
	Day 3		7 / 16	7.5 (2.4-10.1)
	Day 8		2 / 16	6.3 (6.3-6.3)
Cycle 3	Day 1	Predose	2 / 14	3.0 (3.0-3.0)
	Day 8		1 / 14	NA
Cycle 4	Day 1		0 / 4	-
Safety follow up			0 / 4	-
Unscheduled			2 / 3	48.5 (15.0-81.9)

[a]Samples with talimogene laherparepvec DNA below lower limit of quantification (LLOQ, 1.76 copies/µg for blood) were not included in calculations; NA – non-applicable (positive test result were below LLOQ)

Laboratory findings

An overview of the decreasing blood haemoglobin in the safety population is reported in Table 45.

Table 45: Summary of change from baseline in Haemoglobin (g/L), Central Lab Only - Safety population

	GM-CSF (N = 127)	Talimogene Laherparepvec (N = 292)	Total (N = 419)
Change from Baseline			
n	95	185	280
Mean	-2.3	-6.9	-5.4
SD	13.3	13.2	13.4
Median	0.0	-5.0	-3.0
Q1, Q3	-7.0, 4.0	-14.0, 2.0	-12.0, 3.0
Min, Max	-72, 26	-52, 24	-72, 26

N = Number of subjects in the analysis set; n = Number of subjects with non-missing data at the time point of interest; SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile . Safety Population is defined as randomized subjects who have received at least one dose of study treatment.

In Study 005/05, at baseline, 251 subjects (59.9%) were seropositive, 143 subjects were seronegative (34.1%), and 13 subjects (3.1%) had unknown HSV-1 antibody status. Of the 98 subjects who were HSV-1 seronegative at baseline in the talimogene laherparepvec group, definitive post-treatment results were obtained for 85 subjects, 77 of whom seroconverted (3 subjects remained seronegative with results at cycle 3, and 5 subjects remained seronegative with results at cycle 6). No post-baseline HSV-1 serostatus was collected for the GM-CSF group.

Safety in special populations

Age

A summary of the data for AEs categorised by age category is outlined in Table 46.

Table 46: Summary data for AEs by Age Category

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+number(percentage)
Total number of subjects in the talimogene laherparepvec group	150 (51.4)*	76 (26.0)*	51 (17.5)*	15 (5.1)*
Median treatment duration (weeks)	22.93	22.79	23.14	36.86
Total AEs	150 (100.0)	76 (100.0)	49 (96.1)	15 (100.0)
Serious AEs				
– Total	38 (25.3)	20 (26.3)	13 (25.5)	4 (26.7)
- Fatal	4 (2.7)	3 (3.9)	2 (3.9)	1 (6.7)
-Hospitalization/prolong existing hospitalization	NA	NA	NA	NA
-Life-threatening	NA	NA	NA	NA

-Disability/incapacity - Other (medically significant) AE leading to dropout	NA NA	NA NA	NA NA	NA NA
Psychiatric disorders	40 (26.7)	10 (13.2)	7 (13.7)	2 (13.3)
Nervous system disorders Injury, poisoning and procedural complications	58 (38.7) 33 (22.0)	31 (40.8) 11 (14.5)	16 (31.4) 14 (27.5)	7 (46.7) 5 (33.3)
Cardiac disorders	10 (6.7)	5 (6.6)	3 (5.9)	3 (20.0)
Vascular disorders Cerebrovascular disorders (cerebral haemorrhage/infarction)	22 (14.7) 1 (0.7)	12 (15.8) 2 (2.6)	6 (11.8) 0 (0.0)**	3 (20.0) 1 (6.7)
Infections and infestations Anticholinergic syndrome Quality of life decreased	67 (44.7) NA NA	31 (40.8) NA NA	17 (33.3) NA NA	8 (53.3) NA NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	NA	NA	NA	NA
Influenza like illness	51 (34.0)	23 (30.3)	12 (23.5)	3 (20.0)

*Percentage based on the total number of subjects in the talimogene laherparepvec arm in the safety set. **Based on the totality of data as provide by the Applicant.

Safety related to drug-drug interactions and other interactions

The applicant did not submit studies with drug-drug interactions.

Discontinuation due to adverse events

An overview of the Treatment-Emergent AEs leading to discontinuation is provided in Table 47.

Table 47: Treatment-Emergent Adverse Events leading to permanent Study treatment discontinuation by preferred term (primary melanoma analysis set)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting treatment-emergent adverse events leading to study	8 (6.3)	29 (9.9)	37 (8.8)

treatment discontinuation			
Disease progression	1 (0.8)	4 (1.4)	5 (1.2)
Metastatic malignant melanoma	0 (0.0)	2 (0.7)	2 (0.5)
Asthenia	0 (0.0)	1 (0.3)	1 (0.2)
Bone pain	0 (0.0)	1 (0.3)	1 (0.2)
Bronchial hyperreactivity	0 (0.0)	1 (0.3)	1 (0.2)
Cardiac failure congestive	0 (0.0)	1 (0.3)	1 (0.2)
Cellulitis	0 (0.0)	1 (0.3)	1 (0.2)
Cerebral haemorrhage	0 (0.0)	1 (0.3)	1 (0.2)
Deep vein thrombosis	0 (0.0)	1 (0.3)	1 (0.2)
Dehydration	0 (0.0)	1 (0.3)	1 (0.2)
Failure to thrive	0 (0.0)	1 (0.3)	1 (0.2)
Glomerulonephritis	0 (0.0)	1 (0.3)	1 (0.2)
Influenza like illness	0 (0.0)	1 (0.3)	1 (0.2)
Keratitis herpetic	0 (0.0)	1 (0.3)	1 (0.2)
Lymphadenopathy	0 (0.0)	1 (0.3)	1 (0.2)
Metastases to central nervous system	1 (0.8)	1 (0.3)	2 (0.5)
Muscular weakness	0 (0.0)	1 (0.3)	1 (0.2)
Obstructive airways disorder	0 (0.0)	1 (0.3)	1 (0.2)
Performance status decreased	0 (0.0)	1 (0.3)	1 (0.2)
Pleuritic pain	0 (0.0)	1 (0.3)	1 (0.2)
Pneumonitis	0 (0.0)	1 (0.3)	1 (0.2)
Rash	0 (0.0)	1 (0.3)	1 (0.2)
Sepsis	0 (0.0)	1 (0.3)	1 (0.2)
Spinal column stenosis	0 (0.0)	1 (0.3)	1 (0.2)
Tumour haemorrhage	1 (0.8)	1 (0.3)	2 (0.5)
Vomiting	0 (0.0)	1 (0.3)	1 (0.2)
Arthritis	1 (0.8)	0 (0.0)	1 (0.2)
Dyspnoea	1 (0.8)	0 (0.0)	1 (0.2)
Oedema peripheral	1 (0.8)	0 (0.0)	1 (0.2)
Renal failure acute	1 (0.8)	0 (0.0)	1 (0.2)
Small intestinal haemorrhage	1 (0.8)	0 (0.0)	1 (0.2)

Post marketing experience

Talimogene laherparepvec was not marketed at the time of assessment of the marketing authorisation application.

2.6.1. Discussion on clinical safety

The most common treatment emergent adverse events with talimogene laherparepvec were fatigue, chills, pyrexia, nausea, influenza like illness and injection site pain. All these treatment-emergent AEs had a crude incidence of > 25% among those exposed to talimogene laherparepvec in the Primary Melanoma Analysis Set. Almost all subjects (90%) experienced what was determined as "flu-like symptoms". Most of the AEs were mild to moderate in severity.

There were two cases of cerebral hemorrhage in subjects with a history of brain metastases. The potential association of these two events with talimogene laherparepvec can neither be confirmed nor rejected at this stage. As cerebral metastases were applied as trial exclusion criteria for study 005/05, the SmPC section 4.4 has been updated to indicate that there is limited experience with the use of the product in patients with active brain metastases and therefore caution should be exercised when treating such patients.

Cellulitis at the injection site, impaired wound healing and injection site reactions are relevant adverse drug reactions associated with exposure to talimogene laherparepvec and have been included in the RMP as important safety concerns. The local reactions at the injection site may reflect local tumour lysis whereas no signs for AEs reflecting systemic tumour lysis were identified. Herpes simplex virus infection was reported in 5.5% of subjects in the talimogene laherparepvec group and 1.6% of subjects in the GM-CSF group. Most was oral herpes while no testing of wild type versus vaccine strain was performed.

In the pivotal clinical trial (study 1), events of cellulitis did not lead to permanent discontinuation of Imlygic treatment. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds (SmPC section 4.8).

Necrosis or ulceration of tumour tissue may occur following Imlygic treatment. Cellulitis and systemic bacterial infection have been reported. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds (SmPC section 4.4).

In clinical studies, impaired healing at the injection site has been reported. Imlygic may increase the risk of impaired healing in patients with underlying risk factors (e.g. previous radiation at the injection site or lesions in poorly vascularised areas) (SmPC section 4.4).

Consider the risks and benefits of Imlygic before continuing treatment if persistent infection or delayed healing develops (SmPC section 4.4).

Plasmacytoma is considered as an important identified risk. In clinical trials, one case of plasmacytoma at injection site was observed in a patient who was found to have multiple myeloma (SmPC section 4.8).

Plasmacytoma has been reported in proximity to the injection site after administration of Imlygic. Consider the risks and benefits of Imlygic in patients with multiple myeloma or in whom plasmacytoma develops during treatment (SmPC section 4.4).

One subject in the talimogene laherparepvec treatment group experienced a serious event of obstructive airway disorder, which resolved. This event was serious and grade 4 in severity and has

been included in the RMP as an important identified risk . Obstructive airway disorder has been reported following Imlygic treatment. Use caution when injecting lesions close to major airways (SmPC section 4.4).

In the phase 3 melanoma clinical study, the subject incidence of adverse events of deep vein thrombosis was 2.1% (n = 6) in the talimogene laherparepvec group (95% CI: 0.8, 4.4). In Study 005/05, 6 subjects (2.1%) treated with talimogene laherparepvec reported the adverse event of deep vein thrombosis. Of these, 3 adverse events were nonserious and 3 adverse events were serious. DVT has been identified as an important identified risk (SmPC section 4.8).

In all melanoma studies immune-mediated adverse events occurred in 1.7% (n=5) in subjects receiving talimogene laherparepvec versus 0.8% (n=1) subjects receiving GM-CSF group. Thus immune-mediated adverse events have been identified as important identified risks. In clinical studies, immune-mediated events including as glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with Imlygic. Vitiligo was reported in 5.1% of subjects treated with talimogene laherparepvec.Immune-mediated events reported in the pivotal clinical study included one case each of worsening psoriasis in a patient with a prior history of psoriasis, one case of pneumonitis in a patient with a prior history of autoimmune disease, one case of vasculitis, and one case of glomerulonephritis with an etiology of toxic/analgesic nephropathy. Permanent discontinuation of Imlygic treatment was reported in the patient who developed glomerulonephritis. The HCP should consider the risks and benefits of Imlygic before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events (SmPC section 4.4).

The safety data base is small in terms of the level and duration of exposure. This is considered acceptable based on the available data on quality and non-clinical issues indicating a minimal risk for clinically relevant latent infections with talimogene laherparepvec, low virulence in immunocompetent subjects as well as the non-integrating nature of talimogene laherparepvec. However, immunocompetent patients receiving talimogene laherparepvec could later become immunocompromised and, at least in theory, susceptible for disseminated herpetic infection induced by a latent infection with talimogene laherparepvec. Thus, the uncertainties in the clinical safety data support the post approval safety monitoring. A registration study will be set to monitor the long term safety of patients that have received talimogene laherparepvec (see RMP).

Whether patients who are not severely immunocompromised (those with conditions limited to T cell dysfunction such as HIV, AIDS, or patients with common variable immunodeficiency or those who require chronic treatment with steroids or other immunosuppressive agents) may be at increased risk of disseminated herpectic infection has not been established. The potential risk of disseminated herpetic infection and the potential benefits of treatment should be considered before administering talimogene laherparepvec to immunocompromised patients (such as those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency, or those who require chronic high-dose steroids or other immunosuppressive agents). The SmPC 4.4 states to consider the potential risks and potential benefits of treatment with talimogene laherparepvec before administering to immunocompromised patients (such as those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency or those who require chronic, high-dose steroids or other immunosuppressive agents). The SmPC section 4.3 contains a contra-indication in patients who are severely immunocompromised (e.g. patients with severe congenital or acquired cellular and/or humoral immune deficiency). It is also contraindicated to administer talimogene laherparepvec in patients with a history of hypersensitivity to talimogene laherparepvec or any of its excipients.

In clinical studies, herpetic infections (including cold sores and herpes keratitis) have been reported in patients treated with Imlygic. Symptoms of a local or systemic infection possibly related to Imlygic are anticipated to be similar to symptoms caused by wild-type HSV-1 infections (SmPC section 4.4).

90% of patients treated with Imlygic experienced influenza-like symptoms. Pyrexia, chills, and influenza like illness, which can occur any time during Imlygic treatment, generally resolved within 72 hours. These events were reported more frequently within the period of the first 6 treatments, particularly in patients who were HSV-1 negative at baseline (SmPC section 4.8).

Individuals with wild-type HSV-1 infection are known to be at a lifelong risk for symptomatic herpetic infection due to reactivation of latent wild-type HSV-1. Symptomatic herpetic infection due to possible reactivation of Imlygic should be considered (SmPC section 4.4).

Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission (SmPC section 4.4).

Talimogene laherparepvec is sensitive to acyclovir. Consider the risks and benefits of Imlygic treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection. These agents may interfere with the effectiveness of Imlygic if administered systemically or topically directly to the injection site (SmPC section 4.4).

Patients who were HSV-1 seronegative at baseline were reported to have a greater incidence of pyrexia, chills, and influenza-like illness compared with those who were HSV-1 seropositive at baseline, especially within the period of the first 6 treatments (see section 4.8).

Combination with other therapies like chemotherapy or immunosuppressive agents. Immunosuppression can lead to immunodeficiency and put that patient at risk of HSV herpetic infection. Thus this has been identified as an important potential risk (SmPC section 4.4).

Talimogene laherparepvec is intended only be used as prescribed medicine, the supply and traceability of talimogene laherparepvec is to be controlled and monitored. Talimogene laherparepvec is intended only be distributed to qualified centres, which have restricted access and appropriate facilities to handle GMO's, and adequately trained and experienced HCPs (see Annex II of the SmPC).

Accidental exposure to Imlygic (SmPC section 4.4)

Accidental exposure may lead to transmission of Imlygic and herpetic infection. Healthcare professionals and close contacts (e.g. household members, caregivers, sex partners or persons sharing the same bed) should avoid direct contact with injected lesions or body fluids of treated patients during the entirety of the treatment period and up to 30 days after the last treatment administration (see section 6.6). Accidental needle stick and splash-back have been reported in healthcare providers during preparation and administration of Imlygic.

Close contacts who are pregnant or immunocompromised should not change the patient's dressing or clean their injection site. Pregnant women, neonates, and immunocompromised individuals should not be exposed to potentially contaminated materials.

Ensure that patients are able to comply with the requirement to cover injection sites with occlusive dressings (see section 6.6). Patients should also be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of Imlygic to other areas of their body or to their close contacts.

Although it is not known if Imlygic could be transmitted through sexual contact, it is known that wild-type HSV-1 can be transmitted through sexual contact. Patients should be advised to use a latex condom during sexual contact to prevent possible transmission of Imlygic. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with Imlygic (see section 4.6).

Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials (see sections 4.2 and 6.6).

In the event of an accidental exposure to Imlygic, exposed individuals should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare professional. Talimogene laherparepvec is sensitive to acyclovir.

Proximity of close contacts and HCPs to lesions in treated patients in the absence of effective barriers may result in unintentional exposure to talimogene laherparepvec. Exposure may occur via direct contact with injected lesions or via contact with body fluids. A clinical study is in progress to inform whether talimogene laherparepvec is present in ł orolabial and anogenital secretions of treated patients (RMP). The biodistribution and shedding of intralesionally administered talimogene laherparepvec are being investigated in a dedicated study (20120324) (see clinical pharmacology discussion).

Communication of risks and precautions are provided in the SPC and PIL to minimise the risk of transmission to an unintended individuals (including the accidental exposure). A description of the main symptoms of wild type HSV-1 infection, with instructions to inform a medical professional should the patient or a close contact of the patient display symptoms. Instructions for the management of such an infection are included in the SmPC section 6.6. In addition to SPC and PIL, educational materials addressed to the HCP and patients will also communicate risks and precautions to physicians and patients.

A Physician Education Booklet is provided to inform HCPs about important risks associated with talimogene laherparepvec (disseminated herpetic infection in severely immunocompromised individuals, potential harm to the fetus or neonate in pregnancy, herpetic infection in talimogene laherparepvec -treated patients, and accidental exposure of close contacts and HCPs to talimogene laherparepvec).

Patient Safety Brochures are provided to prescribing physicians for distribution to patients receiving talimogene laherparepvec, including information patients can share with family, caregivers, and close contacts, and information on the risks of transmission of talimogene laherparepvec, herpetic infection, and serious infection in immunocompromised individuals.

Patient Alert Cards are provided to prescribing physicians for distribution to patients receiving talimogene laherparepvec.

There is a lack of data from special groups, such as pregnant and lactating women and patients with brain metastases. These have been identified as missing information and will be monitored using routine minimisations measures (SmPC) and with additional risk minimisation measures (managed distribution program, educational material, and a patient alert card). A pregnancy surveillance program will be implemented

There is no data on patients with renal or hepatic impairment, cardiac impairment, ethnic origin, bone metastases, cerebral metastases, patients with more than 3 visceral lesions, ocular melanoma,

mucosal melanoma, treatment of patients with metastatic lesions greater than 3 cm and patients below the age of 40 years. These will be monitored through PSURs.

Imlygic contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine (SmPC section 4.4).

Each 4 mL dose of Imlygic contains approximately 30 mg (1.3 mmol) sodium. To be taken into consideration by patients on a controlled sodium diet (SmPC section 4.4).

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded (or stated) in the patient file (SmPC section 4.4).

No interaction studies have been conducted with Imlygic. Acyclovir and other anti-viral agents may interfere with the effectiveness of Imlygic if administered systemically or topically directly to the injection site. Consider the risks and benefits of Imlygic treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection (SmPC section 4.5).

Transmission of Imlygic via sexual contact (SmPC section 4.6)

All patients should be advised to use a latex condom during sexual contact to prevent possible transmission of Imlygic (see section 4.4).

Contraception (SmPC section 4.6)

Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with Imlygic.

Pregnancy (SmPC section 4.6)

Adequate and well controlled studies with talimogene laherparepvec have not been conducted in pregnant women. No effects on embryo-foetal development have been observed in animal studies (see section 5.3). As a precautionary measure, it is preferable to avoid the use of talimogene laherparepvec during pregnancy.

If a pregnant woman has an infection with wild type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier, and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a foetus or neonate contracts the wild type herpes infection. While there are no clinical data to date on talimogene laherparepvec infections in pregnant women, there could be a risk to the foetus or neonate if talimogene laherparepvec were to act in the same manner.

Transplacental metastases of malignant melanoma can occur. Because talimogene laherparepvec is designed to enter and replicate in the tumour tissue, there could be a risk of foetal exposure to talimogene laherparepvec from tumour tissue that has crossed the placenta.

If Imlygic is used during pregnancy or if the patient becomes pregnant while taking Imlygic, the patient should be apprised of the potential hazards to the foetus and/or neonate.

Breast-feeding (SmPC section 4.6)

It is unknown whether talimogene laherparepvec is transferred into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Imlygic therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility (SmPC section 4.6)

No clinical studies have been performed to evaluate the effects of talimogene laherparepvec on fertility (nonclinical data are discussed in section 5.3).

Talimogene laherparepvec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as dizziness and confusional state (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that talimogene laherparepvec does not adversely affect them.

There is no clinical experience with overdose with Imlygic. Doses up to 4 mL at a concentration of 108 PFU/mL every 2 weeks have been administered in clinical trials with no evidence of dose limiting toxicity. The maximum dose of Imlygic that can be safely administered has not been determined. In the event of a suspected overdose or inadvertent intravenous administration, the patient should be treated symptomatically, e.g. with acyclovir or other anti-viral agents (see section 4.4) and supportive measures instituted as required.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Although the safety database for talimogene laherparepvec is limited and knowledge on long-term safety is missing, the ADRs reported for patients being treated with talimogene laherparepvec appear to be acceptable as most are low grade and manageable. The risk of transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) has been identified as a potential risk. The applicant has included as additional risk minimisation activities educational material for the HCP and the patient to inform about the risk associated with talimogene laherparepvec. The patient alert cards will advise the patient of the risks of talimogene laherparepvec including the risk of transmission of talimogene laherparepvec, signs and symptoms of herpetic infections and on the use of talimogene laherparepvec in pregnancy. The controlled distribution programme is aimed to manage the product supply chain and to ensure that cold storage requirements are observed and to control the distribution of IMLYGIC to qualified centres and up to the patients.

The CHMP endorse the CAT conclusion on clinical safety as described above.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CAT considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The PRAC considered that the risk management plan version 1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CAT endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CAT.

The CAT endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Table 48: Safety concerns

Summary of safety concerns	
Important identified risks	Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) Accidental exposure of HCP to talimogene laherparepvec Obstructive airway disorders Immune-mediated adverse reactions Plasmacytoma at the injection site Deep vein thrombosis Cellulitis at site of injection
Important potential risks	Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) Symptomatic talimogene laherparepvec infection in non-tumour

Summary of safety concerns	
	tissue in treated patients Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection Combination with other therapies like chemotherapy or immunosuppressive agents Recombination of talimogene laherparepvec with wild-type HSV-1 virus may occur Impaired wound healing at site of injection Delayed next line treatment in non-responders Loss of efficacy in patients treated with systemic acyclovir for complications Talimogene laherparepvec-mediated anti-GM-CSF antibody response
Missing information	Additional clinical biodistribution and shedding data in melanoma Pregnant and lactating women Pediatric patients Patients below the age of 40 years Patients with renal or hepatic impairment Treatment of patients with cardiac impairment Patients of race or ethnic origin other than white Long-term safety data Long-term efficacy data Treatment of patients with bone metastases Treatment of patients with cerebral metastases Treatment of patients with more than 3 visceral lesions Treatment of patients with metastatic lesions greater than 3 cm Treatment of patients with ocular melanoma Treatment of patients with mucosal melanoma

Pharmacovigilance plan

Table 49: Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Study 20120139 A registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec Category 3	• To evaluate the long-term safety of talimogene laherparepvec • To monitor subject overall survival	Long-term safety data Long-term efficacy data	Ongoing	Final study report anticipated July 2023
Study 20130193 A post-marketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and healthcare providers; and long-term safety in treated patients Category 3	• To estimate the incidence rate of herpetic lesions containing talimogene laherparepvec DNA among patients for 5 years after initiating talimogene laherparepvec • To estimate the incidence proportion of patients having a herpetic lesion containing talimogene laherparepvec DNA within 6 months of initiating talimogene laherparepvec • To estimate the incidence rate of	Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) Accidental exposure of HCP to talimogene laherparepvec Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require	Planned	Annual interim reports to be included in the PSUR/PBRER and DSUR Final study report anticipated 1Q 2025

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status planned, started,	Date for submission of interim or final reports (planned or actual)
	herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among immunocompromised patients receiving talimogene laherparepvec • To estimate the incidence rate of herpetic lesions containing talimogene laherparepvec DNA among patients after ending use of talimogene laherparepvec (ie, symptomatic reactivation) • To count the number of close contacts and HCPs having a herpetic lesion containing talimogene laherparepvec DNA • To characterize herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among close contacts and HCPs • To characterize adverse drug	high-dose steroids or other immunosuppressive agents) Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) Symptomatic talimogene laherparepvec infection in non-tumour tissue in treated patients Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection Combination with other therapies like chemotherapy or immunosuppressive		

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status planned, started,	Date for submission of interim or final reports (planned or actual)
	reactions and serious adverse drug reactions among patients receiving talimogene laherparepvec • To describe the demographics, disease characteristics, and treatment use among patients receiving talimogene laherparepvec in real world, clinical practice • To characterize overall survival of patients receiving talimogene laherparepvec in real world, clinical practice	agents Long-term safety data Long-term efficacy data		
Study 20120324 A phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma Category 3	• To estimate the proportion of subjects with detectable talimogene laherparepvec DNA in the blood and urine any time after administration of talimogene laherparepvec within the first 3 cycles • To estimate the incidence of clearance of talimogene laherparepvec DNA	Accidental exposure of HCP to talimogene laherparepvec Transmission of talimogene laherparepvec from patient to close contact or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) Symptomatic talimogene	Ongoing in US	Primary analysis clinical study report anticipated August 2016 Final analysis clinical study report anticipated February 2017

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status planned, started,	Date for submission of interim or final reports (planned or actual)
	from blood and urine overall and by baseline HSV-1 serostatus (seronegative versus seropositive) during each of the first 3 cycles • To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus from exterior of occlusive dressing and injected lesion • To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus in oral mucosa swabs during treatment and after end of treatment • To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA in genital swabs during treatment and after end of treatment for subjects injected with talimogene laherparepvec below the waist	laherparepvec infection in non-tumour tissue in treated patients Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients Additional clinical biodistribution and shedding data in melanoma		

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status planned, started,	Date for submission of interim or final reports (planned or actual)
	• To estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin • To describe the efficacy of talimogene laherparepvec as assessed by objective response rate, as well as by best overall response rate, duration of response, and durable response rate achieved in subjects with unresected, stage IIIB-IVM1c melanoma • To describe the safety profile of talimogene laherparepvec in subjects with unresected, stage IIIB-IVM1c melanoma			
Study 20110261 Phase 1, open label, dose de-escalation study to evaluate the tolerability, safety, and activity of	To be determined	Paediatric patients	Planned	Final study report anticipated 2Q 2021

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status planned, started,	Date for submission of interim or final reports (planned or actual)
talimogene laherparepvec in children from birth to < 18 years of age with melanoma or with advanced non-CNS tumours that are amenable to direct injection and for which no effective treatment is known Category 3				
Study Number: To be determined Randomized, controlled study to evaluate the safety and efficacy of talimogene laherparepvec in children from birth to < 18 years of age with a pediatric solid malignant tumour as part of a multi-modal treatment approach Category 3	To be determined	Paediatric patients	Planned	Final study report anticipated 2Q 2026

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 50: Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency)	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Accidental exposure of HCP to talimogene laherparepvec	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 6.6, Special precautions for disposal and other handling	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Obstructive airway disorders	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	need to know before and during Imlygic treatment • Section 4, Possible side effects	
Immune-mediated adverse reactions	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment • Section 4, Possible side effects	None
Plasmacytoma at the injection site	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment • Section 4, Possible side effects	None
Deep vein thrombosis	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Relevant text is provided in the following sections of the Package Leaflet: • Section 4, Possible side effects	
Cellulitis at site of injection	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	None
Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents)	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 6.6, Special precautions for disposal and other handling Relevant text is provided in the following sections of the	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	
Symptomatic talimogene laherparepvec infection in non-tumour tissue in treated patients	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the Package Leaflet:	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 2, What do you need to know before and during Imlygic treatment	
Combination with other therapies like chemotherapy or immunosuppressive agents	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Recombination of talimogene laherparepvec with wild-type HSV-1 virus may occur	None	None
Impaired wound healing at site of injection	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	None
Delayed next line treatment in non-responders	None	None
Loss of efficacy in patients treated with systemic acyclovir for complications	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use Relevant text is provided in the following sections of the Package Leaflet:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 2, What do you need to know before and during Imlygic treatment	
Talimogene laherparepvec-mediated anti-GM-CSF antibody response	None	None
Additional clinical biodistribution and shedding data in melanoma	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 5.2, Pharmacokinetic properties	None
Pregnant and lactating women	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy, and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the Package Leaflet: • Section 2, What do you need to know before and during Imlygic treatment	Managed distribution program, physician education booklet (PEB), patient safety brochure, patient alert card
Pediatric patients	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration	None
Patients below the age of 40 years	None	None
Patients with renal or hepatic impairment	Relevant text is provided in the following sections of the SmPC:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 4.2, Posology and method of administration	
Treatment of patients with cardiac impairment	None	None
Patients of race or ethnic origin other than white	None	None
Long-term safety data	None	None
Long-term efficacy data	None	None
Treatment of patients with bone metastases	None	None
Treatment of patients with cerebral metastases	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use	None
Treatment of patients with more than 3 visceral lesions	None	None
Treatment of patients with metastatic lesions greater than 3 cm	None	None
Treatment of patients with ocular melanoma	None	None
Treatment of patients with mucosal melanoma	None	None

The CHMP endorse the PRAC and CAT advice on the RMP.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary analysis of the phase III study 005/05 talimogene laherparepvec resulted in a statistically significant improvement in the primary endpoint, Durable Response Rate (DRR), compared with GM-CSF (16.3% vs. 2.1%), with unadjusted odds ratio (95% CI) of 8.9 (2.7, 29.2), $p < 0.0001$. Overall survival was a secondary endpoint and the study does not provide enough statistical power to show a statistically significant difference for this endpoint. A trend in increased OS was observed in the talimogene laherparepvec arm, with median OS of 23.3 months in the talimogene laherparepvec treated group and 18.9 months in the GM-CSF treated group (HR 0.79; 95% CI 2.7-29.2; p-value 0.0511).

The analyses of all but one of the secondary endpoints (including ORR, disease burden, TTF, duration of response and response interval) favoured treatment with talimogene laherparepvec over GM-CSF. Time to response onset was fairly similar in the two arms.

Lesion-level response analyses indicated a loco-regional and systemic effect for talimogene laherparepvec. Nearly two-thirds of injected lesions and one-third of non-injected/non-visceral lesions decreased in size by ≥ 50%; and approximately 15% of non-injected/visceral lesions decreased in size by ≥50%. Overall subject-level responses were seen in subjects with non-injected/non-visceral lesions as well as in subjects with non-injected/visceral lesions.

In an analysis grouping disease stages consistent with the presence or absence of visceral disease, the durable response rates (DRR) for talimogene laherparepvec and GM-CSF were 25.2% vs 1.2% in subjects with Stage IIIB-C/IVM1a disease and 5.3% vs 3.6% in subjects with Stage IVM1b-c disease, respectively. For subjects with Stage IIIB-C/IVM1a disease, consistent results were observed also for the objective response rate (40.5% vs. 2.3% GM-CSF, [CR 16.6% vs. 0% GM-CSF]) and overall survival (OS), were a 19.6-month increase in favour of the talimogene laherparepvec arm was found (41.1 vs 21.5 months). Therefore, the indication has been restricted to patients without visceral disease.

Uncertainty in the knowledge about the beneficial effects

Secondary and subgroup analyses of overall survival indicate differences between the survival distributions of the talimogene laherparepvec group compared to the GM-CSF group, in particular after excluding late stage patients. A trend in OS favouring talimogene laherparepvec was observed, however due to the exploratory nature of these analyses the magnitude of the OS gain cannot be concluded on.

There were no samples taken to assess against validated biomarkers that could be predictive of response. Thus, the CAT has imposed three conditions to the marketing authorisation (see below Recommendations section) to further study the role of biomarkers to predict the efficacy of talimogene laherparepvec, and to identify patient subgroups that benefit from talimogene laherparepvec.

Risks

Unfavourable effects

The safety of Imlygic was evaluated in 295 patients (N=436, 295 Imlygic, 141 GM-CSF) in the pivotal study that received at least 1 dose of study treatment (see section 5.1). The median duration of exposure to Imlygic was 23 weeks (5.3 months). Twenty six (26) patients were exposed to Imlygic for at least one year.

The most commonly reported adverse reactions (≥ 25%) in Imlygic-treated patients were fatigue (50.3%), chills (48.6%), pyrexia (42.8%), nausea (35.6%), influenza-like illness (30.5%), and injection site pain (27.7%). Overall, ninety eight per cent (98%) of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis at the injection site (2.1%), however plasmocytoma has also been reported at the injection site but at a much lower frequency (see section 4.4 and 4.8 of the SmPC). Almost all subjects (90%) in the pivotal trial experienced what was determined as "flu-like symptoms" and the risk for such symptoms during the initial treatment cycles was especially elevated among subjects with negative serological HSV-status at baseline. Most of the AEs were mild to moderate in severity (63% grade I-II, 36% grade ≥3 in severity).

There is a risk for disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency).The SmPC already contains a contraindication in section 4.3 for patients who are severely immunocompromised (e.g. patients with severe congenital or acquired cellular and/or humoral immune deficiency) and a warning for immunocompromised patients (such as those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents). It is expected that the risk of transmission of talimogene laherparepvec is low and that the risk of an outbreak with talimogene laherparepvec is also negligible if the appropriate measures for disposing of the dressings are followed to prevent shedding of viruses from the tumour into the environment. Therefore, there is a warning in the SmPC section 4.4 on the accidental exposure of HCP to talimogene laherparepvec.

Obstructive airway disorders have been identified as an important identified risk. A warning has been included in the SmPC section 4.4 to use caution when injecting lesions close to the airways.

In clinical studies, immune-mediated events including as glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with Imlygic. Immune-mediated adverse reactions has been identified an important identified risk in the RMP and will be managed by recommendations in the SmPC and will be monitored through the registry study 20120139.

Deep vein thrombosis is a common ADR (SmPC section 4.8) with talimogene laherparepvec and has been identified as an important identified risk in the RMP and will be monitored through the registry study 20120139.

Uncertainty in the knowledge about the unfavourable effects

The number of subjects with melanoma exposed to talimogene laherparepvec for at least 1 year is 42. The majority (N=26) of these patients were enrolled in the pivotal trial forming the basis of the safety data. Thus, there is a lack of safety data for long-term exposure to talimogene laherparepvec. The cases of vitiligo demonstrate the ability of talimogene laherparepvec to induce an autoimmune reaction to normal melanocytes and against normal cells overall. In the absence of the knowledge of the target

antigens, it is difficult to predict the spectrum of autoimmunity associated with talimogene laherparepvec treatment. Thus, there was a potential signal for other immune mediated events which will be monitored through PSURs.

The totality of the available evidence, i.e. the characteristics of the GMO, the pharmacological data as well as the safety data, indicates that the risk for shedding and transmission of talimogene laherparepvec to third parties is small and reduced with appropriately used occlusive dressings on the injected sites. However, the clinical data available to date is considered of limited value for firm conclusions on the extent and duration of risk for transmission with talimogene laherparepvec. However appropriate recommendations on the length of time required to minimize the risk of transmission are included in the SmPC. Further information on viral shedding will be obtained from Study 20120324, a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma, which is part of the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Talimogene laherparepvec represents a novel therapeutic concept, an oncolytic virus, among anti-cancer therapies. Within the rapidly evolving standard-of-care of the regionally or distantly metastatic melanoma, the unmet medical need for new treatment approaches is acknowledged. Nevertheless, even in the context of novel treatment strategies and first-in-class products, certain principles of efficacy will remain: an anti-cancer medicinal product should demonstrate a true patient benefit, preferably in terms of improved survival, attenuation of disease progression and thereby an alleviation of the symptoms caused by the disease. There is no previous experience of DRR as a primary end point in the regulatory context or within the oncology community, and its clinical value remains to be fully established. It is acknowledged though that a durable response, as well as improved local disease control itself may be a clinical benefit for the patient as it may delay onset or worsening of symptoms and need for further treatment. There are data indicating that there is some consistency between the effects observed from DRR and exploratory subgroup analyses of OS. Although it is acknowledged that the data derive from post-hoc analyses of a single pivotal trial they provide supportive evidence for restricting the indication on the basis of the higher DRR observed in adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease.

The pronounced effect in the subgroup of patients with unresectable melanoma that is regionally or distantly metastatic with no visceral disease is considered biologically plausible, based on the well-known correlation between tumour burden and response to immune therapy, as well as the method of action of talimogene laherparepvec.

In the oncology setting, treatment by talimogene laherparepvec is relatively well-tolerated. The identified safety profile is considered to be compatible with a systemic effect induced by talimogene laherparepvec and activation of the immune system. The other serious or severe unfavourable effects identified for talimogene laherparepvec are considered to be manageable, since the sensitivity of talimogene laherparepvec to acyclovir offers the opportunity to counterbalance any symptoms of viral infection should they be intolerable or a serious risk to the patient.

Benefit-risk balance

Based on the results of the pivotal trial 005/05, the benefits of talimogene laherparepvec in the treatment of Imlygic is indicated 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 (see section 4.4 and 5.1), melanoma patients outweighed the adverse events. Therefore, the CHMP considers that the benefit-risk balance for talimogene laherparepvec in the proposed indication is positive.

Discussion on the benefit-risk balance

During the last few years, several new treatment options have been made available for advanced melanoma patients. This fist-in-class oncolytic virus which targets both the tumour as well as potentiating the immune system for long term immune surveillance is a novel therapy which will add value to the existing therapies. The safety data collected in study 005/05 did not reveal any major safety issues with talimogene laherparepvec monotherapy in melanoma patients, which is an advantage over other systemic therapies which have a higher toxicity and less tolerability.

Although talimogene laherparepvec is associated with an effect on DRR, it cannot be concluded that an effect on overall survival has been established for talimogene laherparepvec in the overall population and there are still uncertainties in the subgroup including stages IIIB, IIIC and IV M1a. A trend in OS favouring talimogene laherparepvec was observed, however due to the exploratory nature of these analyses the magnitude of the OS gain cannot be concluded on.

During the last few years, several new treatment options have been made available for use as the first- and second-line therapy for melanoma patients. In the present and future landscape of therapies for melanoma, the concept of oncolytic immune therapy may however find its place; yet a comprehensive biomarker programme and future studies are expected to help to identify and define the patient population that would respond best to talimogene laherparepvec.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by majority decision that the risk-benefit balance of Imlygic in 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 (see section 4.4 and 5.1), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Imlygic in 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 (see section 4.4 and 5.1), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of IMLYGIC in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to inform about important risks associated with IMLYGIC:

- Herpetic infection occurring throughout the entire body (disseminated herpetic infection) in immunocompromised individuals (those with any congenital or acquired cellular and/or humoral immune deficiency, ie, HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents)
- Accidental exposure of Healthcare Professionals (HCPs) to IMLYGIC
- Spread of IMLYGIC to close contacts or healthcare providers after direct contact with injected lesions or body fluids
- Symptomatic herpetic infection due to latency and reactivation of IMLYGIC or herpes (wild-type

HSV-1) in patients

- Patients with a weakened immune system (immunocompromised patients) treated with IMLYGIC and suffering from concomitant infection
- Combination with other therapies like chemotherapy or immunosuppressive agents
- Pregnant and lactating women

The MAH shall ensure that in each Member State where IMLYGIC is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and use IMLYGIC have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient alert card

- **Guide for healthcare professionals** shall contain the following key elements:
  - Information on the risk of herpetic infection in patients treated by IMLYGIC
  - Information on the risk of disseminated herpetic infection in immunocompromised individuals treated by IMLYGIC
  - Recommendation regarding accidental exposure of IMLYGIC to HCPs:
    - To always wear protective gown/laboratory coat, safety glasses and gloves while preparing or administrating IMLYGIC;
    - To avoid contact with skin, eyes, mucous membranes and ungloved direct contact with injected lesions or body fluids of treated patients;
    - Instruction on first aid after accidental exposure;
    - Immunocompromised and pregnant healthcare professionals should not prepare and administer IMLYGIC.
  - Recommendation regarding the accidental transmission of IMLYGIC from patient to close contacts or HCPs:
    - Instruction on how to behave after administration/accidental transmission and how and how often the dressing has to be changed and who should not change the dressing;
    - Instructions to minimize the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last

administration of IMLYGIC. The following activities should be avoided:

- Sexual intercourse without a latex condom
- Kissing if either party has an open mouth sore
- Common usage of cutlery, crockery, and drinking vessels
- Common usage of injection needles, razorblades and toothbrushes;

- Adequate waste disposal and decontamination, following the recommendations for disposal of biohazardous waste.

- Information on IMLYGIC use in pregnancy
- Instructions how to handle possible adverse events including providing of batch number when reporting adverse drug reactions

- **The patient alert card** shall contain the following key messages:
  - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using IMLYGIC
  - Contact details of the IMLYGIC prescriber
  - Details about IMLYGIC treatment start date, batch number, date administered, product manufacturer and license holder
  - Information of herpetic lesions

- The patient information pack should contain:
  - Patient information leaflet
  - A patient/carer and close contacts guide

- **The Patient/carer and close contacts guide** shall contain the following key messages:
  - A description of the important risks associated with the use of IMLYGIC;
  - Instruction on how to behave after administration and how and how often the dressing has to be changed and who should not change the dressing.
  - Information of the sign and symptoms of the risk of herpetic infection;
  - Information on IMLYGIC use in pregnancy;
  - Recommendation regarding the accidental transmission of IMLYGIC from patient to close contacts or HCPs:
    - Instructions to minimize the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC treatment through 30 days after the last administration of IMLYGIC. The following activities should be avoided:
      - Sexual intercourse without a latex condom

        - Kissing if either party has an open mouth sore
        - Common usage of cutlery, crockery, and drinking vessels
        - Common usage of injection needles, razorblades and toothbrushes;
    - Adequate waste disposal and decontamination, following the recommendations for disposal of biohazardous waste.
    - Instruction on how to behave after accidental transmission.

The controlled distribution programme is aimed to manage the product supply chain to ensure that cold storage requirements are observed and to control the distribution of IMLYGIC to qualified centres and up to the patients.

The MAH shall ensure that in each Member State where IMLYGIC is marketed, a system aimed to control distribution to IMLYGIC beyond the level of control ensured by routine risk minimisation measures. The following requirements need to be fulfilled before the product is dispensed:

- Adequately trained and experienced HCPs in order to minimize the risk of occurrence of specified adverse drug reactions in patients, HCPs, and close contacts of the patients;
- Trained HCPs and support personnel regarding safe and appropriate storage, handling, and administration of IMLYGIC, and clinical follow-up for patients treated with IMLYGIC;
- Provide specified safety information to patients and communicate to patients the importance for sharing this information with family and caregivers;
- Trained HCPs to record batch number information in patient´s charts and on the patient´s alert card for all injections and to provide the batch number when reporting adverse drug reactions.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH should submit the preliminary results of Study 20120325 (a phase 2, multicenter, open-label, single-arm trial to evaluate the correlation between objective response rate and baseline intratumoral CD8+T-lymphocyte density in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec)	31st December 2018
To submit the preliminary results from Study 20110266 (a phase 2, multicenter, randomized, open-label trial assessing the efficacy and safety of talimogene laherparepvec neoadjuvant treatment plus surgery vs surgery alone for resectable stage IIIB to IVM1a melanoma)	31th December 2019
To provide preliminary efficacy results from the phase III part of the Study 20110265 (a multicenter trial evaluating the combination of talimogene laherparepvec with pembrolizumab)	30th June, 2019

The CHMP endorse the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CAT review of data on the quality properties of the active substance, the CAT considers that talimogene laherparepvec is qualified as a new active substance.

The CHMP endorse the CAT conclusion on the new active substance status claim.

APPENDIX 1

Divergent Position

DIVERGENT POSITION

The application is not approvable since too many uncertainties relating to efficacy and safety still remain. The clinical relevance of the effect of Imlygic in the studied patient population (OS HR 79%, 95%CI 0.62-1.00) is unclear and based only a single pivotal trial in the first line setting. Only in a not intended exploratory subgroup analysis (Stage IIIB-IVM1a) an effect on overall survival was observed. The effect of Imlygic on overall survival in this post-hoc selected population cannot be considered convincingly demonstrated. Furthermore, the effect of treatment with Imlygic before or in combination on available effective systemic treatment options in this subgroup is unclear and could even be detrimental. Finally, the potential risk of postponement of currently available, probably more effective treatments for patients is considered unacceptable.

London, 22 October 2015

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Johann Lodewijk Hillege