Clinical trial results:
A Phase 3b, Multicenter, Open-label, Single-arm, Expanded Access Protocol of Talimogene Laherparepvec for the Treatment of Subjects in Europe With Unresected Stage IIIB to IVM1c Melanoma

Summary

EudraCT number	2014-002834-30
Trial protocol	AT
Global end of trial date	08 August 2017

Results information

Result version number	v1 (current)
This version publication date	18 August 2018
First version publication date	18 August 2018

Trial information

Trial identification

Sponsor protocol code	20120328

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02297529
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to provide access of talimogene laherparepvec for subjects with unresected stage IIIB to IVM1c melanoma in select countries in Europe until marketing authorization approval by the European Commission for the treatment of melanoma.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The protocol, informed consent form, other written subject information, and any advertising material were submitted to the Independent Ethics Committee (IEC) for written approval. A copy of the written approval of the protocol and informed consent form must have been received by Amgen before recruitment of subjects into the protocol and shipment of Amgen investigational product.
Before a subject's participation in the expanded access protocol, the investigator was responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the protocol and before any protocol-specific screening procedures or any investigational product(s) were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 11
Worldwide total number of subjects	11
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	4
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 3 centers in Switzerland from 12 August 2015 (first subject enrolled) to 08 August 2017 (date last subject completed study).

Pre-assignment

Screening details:

Eligible subjects were men and women ≥18 years of age with a histologically confirmed diagnosis of melanoma and unresected stage IIIB to IVM1c disease, regardless of prior line of therapy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Talimogene Laherparepvec

Arm description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter.

Arm type	Experimental
Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC®
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

The initial dose of talimogene laherparepvec was up to 4 mL at a concentration of 10 plaque-forming units (PFU)/mL administered by intralesional injection. The initial cycle was 21 days. Subsequent doses consisted of up to 4.0 mL of talimogene laherparepvec at a concentration of 10^8 PFU/mL every 14 days.

Number of subjects in period 1	Talimogene Laherparepvec
Started	11
Completed	10
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL followed by a dose of 10. PFU/mL 21 days after the initial dose and every 14 days thereafter.

Reporting group values	Overall Study	Total	
Number of subjects	11	11	
Age Categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	4	4	
85 years and over	2	2	
Age Continuous Units: years			
arithmetic mean	61.7		
standard deviation	± 17.8	-	
Gender Categorical Units: Subjects			
Female	6	6	
Male	5	5	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Multiple	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	11	11	

End points

End points reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter.

Primary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)[1]

End point description:

Treatment-related adverse events refer to treatment-emergent AEs that have possible or probable relation to study treatment as assessed by investigator.
The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to grade severity of AEs.
The Safety Analysis Set included all subjects who are enrolled and receive at least one dose of talimogene laherparepvec.

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days after the last dose, the median duration of treatment was 13.3 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting was descriptive (summary statistics), with no formal statistical testing performed.

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants				
Any adverse event (AE)	9			
AE ≥ Grade 2	6			
AE ≥ Grade 3	2			
AE ≥ Grade 4	1			
Serious adverse event	2			
AE leading to discontinuation of study drug	1			
Fatal adverse events	0			
Treatment-related adverse events (TRAE)	7			
TRAE ≥ Grade 2	4			
TRAE ≥ Grade 3	1			
TRAE ≥ Grade 4	1			
Treatment-related serious adverse event	1			
TRAE leading to discontinuation of study drug	1			
Treatment-related fatal adverse event	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Detectable Talimogene Laherparepvec DNA in Swab Samples Taken From Cold Sores, Vesicles, and Other Lesions Suspected to be Herpetic in Origin

End point title	Number of Participants with Detectable Talimogene Laherparepvec DNA in Swab Samples Taken From Cold Sores, Vesicles, and Other Lesions Suspected to be Herpetic in Origin[2]

End point description:

Swab samples were to be taken from any cold sore, vesicles, and other lesions suspected to be herpetic in origin (if any) to test for the presence of talimogene laherparepvec deoxyribonucleic acid (DNA).

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days after the last dose, the median duration of treatment was 13.3 weeks.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting was descriptive (summary statistics), with no formal statistical testing performed.

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: participants				

Notes:

[3] - No events were reported for DNA analysis

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after the last dose, the median duration of treatment was 13.3 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter.

Serious adverse events	Talimogene Laherparepvec		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningitis aseptic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermo-hypodermitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Talimogene Laherparepvec		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ovarian theca cell tumour			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	7		
Influenza like illness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	7		
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2 2 / 11 (18.18%) 3 2 / 11 (18.18%) 2		
Hepatobiliary disorders Biliary dilatation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash generalised subjects affected / exposed occurrences (all) Vitiligo subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		

Arthritis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 2 / 11 (18.18%) 3		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all) Soft tissue infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Vitamin B1 deficiency subjects affected / exposed occurrences (all)	 2 / 11 (18.18%) 2 1 / 11 (9.09%) 2 1 / 11 (9.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2015	A superseding protocol was required to address UK regulatory agency requirements. The administrative changes in the superseding protocol consisted of adding a note (Section 4.1.2, exclusion criteria # 220) and throughout protocol as appropriate stating that acceptable methods of effective contraception are defined in the Informed Consent and where required by local laws and regulations country-specific requirements are outlined in country-specific protocol supplements. Administration, typographical and formatting changes were made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported