Clinical trial results:
A Phase 1, Multi center, Open label, Dose De escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects with Advanced Non central Nervous System Tumors That are Amenable to Direct Injection

Summary

EudraCT number	2015-003645-25
Trial protocol	ES FR SE BE IT
Global end of trial date	29 November 2022

Results information

Result version number	v1 (current)
This version publication date	11 June 2023
First version publication date	11 June 2023

Trial information

Trial identification

Sponsor protocol code	20110261

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02756845
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001251-PIP01-11
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	29 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to determine the safety and tolerability of talimogene laherparepvec, as assessed by incidence of dose limiting toxicities (DLT), in pediatric participants with advanced non central nervous system (CNS) tumors that are amenable to direct injection.

Protection of trial subjects:

This trial was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	15
EEA total number of subjects	10

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)	2
Adolescents (12-17 years)	10
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 15 participants were enrolled across 11 centers in Belgium, Canada, France, Spain, Switzerland and the United States from August 2017 to November 2022.

Pre-assignment

Screening details:

Participants were screened to determine if they were eligible to join the trial up to 28 days prior to receiving their first dose. All participants received talimogene laherparepvec.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years

Arm description:

Participants aged 12 to ≤ 21 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Arm type	Experimental
Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	
Other name	TVEC
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Participants were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months.

Arm title	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years

Arm description:

Participants aged 2 to < 12 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

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injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months.

Number of subjects in period 1	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years
Started	13	2
Received Talimogene Laherparepvec	13	2
Completed	0	0
Not completed	13	2
Adverse event, serious fatal	12	2
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years

Reporting group description:

Participants aged 12 to ≤ 21 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Reporting group title	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years

Reporting group description:

Participants aged 2 to < 12 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Reporting group values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years	Total
Number of subjects	13	2	15
Age categorical Units: Subjects			
2 - < 12 years	0	2	2
12 - 21 years	13	0	13
Age Continuous Units: years			
arithmetic mean	15.2	9.0	
standard deviation	± 2.8	± 2.8	-
Sex: Female, Male Units:			
Female	5	0	5
Male	8	2	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	10	1	11
Unknown or Not Reported	1	0	1
Race/Ethnicity, Customized Units: Subjects			
White	9	2	11
Other	3	0	3
American Indian or Alaska Native	1	0	1

End points

End points reporting groups

Reporting group title	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years

Reporting group description:

Participants aged 12 to ≤ 21 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Reporting group title	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years

Reporting group description:

Participants aged 2 to < 12 years were administered an initial dose of talimogene laherparepvec at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Primary: Percentage of Participants Who Experienced a Dose-limiting Toxicity (DLT)

End point title	Percentage of Participants Who Experienced a Dose-limiting Toxicity (DLT)[1]

End point description:

All toxicities were graded using the Common Terminology Criteria for Adverse Events version 4.0.

The occurrence of any of the below was considered a DLT, if judged to be related to talimogene laherparepvec:
•Grade 4 non-hematologic toxicity
•Grade 3 non-hematologic toxicity that lasted > 3 days despite optimal supportive care
•Any ≥ grade 3 non-hematologic laboratory value if medical intervention was required, the abnormality led to hospitalization or the abnormality persisted for > 1 week unless deemed not clinically important per both investigator & sponsor
•Febrile neutropenia grade 3/4
•Thrombocytopenia < 25 x 10^9/L associated with bleeding event that required intervention
•Serious herpetic event
•Grade 5 toxicity
•Any intolerable toxicity that led to permanent discontinuation of talimogene laherparepvec

End point type	Primary

End point timeframe:

Day 1 to Day 35

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: NA

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	2		
Units: Percent of participants				
number (confidence interval 95%)				
Experienced a DLT	0.0 (0.0 to 28.5)	0.0 (0.0 to 84.2)		

Did Not Experience a DLT	100.0 (71.5 to 100.0)	100.0 (15.8 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the date of an initial response of CR or PR to the earlier of PD/death.

99999 - no evaluable data. No participants experienced a response of CR or PR, so DOR could not be calculated.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Days				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who experienced either complete response (CR) or partial response (PR) per modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) response criteria.

CR was defined as the disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR was defined as the decrease in tumor burdena ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.00 to 24.71)	0.0 (0.00 to 84.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR was defined as the number of days from the first dose of talimogene laherparepvec to the first objective assessment of response as per modified irRC-RECIST.

99999 - no evaluable data. No participants experienced a response of CR or PR, so TTR could not be calculated.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Days				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was defined as the time from the first dose of talimogene laherparepvec until objective tumor progression per irRC-RECIST.

TTP was estimated using the Kaplan-Meier method.

1.99999 - no evaluable data. Insufficient number of participants experienced disease progression, so TTP could not be calculated.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Months				
median (full range (min-max))	2.50 (0.0 to 9.0)	1.99999 (1.6 to 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from the first dose to the earlier of disease progression per modified irRC-RECIST or death from any cause.

PFS was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Months				

median (full range (min-max))	3.32 (1.1 to 11.6)	6.42 (1.6 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as as the time from first dose to the event of death from any cause.

OS was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of follow-up; maximum duration of follow-up was 54.51 months

End point values	Cohort A1: Talimogene Laherparepvec - Aged 12 to ≤ 21 Years	Cohort B1: Talimogene Laherparepvec - Aged 2 to < 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	2		
Units: Months				
median (full range (min-max))	9.40 (1.1 to 54.5)	8.02 (4.8 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: Day 1 to end of follow-up, maximum duration of follow-up = 54.51 months. AEs: Day 1 to 30 days after last dose. Maximum duration of treatment = 9.1 months in T-VEC Cohort A1 and 3.6 months in T-VEC Cohort B1

Adverse event reporting additional description:

Adverse events and serious adverse event are reported for all participants who received at least one dose of talimogene laherparepvec. Duration of treatment = ((The date of last dose of study drug - The date of first dose of study drug + 1)/365.25 * 12).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	T-VEC Cohort B1: Aged 2 to < 12 Years

Reporting group description:

Participants aged 2 to < 12 years were administered an initial dose of talimogene laherparepvec (T-VEC) at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Reporting group title	T-VEC Cohort A1: Aged 12 to ≤ 21 Years

Reporting group description:

Participants aged 12 to ≤ 21 years were administered an initial dose of talimogene laherparepvec (T-VEC) at a dose of up to 4.0 mL of 106 PFU/mL followed by a dose of up to 4.0 mL of 108 PFU/mL 21 days (± 3) later. All subsequent injections, up to 4.0 mL of 10^8 PFU/mL were administered every 14 (± 3) days for up to approximately 9 months. Talimogene laherparepvec was administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image ultrasound guidance.

Serious adverse events	T-VEC Cohort B1: Aged 2 to < 12 Years	T-VEC Cohort A1: Aged 12 to ≤ 21 Years	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	5 / 13 (38.46%)	
number of deaths (all causes)	2	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Osteosarcoma metastatic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour haemorrhage			

subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 2 (50.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	1 / 2 (50.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			

subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Vascular device infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	T-VEC Cohort B1: Aged 2 to < 12 Years	T-VEC Cohort A1: Aged 12 to ≤ 21 Years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	13 / 13 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	1 / 2 (50.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Embolism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Chills			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	9	
Face oedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	22	
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	4	
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	2 / 2 (100.00%)	9 / 13 (69.23%)	
occurrences (all)	5	22	
Malaise			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Injection site pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	4	
Injection site inflammation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 2 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	5	
Oedema peripheral			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	4	
Disease progression			
subjects affected / exposed	1 / 2 (50.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 2 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	4	
Dyspnoea exertional			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 2 (50.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
General physical condition abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Heat cramps			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Wound dehiscence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	3	
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 2 (50.00%)	5 / 13 (38.46%)	
occurrences (all)	1	13	
Neuralgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Presyncope			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	4	
Coagulopathy			

subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Dry mouth			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	1 / 2 (50.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	6 / 13 (46.15%)	
occurrences (all)	1	6	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Photosensitivity reaction			

subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Endocrine disorders			
Autoimmune hypothyroidism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	4	
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Joint contracture			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	2 / 13 (15.38%)	
occurrences (all)	1	11	
Musculoskeletal pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	1 / 2 (50.00%)	4 / 13 (30.77%)	
occurrences (all)	2	4	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Mastitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nail infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2017	* The upper age limit of eligible participants has been changed from 18 to 21 years of age * The lowest age cohort (0 to < 2 years of age) has been removed because of the following reasons: − the perceived toxicity risk of treating these pediatric patients, who have an immature immune system, with talimogene laherparepvec − the anticipated low benefit of talimogene laherparepvec treatment for this population for which standard of care and other proven salvage regimens are available for the type of advanced/recurrent/refractory pediatric tumor(s) seen in this age subset * The requirement to enroll participants according to herpes simplex virus type 1 (HSV-1) serostatus has been removed because of the following reasons: − low prevalence of HSV-1 positivity in the pediatric population − the addition of a recommendation to use premedication to mitigate the side effects of talimogene laherparepvec in HSV-1 negative participants * Maximum number of participants enrolled was changed from 36 to 27 subjects because of the changes in the age cohorts.
04 April 2017	Amendment continued: * Background and Rationale was updated with background information that supports changes to the study design. * Eligibility criteria were clarified and updated to reflect changes in the study design. * Recommendation to use premedication with the appropriate antipyretic and/or antiemetic medications prior to each talimogene laherparepvec treatment was added to Dosage, Administration, and Schedule Rules for DLT evaluation were clarified and stopping rules were updated. * Rules for opening younger age cohort were updated. * Rules for dose de-escalation were updated. * Childhood vaccinations that contain live attenuated virus were added to the list of excluded treatments. * Schedule of Assessments table was updated to: − clarify the timing of procedures. − add an additional pregnancy test and performance status assessments * Laboratory Assessments was updated to clarify which tests will be done locally versus centrally. * Text describing reporting procedures for serious adverse events was moved from Reporting Serious Adverse Events After the Protocol-required Reporting Period to Reporting Procedures for Serious Adverse Events. * Exploratory endpoints were updated. * Statistical Considerations was updated to reflect changes in the study design. * Appendix D was updated to clarify assessments for tumor response.

10 October 2018	* Update end of study language to align with the current protocol template language * Update contraception language to align with the current risk and discomforts language * Clarify transfusion timeframe in Inclusion Criterion 115 to ensure that adequate hematologic function is not confounded by a recent transfusion or growth factor support * Clarify that participants with history or evidence of giant congenital melanocytic nevi or dysplastic nevis syndrome are not excluded from the study because such participants are at risk of developing advanced melanoma with injectable disease and will therefore be eligible for the study * Shorten the washout period for prior chemotherapy, treatment dose radiotherapy, or biological cancer therapy from 28 days to 14 days prior to enrollment * Clarify that coagulation tests are only required at screening * Update the number of sites participating in the study * Update disease-related events language * Remove 'Reporting a Safety Endpoint as a Study Endpoint' section as this section is not applicable to this study * Update the matrix for determining the overall response to account for when nontarget lesion assessment was not done * Remove self-evident corrections language
12 June 2020	Updated: * the number of pediatric participants to be enrolled for the study from 18 to 27 to 18 to 24; * the number of DLT evaluable participants from 9 to 6 in the event of a dose de-escalation * the maximum of 18 participants treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable participants in cohort A1. Update sample size considerations and DLT evaluation: * From 6 to 12 DLT-evaluable participants to 18 to 24 participants enrolled and treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable participants in cohort A1 * Clarify the 3+3 phase 1 design is for age cohort opening and dose de-escalation, assuming a true DLT incidence rate < 33% is used (with a minimum of 6 DLT-evaluable participants) * Sample size for cohorts with age between 2 and 12 years are not required. * Clarified that after both cohorts are open, the Dose Level Review Team (DLRT) can review the safety data after the addition of 3 new DLT-evaluable participants in a cohort until there're 9 DLT-evaluable participants in the cohort. Additionally, ad-hoc meetings to review the safety data can be convened anytime, if deemed necessary. These changes were made to maximize the efficiency of the DLRT meeting based on safety need. * Updated the definition for primary completion date to occur 35 days after the last participant has enrolled and received at least 1 dose of talimogene laherparepvec. The definition is modified based on the changes in the minimum number of DLT evaluable participants for each cohort. * Updated objectives/endpoints * Added exploratory objectives and endpoint Inclusion criteria definition for adequate organ function is updated for * hematological: no transfusion/growth factor support within 7 days from screening assessment instead of 4 weeks from screening blood count * hepatic: serum bilirubin ≤ 1.5× baseline value if baseline value was abnormal for a participant with Gilbert's syndrome.

12 June 2020	Amendment continued: Exclusion criteria updated: * for central nervous system (CNS) tumor or clinically active brain metastases updated with the clarification that participants with a history of treated brain metastases shall be eligible if they fulfill the following criteria: radiographic evidence of improvement with CNS-directed therapy, and no interim progression is observed * for receiving treatment in another investigational study device or study drug and major surgery updated to 14 days since ending treatment * Major surgery ≤ 14 days prior to enrollment or has not recovered to CTCAE version 4.0 grade 1 or better from adverse event due to surgery performed more than 14 days prior to enrollment * Updated language for reporting the serious disease-related events as all events to be reported to sponsor or designee within 24 hours

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Participant recruitment ended when 15 participants were enrolled due to difficulties in enrollment.

Notes: