Clinical trial results:
A phase II study of intratumoral application of L19IL2/L19TNF in melanoma patients in clinical stage III or stage IV M1a with presence of injectable cutaneous and/or subcutaneous lesions.

Summary

EudraCT number	2012-001991-13
Trial protocol	IT
Global end of trial date	26 May 2015

Results information

Result version number	v1 (current)
This version publication date	13 July 2022
First version publication date	13 July 2022

Trial information

Trial identification

Sponsor protocol code	PH-L19IL2TNF-02/12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02076633
WHO universal trial number (UTN)	-
Other trial identifiers	INTRACOMBO PHASE 2: PH-L19IL2TNF-02/12

Notes:

Sponsors

Sponsor organisation name	Philogen S.p.A.
Sponsor organisation address	Località Bellaria, 35, Sovicille (SI), Italy, 53018
Public contact	Regulatory Affairs Department, Philogen S.p.A., +39 057717816, regulatory@philogen.com
Scientific contact	Regulatory Affairs Department, Philogen S.p.A., +39 057717816, regulatory@philogen.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	18 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy of L19IL2/L19TNF-treated lesions measured as rate of patients with complete response (CR) at week 12 (day 85).

Protection of trial subjects:

Safety of the patients was carefully evaluated during all the period in which the patient was in the study. During the active treatment phase, regular laboratory analysis of the common clinical parameters were performed, as also physical examination and vital signs monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2012
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	Italy: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	11
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 22 patients were enrolled from 05.12.2012 to 23.05.2014: 13 at the Milan site and 9 at the Siena site.

Pre-assignment

Screening details:

After obtaining patient informed consent, screening evaluations and procedures had to be performed within 14 days prior to the start of therapy. At the screening visit, a full evaluation of the status of patient was performed. Based on the information obtained from the assessments, the patient's eligibility was decided upon.

Period 1

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

Arms

Arm title	Single arm

Arm description:

Patients were treated with a combination of 10 Mio IU of L19IL2 and 312 µg of L19TNF to be administered in an approximate volume of 4.2 ml as a single or multiple intratumoral injection once every week for up to 4 weeks.
L19IL2 was dosed at 10 Mio IU per administration, the amount of L19TNF per administration was 312 µg. However, the dose could be adjusted between 78 and 312 µg per administration according to size and number of lesions and at the investigator's discretion. The total daily dose was distributed between all injectable soft-tissue metastases.

Arm type	Experimental
Investigational medicinal product name	Onfekafusp alfa
Investigational medicinal product code	L19TNF
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intratumoral use

Dosage and administration details:

Up to 312 µg of L19TNF intratumoral injection once every week for up to 4 weeks.

Investigational medicinal product name	Bifikafusp alfa
Investigational medicinal product code	L19IL2
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intratumoral use

Dosage and administration details:

10 Mio IU of L19IL2 intratumoral injection once every week for up to 4 weeks.

Number of subjects in period 1	Single arm
Started	22
Completed	7
Not completed	15
Consent withdrawn by subject	3
Adverse event, non-fatal	1
surgery of residual metastatic lesions	6
Progressive disease	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
median	64		
standard deviation	± 15.22	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	10	10	

Subject analysis sets

Subject analysis set title	Safety Evaluable Population (SE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All eligible patients who received at least one dose of the study treatment. An incorrect drug administration or an early termination of treatment did not result in exclusion of patients from this population.

Subject analysis set title	Efficacy Evaluable Population (EE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All eligible patients who received at least one dose of the study treatment and had at least one post-treatment tumor assessment

Subject analysis set title	Not evaluable patients for efficacy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Not evaluable patients for efficacy

Reporting group values	Safety Evaluable Population (SE)	Efficacy Evaluable Population (EE)	Not evaluable patients for efficacy
Number of subjects	22	20	2
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	11	10	
From 65-84 years	11	10	
85 years and over			
Age continuous			
Units: years			
median	64	61.5	
standard deviation	± 15.22	± 15.44	±
Gender categorical			
Units: Subjects			
Female	12	11	
Male	10	9	

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description:	
Patients were treated with a combination of 10 Mio IU of L19IL2 and 312 µg of L19TNF to be administered in an approximate volume of 4.2 ml as a single or multiple intratumoral injection once every week for up to 4 weeks. L19IL2 was dosed at 10 Mio IU per administration, the amount of L19TNF per administration was 312 µg. However, the dose could be adjusted between 78 and 312 µg per administration according to size and number of lesions and at the investigator's discretion. The total daily dose was distributed between all injectable soft-tissue metastases.	
Subject analysis set title	Safety Evaluable Population (SE)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All eligible patients who received at least one dose of the study treatment. An incorrect drug administration or an early termination of treatment did not result in exclusion of patients from this population.	
Subject analysis set title	Efficacy Evaluable Population (EE)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All eligible patients who received at least one dose of the study treatment and had at least one post-treatment tumor assessment	
Subject analysis set title	Not evaluable patients for efficacy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Not evaluable patients for efficacy	

Primary: Evaluation of the efficacy of L19IL2/L19TNF-treated lesions measured as rate of patients with complete response (CR) at week 12

End point title	Evaluation of the efficacy of L19IL2/L19TNF-treated lesions measured as rate of patients with complete response (CR) at week 12
End point description:	
The primary objective of the study is to evaluate the efficacy of L19IL2/L19TNF-treated lesions measured as rate of patients with complete response (CR) at week 12 (day 85).	
End point type	Primary
End point timeframe:	
From day 1 to week 12	

End point values	Efficacy Evaluable Population (EE)	Not evaluable patients for efficacy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	2		
Units: Subjects	2	0		

Statistical analyses

Statistical analysis title	Two-sided exact binomial statistical test

Statistical analysis description:

A two-sided exact binomial statistical test was applied for the rate of patients with CR, OR, and DC of the L19IL2/L19TNF-treated lesions and all lesions for all the available tumor assessments. The hypothesized value for the null hypothesis was 50%. The duration of OR and DC was calculated using Kaplan Meier estimator for the treated lesions and for all the lesions.

Comparison groups	Efficacy Evaluable Population (EE) v Not evaluable patients for efficacy
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	Binomial test

Secondary: Objective response rate (ORR) at week 12 for injected lesions

End point title	Objective response rate (ORR) at week 12 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Objective Response Rate (ORR) (that being, CR and partial response [PR])

End point type	Secondary

End point timeframe:

From day 1 to week 12

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at week 24 for injected lesions

End point title	Objective response rate (ORR) at week 24 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Objective Response Rate (ORR) (that being, CR and partial response [PR])

End point type	Secondary

End point timeframe:

From day 1 to week 24

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at week 36 for injected lesions

End point title	Objective response rate (ORR) at week 36 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Objective Response Rate (ORR) (that being, CR and partial response [PR])

End point type	Secondary

End point timeframe:

From day 1 to week 36

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 24 for injected lesions

End point title	Disease control rate (DCR) at week 24 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Disease Control Rate (DCR) (that being, CR, PR and stable disease [SD])

End point type	Secondary

End point timeframe:

From day 1 to week 24

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 12 for injected lesions

End point title	Disease control rate (DCR) at week 12 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Disease Control Rate (DCR) (that being, CR, PR and stable disease [SD])

End point type	Secondary

End point timeframe:

From day 1 to week 12

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 36 for injected lesions

End point title	Disease control rate (DCR) at week 36 for injected lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated lesions based on Disease Control Rate (DCR) (that being, CR, PR and stable disease [SD])

End point type	Secondary

End point timeframe:

From day 1 to week 36

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control for injected lesions

End point title	Duration of disease control for injected lesions

End point description:

Assessment of the duration of disease control (DC) in patients with treated lesions

End point type	Secondary

End point timeframe:

From day 1 to end of study

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Days				
median (confidence interval 95%)	346 (176 to 999999999999999.999999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response for injected lesions

End point title	Duration of objective response for injected lesions

End point description:

Assessment of the duration of objective response (OR) in patients with treated lesions

End point type	Secondary

End point timeframe:

From day 1 to end of study

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Days				
median (confidence interval 95%)	309 (75 to 999999999999999.9999999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 12 for treated and non-treated lesions

End point title	Disease control rate (DCR) at week 12 for treated and non-treated lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Disease Control Rate (DCR)

End point type	Secondary

End point timeframe:

From day 1 to week 12

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 24 for treated and non-treated lesions

End point title	Disease control rate (DCR) at week 24 for treated and non-treated lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Disease Control Rate (DCR)

End point type	Secondary
End point timeframe: From day 1 to week 24	

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) at week 36 for treated and non-treated lesions

End point title	Disease control rate (DCR) at week 36 for treated and non-treated lesions
End point description: Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Disease Control Rate (DCR)	
End point type	Secondary
End point timeframe: From day 1 to week 36	

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at week 12 for treated and non-treated lesions

End point title	Objective response rate (ORR) at week 12 for treated and non-treated lesions
End point description: Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Objective Response Rate (ORR)	

End point type	Secondary

End point timeframe:

From day 1 to week 12

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at week 24 for treated and non-treated lesions

End point title	Objective response rate (ORR) at week 24 for treated and non-treated lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Objective Response Rate (ORR)

End point type	Secondary

End point timeframe:

From day 1 to week 24

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at week 36 for treated and non-treated lesions

End point title	Objective response rate (ORR) at week 36 for treated and non-treated lesions

End point description:

Assessment of the efficacy of L19IL2/L19TNF on treated and non-treated lesions based on Objective

Response Rate (ORR)

End point type	Secondary

End point timeframe:

From day 1 to week 36

End point values	Efficacy Evaluable Population (EE)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Subjects	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the signature of the ICF to the end of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0
Reporting groups	
Reporting group title	Safety set (SAF)

Reporting group description: -

Serious adverse events	Safety set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
INJECTION SITE REACTION			
subjects affected / exposed	1 / 22 (4.55%)		
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	Safety set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			

ASTHENIA				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	5			
FATIGUE				
subjects affected / exposed	3 / 22 (13.64%)			
occurrences (all)	3			
CHILLS				
subjects affected / exposed	4 / 22 (18.18%)			
occurrences (all)	6			
INFLUENZA LIKE ILLNESS				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences (all)	2			
INJECTION SITE ERYTHEMA				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	1			
INJECTION SITE PAIN				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	1			
INJECTION SITE REACTION				
subjects affected / exposed	19 / 22 (86.36%)			
occurrences (all)	44			
MALAISE				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	2			
LOCALISED OEDEMA				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	1			
PYREXIA				
subjects affected / exposed	14 / 22 (63.64%)			
occurrences (all)	31			
OEDEMA				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	1			
PAIN				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences (all)	1			

Reproductive system and breast disorders			
VULVOVAGINAL PRURITUS			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
ALLERGIC PHARYNGITIS			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
DYSPNOEA			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
COUGH			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
SEROMA			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
JOINT SPRAIN			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	11 / 22 (50.00%)		
occurrences (all)	13		
MUSCLE CONTRACTIONS INVOLUNTARY			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	3		
MYOCLONUS			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
PRESYNCOPE			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Ear and labyrinth disorders VERTIGO subjects affected / exposed occurrences (all)	 4 / 22 (18.18%) 5		
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) FAECAL INCONTINENCE subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 2 / 22 (9.09%) 5 2 / 22 (9.09%) 3		
Skin and subcutaneous tissue disorders HYPERHIDROSIS subjects affected / exposed occurrences (all) ERYTHEMA subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 2 3 / 22 (13.64%) 3 3 / 22 (13.64%) 3		
Renal and urinary disorders URINARY INCONTINENCE subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1		
Musculoskeletal and connective tissue			

disorders ARTHRALGIA subjects affected / exposed occurrences (all) FLANK PAIN subjects affected / exposed occurrences (all) PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Infections and infestations HERPES ZOSTER subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1		
Metabolism and nutrition disorders HYPERURICAEMIA subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all) DECREASED APPETITE subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

N.A.

Notes: