

**Clinical trial results:****A pilot phase II study with BRENTUXIMAB VEDOTIN as pre-ASCT induction therapy in relapsed/refractory Hodgkin's lymphoma patients non responding to IGEV salvage treatment.****Summary**

EudraCT number	2013-003934-33
Trial protocol	IT
Global end of trial date	12 October 2018

Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021
Summary attachment (see zip file)	FIL_Bridge_synopsis (FIL_BRidge_synopsis.docx)

Trial information**Trial identification**

Sponsor protocol code	FIL_BRidge
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02244021
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione Italiana Linfomi Onlus
Sponsor organisation address	piazza Turati 5, Alessandria , Italy,
Public contact	Secretariat, Fondazione Italiana Linfomi Onlus, 0039 0131206129, segreteria@filinf.it
Scientific contact	Secretariat, Fondazione Italiana Linfomi Onlus, 0039 0131206129, segreteria@filinf.it

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	15 October 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the activity of brentuximab vedotin in terms of complete remission (CT scan and FDG-PET negative) in patients with relapsed/refractory Hodgkin's Lymphoma not responding (FDG-PET positive) to salvage treatment with IGEV.

Protection of trial subjects:

Appropriate precautions should be taken during infusion of the drug, with regular monitoring of vital signs, drugs available for the treatment of anaphylactic reaction, and a physician in attendance. Patients treated with brentuximab vedotin should be monitored closely during the infusion and be advised of the potential to develop allergy-like symptoms post-infusion.

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes following the first infusion of brentuximab vedotin.

During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to medical judgment and institution standards.

If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2014
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: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirteen patients recruited in Italy from first december 2014, with date of last completed at 27 October 2017

Pre-assignment

Screening details:

Inclusion criteria:

1. Classical Hodgkin Lymphoma according to the World Health Organisation (WHO) classification
2. Patients at the first line salvage therapy
4. FDG-PET positivity after two cycles of IGEV treatment
5. PBPCs should have been collected after the first or the second IGEV cycle
6. Age \geq 18 years
7. ECOG performance status of 0-

Period 1

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

Arms

Arm title	Single Arm
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Arm description:

After registration and eligibility check patients will receive a total of 4 courses of the study drug, one every three weeks. Brentuximab vedotin will be administered intravenously at the dose of 1.8 mg/kg. Brentuximab vedotin is to be administered on Day 1 of each 21-day cycle via a 30 minute intravenous (IV) infusion.

Arm type	Single arm study
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin will be administered intravenously at the dose of 1.8 mg/kg. Brentuximab vedotin is to be administered on Day 1 of each 21-day via a 30 minute intravenous (IV) infusion.

Number of subjects in period 1	Single Arm
Started	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	45		
full range (min-max)	19 to 66	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	4	4	
Stage			
Ann Arbor Stage			
Units: Subjects			
Stage IV	3	3	
Stage I-II	10	10	
ECOG-PS			
ECOG Performance Status			
Units: Subjects			
ECOG-PS >1	0	0	
ECOG 0-1	13	13	
Bulky Disease			
Mediastinal size >6 cm or lymph node >10 cm			
Units: Subjects			
Bulky, Yes	1	1	
Bulky, No	12	12	
Hemoglobin			
Units: g/dL			
median	10.7		
full range (min-max)	9.8 to 13.0	-	
WBC			

White Cell Count			
Units: 10 ⁹ /L			
median	4.10		
full range (min-max)	2.30 to 8.20	-	
ALC			
Absolute Lymphocyte Count			
Units: 10 ⁹ /L			
median	0.80		
full range (min-max)	0.40 to 1.40	-	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description: After registration and eligibility check patients will receive a total of 4 courses of the study drug, one every three weeks. Brentuximab vedotin will be administered intravenously at the dose of 1.8 mg/kg. Brentuximab vedotin is to be administered on Day 1 of each 21-day cycle via a 30 minute intravenous (IV) infusion.	
Subject analysis set title	Comparison
Subject analysis set type	Full analysis
Subject analysis set description: Comparison for single arm study	

Primary: Efficacy Evaluation

End point title	Efficacy Evaluation
End point description: Patients will be considered for assessment of efficacy if they have received four courses of Brentuximab vedotin and underwent FDG-PET and CT scan as prescribed by the study protocol. Complete Response will be defined according to recently updated international criteria (Cheson 2007), assuming that a negative PET is defined by Deauville scores 1, 2 and 3.	
End point type	Primary
End point timeframe: Patients assessed for efficacy after 4 cycles of brentuximab vedotin and evaluated by FDG-PET and CT scan. Patients was considered in CR with PET defined by Deauville Score from 1 to 3.	

End point values	Single Arm	Comparison		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10 ^[1]	10		
Units: Complete Response (CR)				
Deauville Negative (1-3)	5	5		
Deauville Positive (4-5)	5	5		

Notes:

[1] - Patients treated with 4 cycles of Brentuximab Vedotin

Statistical analyses

Statistical analysis title	Primary Efficacy end-point
Statistical analysis description: This study will be managed as a pilot phase II trial with a fixed sample size of 13 patients. We do not have results of previous studies with single agent SGN-35 in patients at first diagnosis. For efficacy we considered as precautionary measure the response from PET greater than 30%, regarded as inferior margin of confidence interval at 95%, according to the binomial distribution. So, we expect to observe 8 responsive patients from 13 enrolled (62%, 95%CI 32-86%)	
Comparison groups	Single Arm v Comparison

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.179
Method	One- sample Binomial test
Parameter estimate	Exact Binomial Distribution
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.81

Notes:

[2] - The complete response (CR, according to PET Deauville 1-3) rate was estimated by means of exact binomial distribution, with Clopper-Pearson binomial 95% confidence intervals.

For efficacy we considered as precautionary measure the response from PET greater than 30%, regarded as inferior margin of confidence interval at 95%, according to the binomial distribution

Primary: Safety Evaluation

End point title	Safety Evaluation
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End point description:

For safety we considered neurotoxicity as the most significant event with a frequency for any grade $\leq 50\%$. Based on the binomial distribution we expect to observe ≤ 2 events for 13 enrolled patients (15%, 95%CI 2-45%), so with toxicity less than 50%, respect to the higher margin of confidence interval at 95%.

End point type	Primary
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End point timeframe:

Patients treated with at least 1 cycle of Brentuximab Vedotin.

End point values	Single Arm	Comparison		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13 ^[3]	13		
Units: Neurotoxicity of any CTACE 4.03				
Neurotoxicity, Yes	4	4		

Notes:

[3] - Patients treated with at least 1 cycle of Brentuximab Vedotin

Statistical analyses

Statistical analysis title	Primary Safety end-point
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Statistical analysis description:

Result expressed with th exact binomial distribution, with Clopper-Pearson binomial 95% confidence intervals.

Comparison groups	Single Arm v Comparison
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Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[4]
Parameter estimate	Exact Binomial Distribution
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.61

Notes:

[4] - We observed 4 neurotoxicity: 2 of CTCAE grade 1, both in 3th cycle (hypoesthesia and cramps) and 2 of CTACE grade 2 (1st cycle, dysesthesia and tingling (upper arms); and 4th cycle, paresthesia). Than 4/13, 31% (95%CI 9-61%), with the upper margin greater than 50%.

Secondary: Response after Brentuximab Vedotine and ASCT

End point title	Response after Brentuximab Vedotine and ASCT
End point description:	
End point type	Secondary
End point timeframe:	
Complete Remission after autologous stem-cell transplantation (ASCT) in the 10 patients evaluable for efficacy	

End point values	Single Arm	Comparison		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10 ^[5]	10		
Units: Complete Response				
CR, Yes	8	8		

Notes:

[5] - Patients evaluable for efficacy

Statistical analyses

Statistical analysis title	Response after brentuximab vedotin and ASCT
Statistical analysis description:	
Considering the full treatment (4BV + consolidation with ASCT) over the 10 assessable patients, 8 CR and 2 PD, were observed with a CR rate of 80% (95CI 44-97%).	
Comparison groups	Single Arm v Comparison
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other ^[6]
Parameter estimate	Exact Binomial Distribution
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.97

Notes:

[6] - Observational

Secondary: Progression Free Survival

End point title | Progression Free Survival

End point description:

End point type | Secondary

End point timeframe:

The progression-free survival was measured from the start of treatment to the date of progressive disease or death for any cause, within one year after the end of treatment of the last patient enrolled.

End point values	Single Arm	Comparison		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	13	13		
Units: Kaplan Meier probability				
number (confidence interval 95%)	0.46 (0.19 to 0.70)	0.46 (0.19 to 0.70)		

Statistical analyses

Statistical analysis title | Progression Free Survival

Statistical analysis description:

Kaplan Meier estimate at 12 months of follow-up, from the date of start treatment.

Comparison groups | Single Arm v Comparison

Number of subjects included in analysis | 26

Analysis specification | Pre-specified

Analysis type | other^[7]

Parameter estimate | Kaplan Meier estimates

Point estimate | 0.46

Confidence interval

level | 95 %

sides | 2-sided

lower limit | 0.19

upper limit | 0.7

Notes:

[7] - One arm pilot phase 2 study

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were considered for assessment of safety if they have received at least one administration of Brentuximab Vedotin.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI CTC
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Dictionary version	4.03
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Reporting groups

Reporting group title	Single Arm
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Reporting group description:

Patients treated with at least one administration of Brentuximab Vedotin.

Reported patients with of any grade CTCAE.

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever	Additional description: CTCAE grade 2 in post-ASCT, reported as fever.		
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 13 (84.62%)		
Investigations			
gamma-GT increase, AST increase			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	11		
Vascular disorders			
Deep venous thrombosis			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 11		
Nervous system disorders Hypoesthesia, cramps, Dysesthesia and tingling (upper arms), paresthesia subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 11		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 11 2 / 13 (15.38%) 11 4 / 13 (30.77%) 11 2 / 13 (15.38%) 11 1 / 13 (7.69%) 11		
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 11		
Gastrointestinal disorders Diarrhoea, Mucositis subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 11		
Skin and subcutaneous tissue disorders Cutaneous rash, Eczema subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2017	It was revised the evaluation of Deauville score. In detail: "11.2 Rules for PET interpretation: Following the international recommendations on the use of the Deauville five point scale (Deauville 5ps) for clinical routine and clinical trials using FDG-PET/CT in the initial staging and assessment of treatment response in Hodgkin Lymphoma (HL) (Barrington et al. 2014; Cheson et al. 2014), FDG-PET negativity will be defined in accord to Deauville five-point scale for the evaluation of primary end points. These criteria have been purposely risen for interim-PET interpretation and rely on visual, semi-quantitative assessment according to a 5-point scale for intensity of residual FDG uptake scoring, with liver as reference organ for positivity cutoff. According to these criteria, a score value equal to 1, 2 and 3 will be considered negative while a value equal to 4 and 5 will be considered positive."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported