Clinical trial results:
Phase I/II feasibility study of Brentuximab Vedotin in refractory / relapsed Hodgkin lymphoma patients who are treated by chemotherapy (ICE) in second line and eligible for autologous transplantation

Summary

EudraCT number	2014-002722-13
Trial protocol	FR BE
Global end of trial date	13 July 2021

Results information

Result version number	v1 (current)
This version publication date	17 December 2022
First version publication date	17 December 2022
Summary attachment (see zip file)	BV-ICE_CSR_Final synopsis (BV-ICE_CSR Synopsis final.pdf)

Trial information

Trial identification

Sponsor protocol code	BV-ICE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02686346
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	165 Chemin du grand Revoyet - Batiment 2D, Pierre Benite Cedex, France, 69495
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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	13 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I
To determine the MTD and/or RP2D (Recommended Phase II dose) of BV when administered to adult Hodgkin's lymphoma patients treated with ICE.
Phase II
To evaluate the efficacy of BV in patient treated with ICE as first salvage treatment (establish the fraction of responding patients – metabolic CR) acccording to Lugano classification after the second cycle.

Protection of trial subjects:

Patients who do not answer to study treatment will be treated according to site's standart of care.

Background therapy:

- ICE: Etoposide 100 mg/m², Carboplatine AUC (5) max 800mg, Ifosfamide + Mesna 5 g/m²
- Autologous peripheral blood stem cell transplantation (ASCT) with BEAM (BiCNU = carmustine, Etoposide, Aracytine = cytarabine, Melphalan) or BAM
(Busulfan, Aracytine = cytarabine, Melphalan) conditionning regimen

Evidence for comparator:

No comparator

Actual start date of recruitment	09 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 49
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	53
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I - Recruitment by cohorts of 3 patients (France only)
* Cohort 1: Mar. 9th 2016 to Jun. 6th 2016
* Cohort 2: Aug. 8th 2016 to Sep. 19th 2016
* Cohort 3: Nov. 17th 2016 to Jan. 24th 2017
Phase II - France and Belgium
* France: Jun. 20th 2017 to Mar. 15th 2018
* Belgium: Aug 25th 2017 to Mar. 27th 2018

Pre-assignment

Screening details:

Patients with Hodgkin lymphoma refractory to first line or in first relapse and eligible for high-dose treatment followed by autologous peripheral blood stem cell transplantation.
Screening procedure: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable for phase I and II

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I - Cohort 1

Arm description:

Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase I - Cohort 2

Arm description:

Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase I - Cohort 3

Arm description:

Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase II

Arm description:

Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Number of subjects in period 1	Phase I - Cohort 1	Phase I - Cohort 2	Phase I - Cohort 3
Started	3	4	3
Completed	3	4	3
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Non proven histology	-	-	-

Number of subjects in period 1	Phase II
Started	44
Completed	42
Not completed	2
Consent withdrawn by subject	1
Non proven histology	1

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable since no treatment administration during follow up period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I - Cohort 1

Arm description:

Cycle 1 to 3: BV 1.2mg/kg (100kg max) + ICE, every 21 days
Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase I - Cohort 2

Arm description:

Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days
Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase I - Cohort 3

Arm description:

Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days
Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Arm title	Phase II

Arm description:

Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days
Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	L01XC12
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg vials of a lyophilized powder, to reconstituate with sterile watter and diluted in a 150 mL infusion bag containing 0.9% Sodium Chloride Injection

Number of subjects in period 2	Phase I - Cohort 1	Phase I - Cohort 2	Phase I - Cohort 3
Started	3	4	3
Completed	4	3	3
Not completed	0	1	0
Transferred to other arm/group	-	1	-
Joined	1	0	0
Transferred in from other group/arm	1	-	-

Number of subjects in period 2	Phase II
Started	42
Completed	42
Not completed	0
Transferred to other arm/group	-
Joined	0
Transferred in from other group/arm	-

Period 3	
Period 3 title	Follow up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes

Arm title	Phase I - Cohort 1
Arm description: Visit every 3 months during the first year, then every 6 months during the next 2 years	
Arm type	Follow up period
No investigational medicinal product assigned in this arm	

Arm title	Phase I - Cohort 2
Arm description: Visit every 3 months during the first year, then every 6 months during the next 2 years	
Arm type	Follow up period
No investigational medicinal product assigned in this arm	

Arm title	Phase I - Cohort 3
Arm description: Visit every 3 months during the first year, then every 6 months during the next 2 years	
Arm type	Follow up period
No investigational medicinal product assigned in this arm	

Arm title	Phase II
Arm description: Visit every 3 months during the first year, then every 6 months during the next 2 years	
Arm type	Follow up period
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Phase I - Cohort 1	Phase I - Cohort 2	Phase I - Cohort 3
Started	4	3	3
Completed	4	3	3

Number of subjects in period 3	Phase II
Started	42
Completed	42

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	54	54	
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)	53	53	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Phase I and phase II patients are all from 18 to 65 years old.			
Units: years			
arithmetic mean	34.8		
standard deviation	± 13.1	-	
Gender categorical			
Phase I and phase II patients can be either Female or Male			
Units: Subjects			
Female	21	21	
Male	33	33	

Subject analysis sets

Subject analysis set title	Phase I set
Subject analysis set type	Full analysis

Subject analysis set description:

Patients included and treated in Phase I dose-escalation study.

Subject analysis set title	Phase II Set
Subject analysis set type	Full analysis

Subject analysis set description:

Patients included and treated in phase II study.

Reporting group values	Phase I set	Phase II Set	
Number of subjects	10	42	
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) From 65-84 years 85 years and over	10	41 1	
Age continuous			
Phase I and phase II patients are all from 18 to 65 years old.			
Units: years			
arithmetic mean	33.8	35.7	
standard deviation	± 12.6	± 13.4	
Gender categorical			
Phase I and phase II patients can be either Female or Male			
Units: Subjects			
Female	4	15	
Male	6	27	

End points

End points reporting groups

Reporting group title	Phase I - Cohort 1
Reporting group description:	
Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments	
Reporting group title	Phase I - Cohort 2
Reporting group description:	
Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments	
Reporting group title	Phase I - Cohort 3
Reporting group description:	
Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments	
Reporting group title	Phase II
Reporting group description:	
Assessements: medical history, HL history, staging, CBC, biochemestry, serologies, pregnancy, CT scan, PET scan, cardiac and pulmonary assessments	
Reporting group title	Phase I - Cohort 1
Reporting group description:	
Cycle 1 to 3: BV 1.2mg/kg (100kg max) + ICE, every 21 days Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3	
Reporting group title	Phase I - Cohort 2
Reporting group description:	
Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3	
Reporting group title	Phase I - Cohort 3
Reporting group description:	
Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3	
Reporting group title	Phase II
Reporting group description:	
Cycle 1 to 3: BV 1.8mg/kg (100kg max) + ICE, every 21 days Cycle 4: BV 1.8mg/kg (100kg max) alone, 21 days after day 1 cycle 3	
Reporting group title	Phase I - Cohort 1
Reporting group description:	
Visit every 3 months during the first year, then every 6 months during the next 2 years	
Reporting group title	Phase I - Cohort 2
Reporting group description:	
Visit every 3 months during the first year, then every 6 months during the next 2 years	
Reporting group title	Phase I - Cohort 3
Reporting group description:	
Visit every 3 months during the first year, then every 6 months during the next 2 years	
Reporting group title	Phase II
Reporting group description:	
Visit every 3 months during the first year, then every 6 months during the next 2 years	
Subject analysis set title	Phase I set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients included and treated in Phase I dose-escalation study.	
Subject analysis set title	Phase II Set
Subject analysis set type	Full analysis

Subject analysis set description:

Patients included and treated in phase II study.

Primary: Dose Limiting Toxicty DLT

End point title	Dose Limiting Toxicty DLT[1]

End point description:

Toxicity will be assessed using the NCI CTCAE version 4.0. A DLT is defined as any of the following events (toxicity or abnormal laboratory value) that is assessed as possibly related to BV or BV+ICE, occurring prior initiation of the second cycle : Any grade ≥3 non-hematological toxicity with a duration > 7 days Febrile Neutropenia grade 4 with hospitalization during 7 days or more Bleeding grade 4 with life threatening consequently Progressive multifocal Leukoencephalopathy

End point type	Primary

End point timeframe:

Prior to initiation of cycle 2

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: In this single-arm study, no statistical comparisons are performed between arms.

End point values	Phase I - Cohort 1	Phase I - Cohort 2	Phase I - Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	4	3	
Units: Patient with DLT	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Complete Metabolic Response after C2

End point title	Complete Metabolic Response after C2[2]

End point description:

Complete Metabolic Response (CMR) as judged by the center by Lugano classification after the second cycle.

End point type	Primary

End point timeframe:

Evaluation after cycle 2

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: In this single-arm study, no statistical comparisons are performed between arms.

End point values	Phase II Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Patients with CMR				
Complete metabolic response	26			
Partial metabolic response	13			
No metabolic response	2			
Progressive metabolic disease	0			
Not evaluated	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival at 24 months

End point title	Progression Free Survival at 24 months

End point description:

PFS: patient has a failure event at date of progression or death from any cause.

End point type	Secondary

End point timeframe:

Patients followed up to 3 years from end of treatment.

End point values	Phase II Set			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: months				
number (confidence interval 64.3%)	64.3 (47.9 to 76.7)			

Attachments (see zip file)	BVICE PFS/Figure 170102.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs of grade 2-5 for infections and neurological toxicities and AEs of grade 3-5 for other toxicities regardless relationship to investigational product occurring from the date of informed consent signature to 30 days after last BV administration.

Adverse event reporting additional description:

Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Adverse Event". "Alopecia" and "lymphopenia" toxicity will never be reported as "Adverse event". Monitoring SDV on site was driven for 100% of data

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Subjects receiving BV (global study)

Reporting group description:

Subjects who received experimental BV during the study (52)

Serious adverse events	Subjects receiving BV (global study)		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 52 (38.46%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
INVESTIGATIONS			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
VASCULAR DISORDERS			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences causally related to treatment / all	12 / 18		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	11 / 52 (21.15%)		
occurrences causally related to treatment / all	7 / 12		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subjects receiving BV (global study)		
Total subjects affected by non-serious adverse events subjects affected / exposed	46 / 52 (88.46%)		
Vascular disorders VASCULAR DISORDERS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
General disorders and administration site conditions GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Respiratory, thoracic and mediastinal disorders RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Psychiatric disorders PSYCHIATRIC DISORDERS subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Investigations INVESTIGATIONS subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 7		
Injury, poisoning and procedural complications INJURY, POISONING AND PROCEDURAL COMPLICATIONS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Blood and lymphatic system disorders			

BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all)	41 / 52 (78.85%) 181		
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 7		
Hepatobiliary disorders HEPATOBILIARY DISORDERS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Infections and infestations INFECTIONS AND INFESTATIONS subjects affected / exposed occurrences (all)	15 / 52 (28.85%) 19		
Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2016	- New IB available - ICF updated accordingly - Protocol updated accordingly
27 September 2018	- Addition of an addendum to ICF to comply with RGPD
31 October 2019	- New IB available
24 September 2020	- New IB available
24 June 2021	- New IB available

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 June 2016	Suspension of inclusion between cohort 1 (Phase I) and cohort 2 (Phase I) to look after safety data	08 August 2016
19 September 2016	Suspension of inclusion between cohort 2 (Phase I) and cohort 3 (Phase I) to look after safety data	17 November 2016
24 January 2017	Suspension of inclusion between cohort 3 (Phase I) and Phase II to look after safety data	20 June 2017

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35975738