



## Clinical trial results:

**“Ibrutinib (Imbruvica®), Bortezomib (Velcade®) s.c., Rituximab, CHOP for the treatment of elderly patients (age 61-80 years) with CD20+ diffuse large B-cell lymphoma, IPI 2”**

### Summary

EudraCT number	2015-003429-32
Trial protocol	DE AT
Global end of trial date	12 November 2024

### Results information

Result version number	v1 (current)
This version publication date	30 October 2025
First version publication date	30 October 2025

### Trial information

#### Trial identification

Sponsor protocol code	ImbruVeRCHOP-Trial
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03129828
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr. med. Sophy Denker, M.D., Campus Virchow Clinicum (CVK), Hematology, Oncology and Tumor Immunology, +49 30450 653 569, sophy.denker@charite.de
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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	29 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2024
Global end of trial reached?	Yes
Global end of trial date	12 November 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this clinical trial is to assess the efficacy of the treatment determined as the 2-year PFS for patients with DLBCL. The regimen will be considered unacceptable if  $\leq 60\%$  of patients (i.e.  $\leq 36$  patients in a cohort of 60 patients) are progression-free at 2 years. With this decision rule, the regimen will be correctly rejected with at least 95% power if true 2-year PFS rate falls below 50%. If true 2-year PFS rate is 75%, the treatment will be rejected erroneously with a 0.007 probability. "Responders" (i.e. patients achieving a CR or a PR) vs. "Non-Responders" are based on the Revised Response Criteria for Malignant Lymphoma.

Protection of trial subjects:

Following the principles of Good Clinical Practice and according to international (European) and German law the sponsor established a system to detect any safety signal and to take appropriate measures to protect patient's safety. An immediate reaction to any risk given by the drug or the conduct of the trial is guaranteed.

The DSMB monitored the conduct of the study and the safety aspects of the trial on a regular basis, and had given recommendations to the sponsor whether to stop the trial or to change the trial protocol and have to decide about possible dose reductions of Ibrutinib and/or Bortezomib, especially during the safety run-in phase, if necessary.

Background therapy:

Diffuse large B-cell lymphoma (DLBCL) account for about 30% of all Non-Hodgkin's lymphoma (NHL) and 80% of aggressive NHL, and, thus, reflect the most frequent type of malignant lymphoma. The CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) has been the standard of care for DLBCL since several decades, producing cures in about half of the patients.

Given the still unsatisfying treatment results in DLBCL in general, and the particularly poor outcome in ABC DLBCL, there is urgent medical need to improve the current standard of care, i.e. R-CHOP-like immunochemotherapy, for the entire population of DLBCL patients, or, at least, a molecularly defined subset of patients at particular risk that would selectively benefit from this novel therapeutic concept. Addition of Bortezomib (Velcade®), the clinically approved first-in-class inhibitor of the proteasome with significant activity in multiple myeloma, may have the potential to contribute to this goal in the DLBCL arena. Another novel agent of interest is Ibrutinib (Imbruvica®; a.k.a. PCI-32765), an inhibitor of the Bruton's Tyrosine Kinase (BTK), a signal mediator fairly upstream in the BCR/NF-B signaling cascade. For the treatment of DLBCL, ibrutinib is not yet approved.

Based on the hypothesis that the combined addition of Ibrutinib and Bortezomib to R-CHOP may improve the outcome of those patients even further, we introduce here Ibrutinib-Bortezomib-Rituximab-CHOP (I-B-R-CHOP) – hereafter referred to as "ImbruVerCHOP" – as an innovative study design that augments the standard.

Evidence for comparator: -

Actual start date of recruitment	31 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Germany: 31
Worldwide total number of subjects	38
EEA total number of subjects	38

Notes:

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**Subjects enrolled per age group**

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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)	3
From 65 to 84 years	35
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 8 study sites in Germany and in 4 study sites in Austria, between 17/03/2017 and 12/11/2024.

### Pre-assignment

Screening details:

The study was designed as a single-arm, open, prospective, multi-center, phase I/II study. Concept with no molecular pre selection for patients with newly diagnosed DLBCL, 61-80 years, higher risk profile IPI  $\geq 2$ , good fitness level and available lymphoma lesions for re-biopsy.

### Period 1

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

Blinding implementation details:

no blinding

### Arms

Arm title	Treatment group
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Arm description:

The study was designed as a single-arm, open, prospective, multi-center, phase I/II study. Concept with no molecular pre selection for patients with newly diagnosed DLBCL, 61-80 years, higher risk profile IPI  $\geq 2$ , good fitness level and available lymphoma lesions for re-biopsy.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	CAS 936563-96-1
Other name	Imbruvica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

During the reporting period, new findings on toxicity, reduced treatment adherence and poorer outcome were published in the PHOENIX study (NCT01855750). In the study, patients of a DLBCL subtype were randomized with ibrutinib plus R-CHOP against R-CHOP.

Because of those safety concerns related to the combination of the standard treatment R-CHOP with Ibrutinib, an adjustment of the dose of ibrutinib was made accordingly. Originally the patients received 560 mg of Ibrutinib. The dose was reduced to 420 mg on the 14th of July 2018.

patients received 420 mg (3 x 140 mg capsules) orally once a day, starting at Cycle 1, day d6 until cycle 6, d21

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	CAS 179324-69-7
Other name	Velcade
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Bortezomib s.c. (1.3 mg/m<sup>2</sup> C1 on d3 and d8, all other cycles d1 and d8) have been administered subcutaneously (at a concentration of 2.5 mg/ml)

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan, anti-CD20 antibody
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

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**Dosage and administration details:**

(375 mg/m<sup>2</sup>) was administered i.v. between 24 and 2 hours prior to start of CHOP (d0 or d1). Rituximab was administered 6 times synchronously with CHOP-21 (C1-6). Two additional 3-week cycles were administered after completion of CHOP-21 (C7-8). Patients received premedication consisting of Paracetamol (1,000 mg p.o.) and antihistamines (e.g. Dimetindenmaleat 4 mg i.v.) 30-60 minutes prior to the application of Rituximab. Rituximab was administered intravenously at an initial rate of 50 mg/hr.

Investigational medicinal product name	CHOP-21
Investigational medicinal product code	
Other name	CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISOLONE-VINCRIStINE (21)
Pharmaceutical forms	Infusion, Injection, Coated tablet
Routes of administration	Intravenous bolus use , Intravenous use, Oral use

**Dosage and administration details:**

6 cycles - Cyclophosphamide i.v.,- infusion(750 mg/m<sup>2</sup> d1); Doxorubicin; i.v. -infusion(50 mg/m<sup>2</sup> d1), Vincristine 1 mg absolute, i.v. bolus, d1; Prednisone (100 mg absolute p.o. d1-5) as the standard of care for DLBCL.

<b>Number of subjects in period 1</b>	Treatment group
Started	38
Completed	37
Not completed	1
Consent withdrawn by subject	1

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment group (overall trial)
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Reporting group description: -

Reporting group values	Treatment group (overall trial)	Total	
Number of subjects	38	38	
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	69		
full range (min-max)	62 to 81	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	19	19	
ECOG Performance Status			
Units: Subjects			
ECOG = 0	19	19	
ECOG = 1	17	17	
ECOG = 2	2	2	
Ann Arbor Stage			
Units: Subjects			
Stage I	3	3	
Stage II	7	7	
Stage III	14	14	
Stage IV	14	14	
IPI score			
Units: Subjects			
IPI = 2	20	20	
IPI = 3	10	10	
IPI = 4	8	8	
Pathology			
Units: Subjects			
DLBLC	33	33	
HGBL	2	2	

FL 3 b	1	1	
tFL to DLBCL	1	1	
blasmaplastic lymphoma	1	1	
B symptoms			
Units: Subjects			
Yes	9	9	
No	29	29	
Extranodal Manifestations			
Units: Subjects			
Yes	13	13	
No	25	25	
LDG elevated			
Units: Subjects			
Yes	25	25	
No	13	13	

## End points

### End points reporting groups

Reporting group title	Treatment group
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Reporting group description:

The study was designed as a single-arm, open, prospective, multi-center, phase I/II study. Concept with no molecular pre selection for patients with newly diagnosed DLBCL, 61-80 years, higher risk profile IPI  $\geq 2$ , good fitness level and available lymphoma lesions for re-biopsy.

### Primary: 2-year progression-free survival (PFS)

End point title	2-year progression-free survival (PFS) <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Primary endpoint is the 2-year progression-free survival (2-year PFS) of DLBCL patients, calculated from d1 of C1 up to 40 months

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: The static analysis could not be entered because the study was only one-armed. The primary and secondary endpoints can be viewed as graphs in the charts.

End point values	Treatment group			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: subjects				
overall survival probability at 2-years	28			
overall survival probability at 3 years	26			

Attachments (see zip file)	Results_EudraCT 2015-003429-32.pdf
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### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment until end of follow-up

Adverse event reporting additional description:

AEs: Grade 1-2 and Grade 3-4 were documented in summary form.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	Treatment group
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Reporting group description: -

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 38 (73.68%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia	Additional description: Leukaemia secondary to oncology chemotherapy		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal stromatumor			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung cancer			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lymphoma progress			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Recurrent transformed DLBCL			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Relapse of lymphoma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
thromboembolic event			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
platelet count increased			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hernia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture	Additional description: Wrist fracture		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
colonic perforation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
catheter related infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pneumonia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 38 (2.63%)		
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 %

<b>Non-serious adverse events</b>	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 38 (89.47%)		
Investigations			
Lymphocyte count decreased Grade 1-2			
subjects affected / exposed	12 / 38 (31.58%)		
occurrences (all)	83		
Lymphocyte count decreased Grade 3-4			
subjects affected / exposed	12 / 38 (31.58%)		
occurrences (all)	43		
Platelet count decreased Grade 1-2			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	61		
Platelet count decreased Grade 3-4			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	28		
Neutrophil count decreased Grade 1-2			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	8		
Neutrophil count decreased Grade 3-4			
subjects affected / exposed	12 / 38 (31.58%)		
occurrences (all)	24		
white blood cell decreased Grade 1-2			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	6		
white blood cell decreased Grade 3-4			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	11		

Nervous system disorders peripheral neuropathy (PNP) Grade 1-2 subjects affected / exposed occurrences (all)  peripheral neuropathy (PNP) Grade 3-4 subjects affected / exposed occurrences (all)	14 / 38 (36.84%) 30  4 / 38 (10.53%) 5		
Blood and lymphatic system disorders Anemia Grade 1-2 subjects affected / exposed occurrences (all)  Anemia Grade 3-4 subjects affected / exposed occurrences (all)	19 / 38 (50.00%) 99  8 / 38 (21.05%) 16		
General disorders and administration site conditions Fatigue Grade 1-2 subjects affected / exposed occurrences (all)  Fatigue Grade 3-4 subjects affected / exposed occurrences (all)	9 / 38 (23.68%) 10  1 / 38 (2.63%) 3		
Gastrointestinal disorders Nausea Grade 1-2 subjects affected / exposed occurrences (all)  Diarrhoea Grade 1-2 subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 11  8 / 38 (21.05%) 8		
Skin and subcutaneous tissue disorders Alopecia Grade 1-2 subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5		
Metabolism and nutrition disorders Hypokalaemia Grade 1-2 subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 8		

Hyperkalaemia Grade 3-4 subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 3		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2017	- update protocol V1.8 08-11-2016, Changes in interpretation of scientific documents/value of the trial
26 May 2017	- updated IBs: Investigators Brochure from Janssen-Cilag International Ibrutinib Ed 10, dated 29/08/2016; Ed 10.1,dated 08/12/2016; Ed 10.2 dated 03/02/2017
15 August 2017	- addition of a new site (Würzburg)
28 August 2017	- addition of a new site (Freiburg)
19 October 2017	- addition of a new site at Campus Mitte Charité Berlin
26 February 2018	- addition of a new site (Frankfurt am Main)
13 June 2018	- updated version of IB of ibrutinib (Imbruvica) (Ed.11), new PICF, Adaption of the PICF due to the General Data Protection Regulation 2016/679
05 October 2018	- update protocol V1.9_09/08/2018, The dosage of the IMP Ibrutinib has been changed from 560 mg p.o. to 420 mg p.o. daily, new document: PICF Pre-Screening
21 May 2019	- addition of 4 new sites (Kiel/Luebeck/Marburg/Neumuenster)
14 August 2020	- update protocol V2.0 dated 02/06/2020, new nonclinical and clinical data; extension of the duration of the clinical trial due to problems in patient recruitment
12 May 2021	-update protocol V2.4 dated 30/12/2020 (inclusion criteria), update IB and SmPCs
23 May 2022	- update Investigator's Brochure (V15 dated 10/12/2021)
21 September 2022	- update protocol V2.6 dated 29/08/2022, new recommendations to Ibrutinib dose modifications in case of cardiac failure ore cardiac arrhythmias
08 December 2022	-update protocol V2.7 dated 07/11/2022, extension of the study duration, PICF V 1.4.7

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31903182>

<http://www.ncbi.nlm.nih.gov/pubmed/34414850>