



## 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 |
|-----------------------|--------------------|

#### 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 |
|-----------|-----------------|

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) |
|-----------------------|---------------------------------|

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  |  |
| blasmapiastic 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 |
|-----------------------|-----------------|

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> |
|-----------------|-------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

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 |
|----------------------------|------------------------------------|

### 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 |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Treatment group |
|-----------------------|-----------------|

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               |  |  |

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

|                                                                             |                     |  |  |
|-----------------------------------------------------------------------------|---------------------|--|--|
| Hyperkalaemia Grade 3-4<br>subjects affected / exposed<br>occurrences (all) | 2 / 38 (5.26%)<br>3 |  |  |
|-----------------------------------------------------------------------------|---------------------|--|--|

## 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>