Clinical trial results:
A Phase I/II, Multi-centre Trial to Assess the Safety, Efficacy, and Pharmacokinetics of Eltrombopag, Administered to Thrombocytopenic Chronic Lymphocytic Leukemia Patients Prior to Alkylating Agents and/or Purine Analogue-based Therapy

Summary

EudraCT number	2010-023022-20
Trial protocol	DE AT
Global end of trial date	11 November 2013

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	CLL2S

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01397149
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Ulm (Ulm University Hospital, Ulm, Germany)
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
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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	17 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I:
The primary objective is to find the safe and potentially efficacious dose of eltrombopag to achieve a durable increase in platelet count.
Phase II:
The primary objective of phase II is to confirm the effect of the selected dose from Phase I in correcting thrombocytopenia to enable patients to receive alkylating agents and/or purine analogue-based therapy.

Protection of trial subjects:

Eltrombopag may increase the risk of thrombotic/thromboembolic events. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome and portal hypertension). Eltrombopag administration may cause hepatotoxicity. Serum ALT, AST, and bilirubin should be measured prior to initiation of eltrombopag, and every 2 to 4 weeks thereafter during treatment. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. Permanently discontinue eltrombopag if ALT levels increase to ≥3X the upper limit of normal (ULN).
Exercise caution when administering eltrombopag to patients with hepatic disease.
Eltrombopag is a thrombopoietin (TPO) receptor agonist and TPO-receptor agonists may increase the risk for the development or progression of reticulin fiber deposition within the bone marrow. Prior to initiation of eltrombopag, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, examine peripheral blood smears and CBCs monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with eltrombopag and consider a bone marrow biopsy, including staining for fibrosis. Cataracts were observed in toxicology studies of eltrombopag in rodents. Routine monitoring of patients for cataracts is recommended. Patients treated with eltrombopag who experience visual difficulties should have an appropriate ophthalmologic evaluation.

Background therapy:

not applicable.

Evidence for comparator:

not applicable.

Actual start date of recruitment	01 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	3
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was open from August 2011. The first patient was included in May 2012. The study was open for recruitment for approximately 2 years and 2 months. During this time, only 4 patients were recruited for the phase I escalation part of the trial at 3 sites, which equals a recruitment rate of about one patient per 6 months.

Pre-assignment

Screening details:

Subjects eligible for enrolment in the study must meet all of the following criteria:
1. Confirmed diagnosis of CLL
2. Platelet count <50 000/µl at time of screening (measured and confirmed twice)
During the recruitment phase of the study 4 patients were screened and 4 patients were enrolled.

Period 1

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

Blinding implementation details:

This was an Phase I, Multicenter, open-label dose escalation study.

Arms

Arm title	Eltrombopag

Arm description:

Phase I is a single arm dose-escalation trial part, designed to test 4 doses of eltrombopag (75mg, 150mg, 225mg, 300mg) to find the appropriate, feasible dose of eltrombopag to achieve a durable increase in platelet count (from <50,000/µl to ≥100,000/µl). Eltrombopag will be administered once daily to thrombocytopenic patients with platelet counts < 50,000/µl. Each subject will be dosed at the respective dose level for 2 weeks (unless platelet counts rise to > 400,000/µl). There is no intra-individual dose escalation.
At first, three subjects will be enrolled at each dose level. If no unacceptable dose-limiting toxicity (DLT) is observed, escalation to the next higher dose step is performed. In case of observation of non-acceptable toxicity in 2 cases or more, the next lower dose is declared as MTD (or the trial terminated completely if this happens on the first dose level). In case of dose-limiting toxicity in one out of 3 patients, another 3 patients are treated on this level.

Arm type	Experimental
Investigational medicinal product name	Eltrombopag
Investigational medicinal product code	B02BX05
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

In phase I, four doses of eltrombopag (75mg, 150mg, 225mg, 300mg) will be tested. Eltrombopag will be administered orally once daily. Each patient will be dosed at each dose level for 2 weeks. It is recommended that investigation product is taken about the same time on each day. Separate subjects must be enrolled for each dose level. No subject is allowed to receive investigational product at more than one dose level. The number of patients and the escalation strategy is described in the study protocol.

Number of subjects in period 1	Eltrombopag
Started	4
Completed	4

Baseline characteristics

Reporting groups

Reporting group title	Treatment phase

Reporting group description: -

Reporting group values	Treatment phase	Total	
Number of subjects	4	4	
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)	3	3	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	4	4	
Platelet count at baseline			
Major and important Inclusion criterion: Platelet count <50 000/µl at time of screening (measured and confirmed twice).			
Units: Subjects			
platelet count below 50G/L at baseline	4	4	
Binet Stage at diagnosis			
Binet staging system Binet stage A: The patient has fewer than 3 areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage C: Presence of anemia and/or thrombocytopenia.			
Units: Subjects			
Binet Stage A	3	3	
Binet Stage C	1	1	
Binet Stage at Baseline			
Binet staging system Binet stage A: The patient has fewer than 3 areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage C: Presence of anemia and/or thrombocytopenia.			

Units: Subjects			
Binet Stage C	4	4	
ß-Symptoms at baseline			
Disease-related symptoms (previously defined as ß-symptoms) as defined by any of the following: Unintentional weight loss ≥10% within the previous 6months. Significant fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities). Fevers ≥100.5°F or 38.0 °C for 2 or more weeks without evidence of infection. Night sweats for ≥1 month without evidence of infection.			
Units: Subjects			
ß-symptoms present	2	2	
ß-symptoms absent	2	2	
Eastern Cooperative Oncology Group Performance Status			
GRADE ECOG PERFORMANCE STATUS 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead			
Units: Subjects			
ECOG 0	2	2	
ECOG 1	1	1	
ECOG 2	1	1	

Subject analysis sets

Subject analysis set title	Final analysis
Subject analysis set type	Full analysis

Subject analysis set description:

A final analysis was not conducted, because only 4 patients were enrolled and recruitment was prematurely closed.

Reporting group values	Final analysis		
Number of subjects	4		
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)	3		
From 65-84 years	1		
85 years and over	0		
Gender categorical Units: Subjects			
Female			
Male			

Platelet count at baseline			
Major and important Inclusion criterion: Platelet count <50 000/µl at time of screening (measured and confirmed twice).			
Units: Subjects			
platelet count below 50G/L at baseline	4		
Binet Stage at diagnosis			
Binet staging system Binet stage A: The patient has fewer than 3 areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage C: Presence of anemia and/or thrombocytopenia.			
Units: Subjects			
Binet Stage A	3		
Binet Stage C	1		
Binet Stage at Baseline			
Binet staging system Binet stage A: The patient has fewer than 3 areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thombocytopenia. Binet stage C: Presence of anemia and/or thrombocytopenia.			
Units: Subjects			
Binet Stage C	4		
ß-Symptoms at baseline			
Disease-related symptoms (previously defined as ß-symptoms) as defined by any of the following: Unintentional weight loss ≥10% within the previous 6months. Significant fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities). Fevers ≥100.5°F or 38.0 °C for 2 or more weeks without evidence of infection. Night sweats for ≥1 month without evidence of infection.			
Units: Subjects			
ß-symptoms present	2		
ß-symptoms absent	2		
Eastern Cooperative Oncology Group Performance Status			
GRADE ECOG PERFORMANCE STATUS 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead			
Units: Subjects			
ECOG 0	2		
ECOG 1	1		
ECOG 2	1		

End points

End points reporting groups

Reporting group title	Eltrombopag

Reporting group description:

Phase I is a single arm dose-escalation trial part, designed to test 4 doses of eltrombopag (75mg, 150mg, 225mg, 300mg) to find the appropriate, feasible dose of eltrombopag to achieve a durable increase in platelet count (from <50,000/µl to ≥100,000/µl). Eltrombopag will be administered once daily to thrombocytopenic patients with platelet counts < 50,000/µl. Each subject will be dosed at the respective dose level for 2 weeks (unless platelet counts rise to > 400,000/µl). There is no intra-individual dose escalation.
At first, three subjects will be enrolled at each dose level. If no unacceptable dose-limiting toxicity (DLT) is observed, escalation to the next higher dose step is performed. In case of observation of non-acceptable toxicity in 2 cases or more, the next lower dose is declared as MTD (or the trial terminated completely if this happens on the first dose level). In case of dose-limiting toxicity in one out of 3 patients, another 3 patients are treated on this level.

Subject analysis set title	Final analysis
Subject analysis set type	Full analysis

Subject analysis set description:

A final analysis was not conducted, because only 4 patients were enrolled and recruitment was prematurely closed.

Primary: Dose limiting toxicity

End point title	Dose limiting toxicity[1]

End point description:

During the course of the trial, the first three patients were treated on the first dose level, and received treatment with 75 mg eltrombopag for 14 days, before start of their planned therapy for CLL. No dose limiting toxicity was observed in these patients, and dose level 100 mg was therefore opened on 19.03.2013 One additional patient received treatment on the second dose level, also with no DLT observed, when the study was prematurely stopped due to low recruitment rate. Please refer to part 13.1 of the report for a detailed description of patients therapy course

End point type	Primary

End point timeframe:

August 2011-November 2013

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 statistical analysis was not done, due to the early termination of the trial with only four patients. The study had to be closed early due to insufficient recruitment. Only four patients were included in the Phase I part in two dose levels. Phase II of this trial was not started. Thus, it is not possible to draw any conclusions on the efficacy or safety of this supportive treatment.

End point values	Final analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: number				
Patients with DLT	0			
Patients without DLT	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

August 2011-November 2013

Adverse event reporting additional description:

A statistical analysis of SAE and AE has not been done, because only 4 pateinst have been enrolled.

Assessment type	Non-systematic

Dictionary used

Dictionary name	not done
Dictionary version	n.a.

Reporting groups

Reporting group title	Eltrombopag

Reporting group description:

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At first, three subjects will be enrolled at each dose level. If no unacceptable dose-limiting toxicity (DLT) is observed, escalation to the next higher dose step is performed. In case of observation of non-acceptable toxicity in 2 cases or more, the next lower dose is declared as MTD (or the trial terminated completely if this happens on the first dose level). In case of dose-limiting toxicity in one out of 3 patients, another 3 patients are treated on this level.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The trial was terminated early. An analysis regarding the safety of this trial was not conducted.

Serious adverse events	Eltrombopag		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertensive crisis	Additional description: Onset date was 01.01.2013, outcome recovered.		
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia	Additional description: Onset date 22.10.2013, outcome ongoing at time point of study closure		
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Eltrombopag		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 4 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2013	The initial study protocol was amended once during the course of the trial. The amendment consisted mainly in a change of inclusion/exclusion criteria and allowed the investigators to enrol also patients with more than three previous therapy lines for the treatment of CLL. Inclusion criteria after change according to protocol amendment: 3. Patient is planned to receive alkylating agents and/or fludarabine-based therapy as 2nd or higher-line treatment Exclusion criteria after change according to protocol amendment: 3. No prior therapy for CLL

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 November 2013	Recruitment was open from August 2011. The first patient was included in May 2012. The study was open for recruitment for approximately 2 years and 2 months. During this time, only 4 patients were recruited for the phase I escalation part of the trial at 3 sites, which equals a recruitment rate of about one patient per 6 months. Due to this very low recruitment rate the study was closed prematurely in November 2013, and the phase II part of the trial was not started The information about the premature closure of the trial was sent to the respective competent authorities and ethic committees on 11.11.2013 (according to e.g. national legislation § 13 GCP-V, Abs. 8).	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the premature closure of the trial with only 4 enrolled patients, no relevant conclusions can be drawn from this study. No major unexpected safety problems were detected in these patients.

Notes: