



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 |
| Public contact | Study Chairman, Prof. Dr. S. Stilgenbauer Universitätsklinikum Ulm, Klinik für Innere Medizin III Albert-Einstein, 49 73150045501, stephan.stilgenbauer@uniklinik-ulm.de |
| Scientific contact | Studienzentrale der Deutschen CLL Studiengruppe Klinik I für Innere Medizin, Uniklinik Köln, Prof. Dr. S. Stilgenbauer Universitätsklinikum Ulm, Klinik für Innere Medizin III Albert-Einstein, 49 22147888220, anna-maria.fink@uk-koeln.de |

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 $\geq 3X$ 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/ μ l 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/ μ l to \geq 100,000/ μ l). Eltrombopag will be administered once daily to thrombocytopenic patients with platelet counts < 50,000/ μ l. Each subject will be dosed at the respective dose level for 2 weeks (unless platelet counts rise to > 400,000/ μ l). 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 thrombocytopenia. | | | |
| Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thrombocytopenia. | | | |
| 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 thrombocytopenia. | | | |
| Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thrombocytopenia. | | | |
| Binet stage C: Presence of anemia and/or thrombocytopenia. | | | |

| | | | |
|--|---|---|--|
| Units: Subjects | | | |
| Binet Stage C | 4 | 4 | |
| β-Symptoms at baseline | | | |
| Disease-related symptoms (previously defined as β-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). Fever ≥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 | | | |
| β-symptoms present | 2 | 2 | |
| β-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 thrombocytopenia. | | | |
| Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thrombocytopenia. | | | |
| 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 thrombocytopenia. | | | |
| Binet stage B: The patient has 3 or more areas of lymph-node involvement but no anemia or thrombocytopenia. | | | |
| Binet stage C: Presence of anemia and/or thrombocytopenia. | | | |
| Units: Subjects | | | |
| Binet Stage C | 4 | | |
| β-Symptoms at baseline | | | |
| Disease-related symptoms (previously defined as β-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). | | | |
| Fever ≥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 | | | |
| β-symptoms present | 2 | | |
| β-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: | |
| <p>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 $<50,000/\mu\text{l}$ to $\geq 100,000/\mu\text{l}$). Eltrombopag will be administered once daily to thrombocytopenic patients with platelet counts $< 50,000/\mu\text{l}$. Each subject will be dosed at the respective dose level for 2 weeks (unless platelet counts rise to $> 400,000/\mu\text{l}$). There is no intra-individual dose escalation.</p> <p>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.</p> | |
| 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: | |
| <p>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</p> | |
| End point type | Primary |
| End point timeframe: | |
| August 2011-November 2013 | |
| Notes: | |
| <p>[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.</p> <p>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.</p> | |

| 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 patients 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:

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 $<50,000/\mu\text{l}$ to $\geq 100,000/\mu\text{l}$). Eltrombopag will be administered once daily to thrombocytopenic patients with platelet counts $< 50,000/\mu\text{l}$. Each subject will be dosed at the respective dose level for 2 weeks (unless platelet counts rise to $> 400,000/\mu\text{l}$). 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.

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 | <p>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.</p> <p>Inclusion criteria after change according to protocol amendment:</p> <p>3. Patient is planned to receive alkylating agents and/or fludarabine-based therapy as 2nd or higher-line treatment</p> <p>Exclusion criteria after change according to protocol amendment:</p> <p>3. No prior therapy for CLL</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 11 November 2013 | <p>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</p> <p>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).</p> | - |

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: