Clinical trial results:
A single-arm phase II trial to assess the efficacy of Midostaurin (PKC412) added to standard primary therapy in patients with newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML

Summary

EudraCT number	2011-002567-17
Trial protocol	DE
Global end of trial date	30 October 2019

Results information

Result version number	v1 (current)
This version publication date	24 November 2021
First version publication date	24 November 2021

Trial information

Trial identification

Sponsor protocol code	TUD-MIDOKI-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01830361
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis Study code: CPKC412ADE01T

Notes:

Sponsors

Sponsor organisation name	Technische Universität Dresden
Sponsor organisation address	Helmholtzstraße 10, Dresden, Germany, 01069
Public contact	Head of Clinical Trial Dept., Medizinische Fakultät C. G. Carus, +49 03514583775, christoph.roellig@uniklinikum-dresden.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	23 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2019
Global end of trial reached?	Yes
Global end of trial date	30 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of tyrosine-kinase inhibitor midostaurin in c-KIT or FLT3-ITD mutated t(8;21) AML
To assess the efficacy of midostaurin depending on the type of c-KIT mutation

Protection of trial subjects:

The ECG recordings for the assessment of safety were performed as 12-lead standard ECGs. Echocardiography assessment were done for the determination of LVEF in M-Mode technique. A regular toxicity assessment was obtained as outlined in the study evaluations. Furthermore, the primary endpoint of this trial, event-free survival was a combined efficacy and safety endpoint and was therefore also used for the assessment of safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	17
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between March 2013 and December 2017, 18 patients were enrolled, displaying 15 KIT (88%) and 4 FLT3-ITD (20%) mutations.

Pre-assignment

Screening details:

Sreening examinations were done to determine the patients eligibility for the study within 7 days before study entry.

Period 1

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

Arms

Arm title	Midostaurin

Arm description:

After inclusion in the study, patients received one cycle of standard DA (days 1-7) in combination with midostaurin treatment (days 8-21). After confirmation of responsive disease and complete remission, patients continued with three cycles of high-dose cytarabine (HiDAC, days 1, 3, 5) in combination with midostaurin (days 8-21), which was administered depending on adequate blood counts and sufficient organ function. After a minimum of 14 days after the last midostaurin application in the last cycle of MidoHiDAC, i.e. earliest on day 36 after the beginning of the last cycle of MidoHiDAC, patients had to start maintenance treatment.

Arm type	Experimental
Investigational medicinal product name	Midostaurin
Investigational medicinal product code	PKC412
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

- second cycle of induction therapy: one cycle of standard DA (days 1-7) in combination with midostaurin treatment (50 mg oral, twice a day, days 8-21)
- consolidation therapy: three cycles of high-dose cytarabine (HiDAC, days 1, 3, 5) in combination with midostaurin (50 mg oral, twice a day, days 8-21)
- maintenance therapy: midostaurin (50 mg oral, twice a day) continuously for 12 cycles with 28 days per cycle (max. total of 336 days)

Number of subjects in period 1	Midostaurin
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	18	18	
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)	17	17	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	8	8	
Male	10	10	

End points

End points reporting groups

Reporting group title	Midostaurin

Reporting group description:

After inclusion in the study, patients received one cycle of standard DA (days 1-7) in combination with midostaurin treatment (days 8-21). After confirmation of responsive disease and complete remission, patients continued with three cycles of high-dose cytarabine (HiDAC, days 1, 3, 5) in combination with midostaurin (days 8-21), which was administered depending on adequate blood counts and sufficient organ function. After a minimum of 14 days after the last midostaurin application in the last cycle of MidoHiDAC, i.e. earliest on day 36 after the beginning of the last cycle of MidoHiDAC, patients had to start maintenance treatment.

Primary: 2-year event-free survival

End point title	2-year event-free survival[1]

End point description:

The primary endpoint is a binary variable indicating event-free-survival at 2 years. The nullhypothesis of this trial was that the 2-year-EFS rate is worse or equal to 0.5 under the experimental treatment. The alternate hypothesis was that the 2-year-EFS rate is equal to 0.8 or greater. In an exact single stage phase 2 design, 18 patients have to be enrolled to be able to detect the critical difference in the EFS rates of 0.3 with a power of 80% and a one-sided significance level of 5%. The nullyhpothesis could be rejected if after 2 years, 13 or more patients were without an event. The calculation is based on the exact binomial distribution as described in A'Hern (2001).

End point type	Primary

End point timeframe:

2-year Event-free Survival (EFS)

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: further information can be found in the publication (see online references)

End point values	Midostaurin			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 95%)	55.6 (31 to 79)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs were documented from the first administration of study drug up to 30 days after the last administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Frequency threshold for reporting non-serious adverse events: 5 %

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: further information can be found in the publication (see online references)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2014	- It can be assumed that patients who acquired a translocation t(8; 21) with c-KIT or FLT-ITD mutation secondary to chemotherapy or radiotherapy for another malignant disease will benefit from midostaurin just as much as patients who such a genetic constellation primary, ie without prior antineoplastic therapy. For this reason, previous radio or chemotherapy was deleted as an exclusion criterion. - Sections were added to the protocol that describe the interactions with the substances that enhance and inhibit the effect. - The interactions between midostaurin and CYP3A4 attenuating / enhancing substances have been described in more detail.
29 June 2015	- The recommendations for control and the required dose adjustments in the event of an increase in lipase and possibly occurring pancreatitis during the individual therapy phases have been supplemented according to Investigator's Brochure Version 18. - The prescribed storage temperature of midostaurin has been changed to "not above 25 ° C".
13 July 2018	- Change of LKP: From 05/01/2018 on, Prof. Röllig took over the tasks of the previous LKP of Prof. Ehninger. - In the Investigator's Brochure Edition 21, the times for the necessary contraception have been significantly extended. This was included as an additional point in the inclusion and exclusion criteria. - The protocol section 5.4 Pregnancy, breast-feeding, contraception and fertility was supplemented according to the changes and requirements to prevent pregnancy from the investigator's brochure Edition 21. Safe birth control times have been extended from 4 weeks to at least 4 months after the last dose of midostaurin for women and men. - Since, according to the Investigator's brochure, a pregnancy test must be carried out in women of childbearing potential within 7 days before the start of Midostaurin administration, the determination of ß-HCG was added on day 1 of the 2nd induction and every consolidation cycle and before the start of maintenance therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported