Clinical trial results:
Ponatinib plus reduced-intensity chemotherapy in the first-line treatment of adult patients with Ph-positive acute lymphoblastic leukemia.

Summary

EudraCT number	2019-004540-29
Trial protocol	CZ
Global end of trial date	29 June 2023

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Pona-CELL study - FINAL REPORT (Pona-CELL study_FINAL REPORT.pdf)

Trial information

Trial identification

Sponsor protocol code	Pona-CELL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ústav hematologie a krevní transfuze Praha
Sponsor organisation address	U Nemocnice 2094/1, Praha, Czechia, 12800
Public contact	Cyril Šálek, Doc. MUDr. Mgr. Ph.D., Ústav hematologie a krevní transfuze, +420 221977301, jana.brzonova@uhkt.cz
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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	03 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2023
Global end of trial reached?	Yes
Global end of trial date	29 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the percentage of complete molecular responses after two cycles of induction therapy composed of chemotherapy plus ponatinib.

Protection of trial subjects:

Ethical Conduct of the Study
The study has been conducted in compliance with ethical principles set in the Declaration of Helsinki in latest revision, the approved protocol, the good clinical practice (GCP) and requirements provided in the Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2) - Current Step 4 version dated 9 Nov. 2016, the Regulation (EU) No.536/2014 of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, the national Act 378/2007 Coll., on Pharmaceuticals, and Decree 226/2008 Coll., on good clinical practice, as amended. The ethical and regulatory approvals were available before any subject was exposed to any study-related procedure, including screening tests for eligibility.
The Sponsor has concluded a liability insurance policy that covers the investigator and the Sponsor, and also the damages in the event of the death of the trial subject or in the event of an injury to the health of the trial subject arising due to the conduct of the clinical trial.

Background therapy:

Pre-phase:
dexamethasone 10 mg/m2 day -5 till -1
cyclophosphamide 200 mg/m2 day - 3 till -1
methotrexate 15 mg intrathecally once during the pre-phase.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	16 February 2021
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	Czechia: 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:

Suitable subjects were identified, contacted, informed and recruited by the Principal Investigator in each of the trial sites concerned. No public advertising for participation in the study was used, the subjects were selected from patients treated in the University Hospital departments of hemato-oncology.

Pre-assignment

Screening details:

Eligible subjects were duly consented patients suffering from Ph-positive acute lymphoblastic leukemia (ALL). Inclusion and exclusion criteria were checked
and documented at the Screening visit.

Period 1

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

Arms

Arm title	Study drug (ponatinib)

Arm description:

Ponatinib administration during specified phases of the trial (Induction, Consolidation and Maintenance, at 30 mg/day continuously).

Arm type	Experimental
Investigational medicinal product name	Ponatinib (Iclusig)
Investigational medicinal product code	EU/1/13/839/006
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 30 mg tablet daily, continuously since day 1 of Induction I until end of Consolidation I, followed by 1 tablet 15 mg/day since Consolidation II until end of Maintenance (month 36).

Number of subjects in period 1	Study drug (ponatinib)
Started	4
Completed	4

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Drugs given routinely prior to the induction therapy according to the GMALL 07/2003 and CELL Ph+ 2012 protocols which are a current standard of care in the Czech Republic. This treatment does not have any investigational character.

Reporting group values	Overall trial	Total	
Number of subjects	4	4	
Age categorical			
Age 18 years, as stated in Inclusion criteria.			
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	
Age continuous			
Units: years			
median	37.86		
full range (min-max)	25.11 to 65.70	-	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	2	2	

Subject analysis sets

Subject analysis set title	Trial analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Efficacy: Defined as a proportion of patients reaching the complete molecular response after two cycles of induction therapy plus ponatinib. Molecular response will be monitored by quantification of BCR-ABL transcript and by patient-specific BCR-ABL genomic fusion, both by ddPCR in bone marrow.

Reporting group values	Trial analysis set		
Number of subjects	4		
Age categorical			
Age 18 years, as stated in Inclusion criteria.			
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		
Age continuous			
Units: years			
median	37.86		
full range (min-max)	25.11 to 65.70		
Gender categorical			
Units: Subjects			
Female	2		
Male	2		

End points

End points reporting groups

Reporting group title	Study drug (ponatinib)

Reporting group description:

Ponatinib administration during specified phases of the trial (Induction, Consolidation and Maintenance, at 30 mg/day continuously).

Subject analysis set title	Trial analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Efficacy: Defined as a proportion of patients reaching the complete molecular response after two cycles of induction therapy plus ponatinib. Molecular response will be monitored by quantification of BCR-ABL transcript and by patient-specific BCR-ABL genomic fusion, both by ddPCR in bone marrow.

Primary: Molecular response

End point title	Molecular response

End point description:

MRD response after two cycles of induction therapy plus ponatinib, i.e. at the start of consolidation treatment (assessed at week 11). MRD response will be
measured centrally by quantification of BCR-ABL1 transcript using ddPCR method.

End point type	Primary

End point timeframe:

Determined at week 11.

End point values	Study drug (ponatinib)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: BCR-ABL1 transcripts				
number (not applicable)	4			

Statistical analyses

Statistical analysis title	Statistical methods and sample size

Statistical analysis description:

The null hypothesis was a complete molecular remission rate of 36%. The assumption was that the number of complete molecular responders will improve to 60%. Assuming a 10% drop-out rate, a total of 32 patients was to be enrolled, but it failed. Statistical methods: One sample binomial Z-test for primary endpoint; Kaplan-Meier method for PFS and OS, multivariant analysis for secondary endpoints.

Comparison groups	Study drug (ponatinib)

Number of subjects included in analysis	4
Analysis specification	Pre-specified
Analysis type	other[1]

Notes:

[1] - Data from all patients who achieve at least primary endpoint will be used for statistical analysis. The primary endpoint will be tested by one sample binomial Z-test with null hypothesis that the proportion of patients achieving molecular remission is equal or greater than 60%. The proportion and 95% confidence interval will be calculated.

Secondary: Other efficacy and safety assessments

End point title	Other efficacy and safety assessments

End point description:

1. Complete remission (CR) and complete remission with incomplete blood count recovery (CRi) at the end of Induction cycle I and Induction cycle II.
2. Progression-free survival (PFS) is defined in responding patients (CR/CRi) by the time between the day of CR/CRi documentation until date of relapse, or death;
3. Overall survival (OS) is defined by the time between the start of leukemia-specific therapy until date of death of any cause;
4. AlloSCT in the first complete remission. Indications for alloSCT are defined in the protocol;
5. Severity of adverse event within 30 days after end of ponatinib administration. Grading of AE based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

End point type	Secondary

End point timeframe:

Throughout the subject´s participation in the trial.

End point values	Trial analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: number of subjects or number of days	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Since the start of Induction I until the ned of Maintenance period.	
Adverse event reporting additional description:	
All AEs have been collected and assessed using the NCI Common Terminology Criteria for Adverse Events, version 5.0.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	Subjects who received IMP
Reporting group description:	
Subjects who received IMP.	

Serious adverse events	Subjects who received IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer recurrent.	Additional description: Not related to IMP.		
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Not related to IMP.		
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subjects who received IMP		
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 4 (100.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2022	Purpose of the amendment: to expand the study population to elderly patients; to adjust the doses of chemotherapy for age in two steps (for subjects over 55 and 70 years); to enable elderly patients who have reached complete remission without a deep molecular response to stay in the study without the need to undergo an allogeneic stem cell transplantation (which is considered risky in this age category and is not routinely performed).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Limitation due to small sample size: The actual amount of data obtained was critically insufficient for the statistics originally scheduled, as only 4 subjects were enrolled and treated with IMP per protocol; more info provided in attached document.

Notes: