SUMMARY, including results

Study title	Ponatinib plus reduced-intensity chemotherapy in the first-line treatment of adult patients with Ph-positive acute lymphoblastic leukemia in adults.
Brief title	Pona-CELL
EudraCT number	2019-004540-29
Sponsor	Ústav hematologie a krevní transfuze, Praha, Česko / Institute of Hematology and Blood Transfusion, Prague, Czechia
Study type and phase	Investigator-initiated, open-label, one treatment arm prospective multicenter phase II clinical trial.
Study subjects	Previously untreated Ph-positive B-precursor ALL patients aged ≥18 years.
Investigational medicinal product (IMP)	Ponatinib (Iclusig®)
Trial sites and Investigators	Single country: Czech Republic Sites and Principal investigators: CELL – Czech Leukemia Study Group centers in Ústav hematologie a krevní transfuze, Prague - C. Šálek, and Hematology Departments of University Hospitals (Fakultní nemocnice) in Brno – M. Doubek, Hradec Králové - M. Horáček, Olomouc – T. Szotkowski, Ostrava – Z. Kořístek, Plzeň – M. Karas and Královské Vinohrady, Prague – J. Novák.
Number of subjects	Planned: 32 ALL patients. However, eventually only 4 subjects were enrolled.
Human tissue analysis	Blood, Bone Marrow.
Pharmacokinetics	None
Study duration	Total study duration: planned 7 years • Enrolment period: 48 months. • Maximum treatment and follow-up duration per patient: 36 months.
Rationale	1) Ponatinib plus chemotherapy (hyper-CVAD) induced 100% complete remissions in intensively treated patients (median age 47 years) with Ph-positive ALL. Eighty percent of patients have reached a complete molecular response (Jabbour, Lancet Oncol 2015). 2) CMR at 3 months of therapy has impact on survival in patients with Ph-positive ALL treated with tyrosine kinase inhibitors (TKI) plus chemotherapy. Ponatinib has the highest probability to reach CMR at 3 months in comparison to other TKI's (39% for imatinib, 54% for dasatinib, 87% for ponatinib). Three-year OS and EFS for patients reaching CMR were 79% and 69% (vs. 56% and 42% for those in a hematological remission, but not CMR) (Short, Blood 2016). 3) Patients achieving CMR do not benefit from alloSCT, whereas patients with persistent MRD do benefit on French GRAAPH-2005 trial. Patients in CMR undergoing autologous stem cell transplantation, or being treated with TKI plus chemotherapy without transplantation had similar outcome as patients after alloSCT on same trial (Chalandon, Blood 2015). 4) Lower doses of ponatinib (30 mg) have better safety profile than high doses (45 mg) without compromising efficacy in patients with CML (Dorer, Leuk Res 2016).

Objectives	Primary objective: - To evaluate the percentage of complete molecular responses after two cycles of remission induction therapy composed of two cycles of chemotherapy plus ponatinib. Secondary objectives: - To evaluate rate of complete remissions (CR and/or CRi) after the first and second cycles of remission induction therapy; - To evaluate progression-free survival (PFS) in patients treated with ponatinib plus reduced-intensity chemotherapy; - To evaluate overall survival (OS) in patients treated with ponatinib plus reduced-intensity chemotherapy; - To determine the percentage of patients undergoing allogeneic stem cell transplantation (alloSCT) due to the suboptimal molecular response after two cycles of ponatinib-based induction regimen; - To evaluate the incidence and seriousness of adverse events.
Main eligibility criteria	Inclusion criteria - Patients with newly diagnosed, previously untreated, Ph-positive [either t(9;22) and/or *BCR-ABL* positive] B-precursor acute lymphoblastic leukemia; - Age ≥18 years; - Eligible to intensive chemotherapy, due to general health status; - ECOG performance status ≤2; - Absence of significant liver disease, as defined by the following criteria: total serum bilirubin ≤1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome, alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5 x ULN if leukemic involvement of the liver is present, and aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 x ULN if leukemic involvement of the liver is present; - Adequate pancreatic function as defined by serum amylase and lipase ≤1.5 × ULN; - Diagnostic sample of bone marrow (or peripheral blood with >50% of blasts) available for central MRD assessment; - Subject has provided written informed consent prior to any screening procedure. Exclusion criteria - Lymphoid blast crisis of CML; - Active serious infection not controlled by oral or intravenous antibiotics; - Active known HBV or HCV hepatitis or positive HIV serology; - History of acute pancreatitis within 1 year of study or history of chronic pancreatitis; - Uncontrolled hypertriglyceridemia (triglycerides > 5.1 µmol/L); - Clinically significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to: any history of myocardial infarction, stroke, or revascularization; unstable angina or transient ischemic attack within 6 months prior to enrolment; congestive heart failure within 6 months prior to enrolment or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards; history of clinically significant (as determined by the treating physician) atrial arrhythmia; any history of ventricular arrhythmia; any history of venous thromboembolism including deep

	venous thrombosis or pulmonary embolism; - Uncontrolled hypertension (diastolic blood pressure >90 mmHg; systolic >140 mmHg). Patients with hypertension should be under treatment on study entry to effect blood pressure control; - Creatinine levels > 160 µmol/L or estimated creatinine clearance of < 50 mL/min; - GI disease and/or major GI surgery that may significantly alter the absorption of study drug - Hypersensitivity to the active substance or to any of the excipients, especially galactose intolerance. - Taking any medications or herbal supplements that are known to be strong inhibitors of CYP3A4 within at least 14 days before the first dose of ponatinib (see chapter 4.5 of SPC attached to the protocol) - Female patients who are pregnant or breast feeding or patients of childbearing potential not willing to use highly effective methods of contraception during the study and for 3 months following the last dose of study drug; - Male patients whose sexual partner(s) are women of childbearing potential who are not willing to highly effective methods of contraception, one of which includes a condom, during the study; - Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention; - Any concurrent severe and/or uncontrolled medical condition, which could, in the opinion of the investigator, compromise participation in the study; - Concurrent participation in another clinical study with an investigational medical product.
Treatment plan	***Pre-phase:*** dexamethasone 10 mg/m^2 day -5 till -1 cyclophosphamide 200 mg/m^2 day - 3 till -1 methotrexate 15 mg intrathecally once during the pre-phase ***day 1-5: screening to the study*** ***Induction I:*** ponatinib 30 mg/day since day 1 rituximab 375 mg/m^2 day 1 (if CD20+ at diagnosis) dexamethasone 10 mg/m^2 day 1-2, 8-11 vincristine 2 mg day 1, 8, 15 filgrastim 5 µg/kg since ANC <1x10^9/L until recovery Patients with CNS leukemia at diagnosis will be administered triple intrathecal therapy (methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg) 2-3x weekly until CNS negativity in two consecutive exams is reached. *day 23: bone marrow aspiration, central BCR-ABL assessment* ***Induction II:*** ponatinib 30 mg/day continuously rituximab 375 mg/m^2 day 23 (if CD20+ at diagnosis)

	cyclophosphamide 1000 mg/m^2 day 24 cytarabine 75 mg/m^2 day 26-29, 33-36 filgrastim 5 µg/kg since ANC <1x10^9/L until recovery methotrexate 15 mg intrathecally at days 26 and 33 methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg intrathecally at day 40 **week 7–10 (8–11): CNS radiotherapy** Patients with CNS infiltration at diagnosis will undergo fractionated radiotherapy of the neurocranium with the total dose of 23.4 Gy (13 fractions by 1.8 Gy). Ponatinib 30 mg/day will not be interrupted during the radiotherapy. Patients without proven CNS leukemia at diagnosis will be treated by Ponatinib only during this period. ***week 11: bone marrow aspiration, central BCR-ABL assessment (primary endpoint)*** *Patients not in CR at week 11 will end the study.* ***Consolidation I*** *week 12 (±1 week):* ponatinib 30 mg/day continuously rituximab 375 mg/m^2 day 1 (if CD20+ at diagnosis) dexamethasone 10 mg/m^2 day 1-4 vindesine 3 mg/m^2 day 2 (max. dose 5 mg) methotrexate 1.5 g/m^2 day 2 (1 g/m^2 if >55 years; 0.5 g/m^2 if >70 years) cytarabine 2x 2 g/m^2 day 5 (2x 1 g/m^2 if >55 years) filgrastim 5 µg/kg since day 6 until recovery methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg intrathecally after elimination of methotrexate from plasma (approx. day 8 ± 2 days) **week 16:** ***bone marrow aspiration, central BCR-ABL assessment*** *Patients in CMR at week 11 will be treated with 5 additional blocks of chemotherapy followed by maintenance therapy;* *Patients with molecular failure at week 11 will end the study and be directed to alloSCT.* *Patients aged 55 years or more who did not meet the primary endpoint at week 11 but are in continuous CR with* BCR-ABL1 *transcript <0.1% may be treated with consolidation and maintenance therapy according to the study protocol without alloSCT at the investigator's discretion.* ***Consolidation II*** *week 18 (±1 week):* ponatinib 15 mg/day continuously rituximab 375 mg/m^2 day 1 (if CD20+ at diagnosis) cyclophosphamide 500 mg/m^2 day 2,3 VP-16 75 mg/m^2 day 2,3 methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg at day 1 ***Consolidation III + V*** *week 24+36 (±1 week):* ponatinib 15 mg/day continuously rituximab 375 mg/m^2 day 1 (if CD20+ at diagnosis) methotrexate 1.5 g/m^2 day 2 (1 g/m^2 if >55 years; 0.5 g/m^2 if >70

	years) vincristin 1 mg day 2 purinethol 60 mg/m^2 day 2-8 methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg at day 1 *day 1: bone marrow aspiration, central BCR-ABL assessment* ***Consolidation IV + VI*** *week 30+42 (±1 week):* ponatinib 15 mg/day continuously rituximab 375 mg/m^2 day 1 (if CD20+ at diagnosis) dexamethasone 10 mg/m^2 day 1-4 cytarabine 1.5 g/m^2 day 1+3+5 (1 g/m^2 if >55 years; omitted in patients >70 years if in complete molecular response) methotrexate 15 mg + cytarabine 40 mg + dexamethasone 4 mg at day 1 ***Maintenance*** *month 12–36:* ponatinib 15 mg/day continuously 24 months *every 4 months: bone marrow aspiration, central BCR-ABL assessment* *every 2 months: PB count and serum lipase assessment*
Definitions of response	• **complete remission (CR):** ≤ 5% blasts in the bone marrow, no evidence of disease (absence of circulating blasts, no extramedullary involvement), full recovery of peripheral blood counts (platelets ≥ 100.000/µl, and ANC ≥ 1.000/µl) • **complete remission with incomplete blood count recovery (CRi):** same as CR but platelets < 100,000/µL, and/or ANC < 1,000/µL • **progressive disease (PD):** no CR/CRi after two courses of remission induction therapy • **relapse:** recurrence of leukemia in subjects who achieved a confirmed CR/CRi and subsequently no longer meet the CR/CRi criteria • **complete molecular remission (CMR):** *BCR-ABL1* below the Limit of Quantification by ddPCR • **molecular failure:** a failure to achieve CMR by the time scheduled for analysis of primary endpoint • **molecular reappearance:** detection of quantifiable *BCR-ABL1* transcript by ddPCR transcript in a patient who has previously achieved CMR
IMP details	Ponatinib (Iclusig®), 15 mg, coated tablets. Starting dose 30 mg once daily (QD), administered orally, dose adjustments as per protocol. To be taken with or without food, tablets swallowed whole.
Dose adjustments for toxicity	**<u>Myelosuppression:</u>** **• ANC < 1.0 x 10^9/L or platelet < 50 x 10^9/L during induction and consolidation phase:** • if lasting ≤ 21 days of each respective cycle: Ponatinib should be continued together with G-CSF (filgrastim) daily and platelet transfusions as per institutional guidelines • if lasting > 21 days of each respective cycle: Ponatinib should be discontinued and resumed at original dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L

	• **ANC < 1.0 x 10^9/L or platelet < 50 x 10^9/L during maintenance phase:** • Ponatinib should be withheld and resumed at the same dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L; it should be permanently discontinued if myelosuppression reoccurs for the third time **<u>Arterial occlusion and venous thromboembolism:</u>** • Ponatinib should be immediately interrupted if developing of an arterial occlusive event or a venous thromboembolism is suspected. Ponatinib may be resumed at 15 mg after the event is resolved, however, a benefit-risk consideration should guide a decision to restart the therapy. • Hypertension may contribute to risk of arterial occlusive events. Ponatinib should be temporarily interrupted if hypertension is not medically controlled. **<u>Pancreatitis and elevation of amylase and/or lipase</u>** • **Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN) only:** Occurrence at 30 mg: • Ponatinib should be withheld and resumed at 15 mg after recovery to ≤ Grade 1 (< 1.5 x ULN) Occurrence at 15 mg: • Ponatinib discontinuation should be considered • **Grade 3 pancreatitis:** Occurrence at 30 mg: • Ponatinib should be withheld and resumed at 15 mg after recovery to < Grade 2 Occurrence at 15 mg: • Ponatinib discontinuation should be considered • **Grade 4 pancreatitis:** Ponatinib should be discontinued **<u>Hepatic toxicity</u>** • **Elevation of liver transaminase > 3 × ULN or Persistent grade 2 (longer than 7 days) or Grade 3 or higher:** Occurrence at 30 mg: • Ponatinib should be interrupted and resumed at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade Occurrence at 15 mg while on ponatinib and concomitant chemotherapy: • Ponatinib should be discontinued and resumed after recovery to ≤ Grade 1, or recovery to pre-treatment grade Occurrence at 15 mg while on ponatinib monotherapy: • Ponatinib should be discontinued • **Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase > 2 × ULN:** Occurrence while on ponatinib and concomitant chemotherapy: • Ponatinib should be discontinued and resumed at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade Occurrence while on ponatinib monotherapy: • Ponatinib should be discontinued If treatment interruption for any of the above toxicities lasts for more than 28 days, a risk/benefit should be evaluated and permanent discontinuation of ponatinib should be considered. The definitive decision should be made by the PI after consultation with the Primary Study Coordinator.

	Grading of AE based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
Efficacy and safety assessment	**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. **Safety:** All AEs will be collected and assessed using the NCI Common Terminology Criteria for Adverse Events, version 5.0. Adverse events (AE): all AEs encountered during the study corresponded to the expected profile in the patient population concerned. Two serious AEs (SAE) occurred: "Laryngeal cancer recurrent" and "Febrile neutropenia"; both in 1 subject and considered to be unrelated to the IMP.
Statistical methods and sample size	The primary endpoint was MRD response after two cycles of induction chemotherapy therapy plus ponatinib. The expected, but unmet, accrual rate was 1 pat. per 1-2 month (12 patients per year). The null hypothesis was a complete molecular remission rate of 36% based on analysis of patients treated with Ph+ Junior CELL 2012 protocol in Prague and Brno in 2007-2017. The assumption was that the number of complete molecular responders will improve to 60%. Number of subjects required by power analysis (one sample binomial Z-test) for alpha risk 0.15 and study power 0.70 for null hypothesis 36% and cut-off value of 60% to reject the null hypothesis is 29 patients for the primary endpoint. Considering a 10% drop-out rate, a total of 32 patients was planned to be enrolled. Statistical methods: One sample binomial Z-test for primary endpoint; Kaplan-Meier method for PFS and OS, multivariant analysis for secondary endpoints.
Resumé of evaluable data	The study was terminated prematurely, mainly due to an unexpectedly low enrolment rate. Only 4 patients with a median age of 38 years (range 25-65 years) were included and treated with the study drug (ponatinib). All achieved complete remission. The primary objective: Complete molecular remission at week 11 was achieved in 2 patients. The remaining two patients had quantifiable residual disease at 10e-4 and 10e-5 levels. Three patients underwent allogeneic stem cell transplantation, the last one terminated the study treatment due to relapse of preexisting head and neck cancer (which was in remission at the time of enrolment in the study). All patients were alive with a median follow-up of 23 months at the time of this report on August 13, 2024.

Declaration of the end of trial form

NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINE FOR HUMAN USE TO THE COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

For official use

Date of receipt:	Competent authority registration number: Ethics committee registration number:

To be filled in by the applicant

A MEMBER STATE IN WHICH THE DECLARATION IS BEING MADE: Czech Republic

B TRIAL IDENTIFICATION

B.1 EudraCT number:	**2019-004540-29**
B.2 Sponsor's protocol code number:	**Pona-CELL**
B.3 Full title of the trial:	**Ponatinib plus reduced-intensity chemotherapy in the first-line treatment of adult patients with Ph-positive acute lymphoblastic leukemia**

C APPLICANT IDENTIFICATION (please tick the appropriate box)

C.1	**DECLARATION FOR THE COMPETENT AUTHORITY**	☒
C.1.1	Sponsor	☐
C.1.2	Legal representative of the sponsor	☐
C.1.3	Person or organisation authorised by the sponsor to make the application.	☒
C.1.4	**Complete below**:	
C.1.4.1	Organisation:	Ústav hematologie a krevní transfuze
C.1.4.2	Name of person to contact:	Doc.MUDr. Mgr. Cyril Šálek, Ph.D.
C.1.4.3	Address:	U Nemocnice 2094/1 128 20 Praha 2 Czechia
C.1.4.4	Telephone number:	00420 221 977 301
C.1.4.5	Fax number:	
C.1.4.6	E-mail	cyril.salek@uhkt.cz

C.2	**DECLARATION FOR THE ETHICS COMMITTEE**	☐
C.2.1	Sponsor	☐
C.2.2	Legal representative of the sponsor	☐
C.2.3	Person or organisation authorised by the sponsor to make the application.	☐
C.2.4	Investigator in charge of the application if applicable[1]:	
	• Co-ordinating investigator (for multicentre trial):	☐
	• Principal investigator (for single centre trial):	☐
C.2.5	**Complete below**:	
C.2.5.1	Organisation:	
C.2.5.2	Name:	
C.2.5.3	Address:	
C.2.5.4	Telephone number:	
C.2.5.5	Fax number:	
C.2.5.6	E-mail:	

[1] According to national legislation

D END OF TRIAL

D.1	**Is it the end of the trial in this Member State?**		yes ☒ no ☐
D.1.1	If yes, give date (YYYY/MM/DD):	2023/06/29	

D.2	**Is it the end of the complete trial in all countries concerned by the trial?**		yes ☒ no ☐
D.2.1	If yes, give date (YYYY/MM/DD):	2023/06/29	

D.3	**Is it a premature ending of the trial?**		yes ☒ no ☐
D.3.1	If yes, give date (YYYY/MM/DD):	2023/06/29	
D.3.2	What is (are) the reason(s) for the premature ending?		
D.3.2.1	Safety		yes ☐ no ☒
D.3.2.2	Lack of efficacy		yes ☐ no ☒
D.3.2.3	The trial has not commenced		yes ☐ no ☒
D.3.2.4	Other		yes ☒ no ☐
D.3.3	If yes to any of the above questions, briefly describe in an annex (free text):		
D.3.3.1	The justification for premature ending of the trial:	Clinical Trial Timelines specified in the protocol could not be met due to low recruitment rate. It was agreed that the recruitment had to be terminated prematurely and afterwards the whole clinical trial.	
D.3.3.2	Number of patients still receiving treatment at time of premature termination in the MS concerned by the declaration and their proposed management:	0	
D.3.3.3	The consequences of early termination for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product:	N/A	

E SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

E.1 I hereby confirm that/confirm on behalf of the sponsor that (delete which is not applicable):

- The above information given on this declaration is correct; and
- That a summary of the clinical trial report will be submitted to the competent authority and ethics committee concerned as soon as available and within a 1 year deadline after the end of the trial in all countries.

E.2	**APPLICANT TO THE COMPETENT AUTHORITY** (as stated in C.1)		☒
E.2.1	Date :	30-June-2023	
E.2.2	Signature :		
E.2.3	Print name:	Cyril Šálek, MD	

E.3	**APPLICANT TO THE ETHICS COMMITTEE** (as stated in C.2) **:**		☐
E.3.1	Date :		
E.3.2	Signature :		
E.3.3	Print name:		