# Trial Results Report[1]

| Name of Sponsor/Company:<br>Dekan des Fachbereichs Medizin der Goethe Universität - Frankfurt, Germany<br><br>To be represented by the coordinating investigator (LKP according to German drug law) | Individual Study Table: [2]<br><br>Not applicable | *For national authority use only* |
|---|---|---|
| Name of Finished Product:<br>Iclusig®, | | |
| Name of Active Substance:<br>Ponatinib | | |

Title of Study[3]

**GMALL-MOLACT2-PONA:**
"A confirmatory multicenter, single-arm study to assess the effi-cacy, safety, and tolerability of ponatinib (Iclusig®) in adult pa-tients with minimal residual disease (MRD) in Philadelphia-Chro-mosome positive acute lymphoblastic leukemia"

The trial has been conducted according to
Protocol Version 1.3 (01.09.2020)

Investigators

„Leiter der Klinischen Prüfung" according to German drug law:
Dr. Heike Pfeifer

Study centre(s)

17 hospitals

Publication (reference)

Due to premature recruitment stop after enrolment of only two patients no further publication of data is planned.

[1] § 42b AMG (german drug law), according to ICH E3
[2] Referring to Part of the Dossier (Volume, Page)
Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich
[3] Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren

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Studied period (years): date of first enrolment, date of last completed[4]

01.07.2021 - First Patient In (FPI)

22.04.2022 – Last Patient In (LPI)

11.05.2022 - Premature recruitment stop
As the recruitment rate proved to be too low to achieve the final objectives of the study in a reasonable time, the study was terminated prematurely

12.07.2022 - Last enrolled patient End of Treatment (Patient No.2) (LP-EoT)

09.11.2022 – Last patient last visit

10.03.2023 – Data base closed

Phase of development

Phase II

Objectives

**Primary objective:**

- To evaluate the efficacy of ponatinib to induce molecular remission in patients

**Secondary objectives:**

- Remission duration, relapse-free survival and overall survival
- Relapse localisation and relapse characteristics
- Efficacy of ponatinib in patients
- Safety and tolerability of ponatinib in patients
- Effect of ponatinib on duration of MRD response and molecular remission
- Effect of ponatinib on the kinetics on MRD response
- Outcome of SCT after ponatinib including mortality rate
- Outcome of patients without SCT after ponatinib
- Patient's quality of life during and after therapy

Methodology

This trial was an open-label, multicenter, phase II pilot study to confirm the efficacy, safety and tolerability of ponatinib in adult patients with minimal residual disease (MRD) positive Ph+ALL. The primary objective was the induction of complete MRD response by ponatinib.

[4] Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/ Studienabbrüche unter Angabe der Gründe aufgeführt werden

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Number of patients (planned and analysed)

Planned subject number was 20 patients with Philadelphia-Chromosome and/or BCR-ABL1 positive acute lymphoblastic leukemia MRD-positive after consolidation I (<=55 years) or consolidation II (>55 yrs) and prior treatment with at least one tyrosine kinase inhibitor.

Before halt of recruitment in May 2022, 2 patients had been enrolled and could be analyzed. The descriptive analysis will be performed based on the data available from the closed database.

Diagnosis and main criteria for inclusion

**Indication:**
MRD-positive Philadelphia-Chromosome positive ALL and/or BCR-ABL positive acute lymphoblastic leukemia

**Inclusion Criteria:**

1. Patients with Philadelphia-Chromosome/BCR-ABL1 positive ALL in complete hematological remission defined as less than 5% blasts in bone marrow after at least three intense chemotherapy blocks (e.g., GMALL induction I-II/consolidation I for patients < 55 years or after consolidation II for patients > 55 years) who received treatment with at least one tyrosine kinase inhibitor
2. Presence of minimal residual disease (MRD) in molecular failure or with molecular relapse documented after an interval of at least 2 weeks from last systemic chemotherapy (Definition of Molecular failure/Mo-lecular Relapse: BCR-ABL1/ABL1>10E-04 and BCR-ABL1 copies > 10)
3. Molecular evaluation for BCR-ABL1 performed
4. Bone marrow function as defined below:
   ANC (Neutrophils) ≥ 1,000/µL
   Platelets ≥ 50,000/µL (transfusion permitted)
   HB level ≥ 9g/dl (transfusion permitted)
5. ECOG performance status ≤2
6. Normal QTcF interval ≤450 ms for males and ≤470 ms for females
7. Normal serum levels > LLN (lower limit of normal) of potassium and magnesium, or corrected to within normal limits with supplements, prior to the first dose of study medication
8. Adequate renal, hepatic and pancreatic function
9. Minimum life expectancy of ≥3 months
10. Negative pregnancy test and agree to use effective form of contraception (as applicable)
11. Age ≥18 years
12. Ability to understand and willingness to sign a written informed consent
13. Signed and dated written informed consent is available

**Exclusion Criteria:**

1. Ph-negative ALL
2. Presence of circulating blasts or current extramedullary involvement by ALL
3. Current detection of ALL blast cells in cerebro-spinal fluid
4. Any cancer chemotherapy or immunotherapy after sampling for the MRD test which leads to study inclusion (except for intrathecal prophylaxis and continued tyrosine kinase inhibitor)
5. Autologous hematopoietic stem cell transplantation (SCT) or allogeneic SCT
6. Treatment with any investigational product within four weeks prior to study treatment or within five terminal elimination half-lives of a preceding investigational medicinal product or of its relevant metabolite. The longer period of time will apply
7. History of malignancy other than ALL diagnosed within 5 years prior to start of protocol-specified therapy with the exception of:
    a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    b. Adequately treated cervical carcinoma in situ without evidence of disease
    c. Adequately treated breast ductal carcinoma in situ without evidence of disease
    d. Prostatic intraepithelial neoplasia without evidence of prostate cancer
8. Active infection, any other concurrent disease or medical condition that are deemed to interfere with the conduct of the study as judged by the investigator
9. Pregnant and nursing women
10. Woman of childbearing potential and is not willing to use highly effective methods (as defined in the protocol) of contraception while receiving study treatment and for an additional 3 months after the last dose of study treatment (Pearl-Index <1%). Women of childbearing potential are defined as mature women without hysterectomie or surgical sterilization or women without menopause. Menopause means without menstruation for natural reasons for one year
11. Male who has a female partner of childbearing potential, and is not willing to use highly effective forms (as defined in the protocol) of contraception while receiving study treatment and for at least an additional 3 months after the last dose of study treatment (Pearl-Index <1%)
12. Tyrosine kinase inhibitor (TKI) treatment within 3 days prior to receiving the first dose of ponatinib
13. Treatment with medications that are known to be associated with torsades de pointes
14. Prior treatment with ponatinib
15. History or presence of clinically significant bleeding or coagulation disorder unrelated to completed ALL treatment elements, e.g asparaginase treatment
16. History of pancreatitis within 1 year of study start or history of chronic pancreatitis, serum lipase and am-ylase ≥1.5 x ULN
17. Known impaired cardiac function, including any of the following:
    a. LVEF < 40%
    b. Complete left bundle branch block
    c. Right bundle branch block plus left anterior hemiblock, bifascicular block
    d. History of or presence of clinically significant ventricular or atrial tachyarrhythmias
    e. Clinically significant resting bradycardia (< 50 beats per minute)
    f. Congenital long QT syndrome or QTcF >470 msec on screening ECG. If QTc > 470 msec and electrolytes are not within normal ranges before ponatinib dosing, electrolytes should be corrected and then the patient rescreened for QTcF criterion.
    g. Previous myocardial infarction
    h. Other clinically significant heart disease (e.g. unstable angina, congestive heart failure, uncontrolled hypertension)
    i. History of or presence of clinically relevant peripheral vascular disease or other vascular steno-sis or occlusion,
    j. Any history of ischemic stroke or transient ischemic attacks (TIAs)
18. Inadequate hepatic functions defined as ASAT or ALAT > 2.5 times the institutional upper limit of normal (ULN) or > 5 times ULN if considered due to leukemia
19. Total bilirubin >1.5 fold the institutional ULN unless considered to be due to organ involvement by the leukemia or to M. Gilbert / M. Meulengracht
20. Concurrent severe diseases which exclude the administration of therapy
21. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)
22. Major surgery within 14 days prior to first dose of ponatinib

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23. Ongoing or active infection
24. Malabsorption syndrome or other gastrointestinal illness that could affect absorption of Ponatinib
25. Any other condition or illness that would compromise safety

## Test product, dose and mode of administration, batch number

Ponatinib 30 mg once daily p.o..

Standard trading packages of Iclusig 15 mg tablets have been provided for the trial.
Used batch numbers are: PR090899

## Duration of treatment

Patients was administered for at least one cycle and an optional second cycle:
Ponatinib 30 mg is given once daily, orally from d 1 – d 28.

In the event of extramedullary or hematological relapse within the treatment period, treatment with ponatinib was terminated.
Increasing MRD-levels without the occurrence of overt hematological relapse during the treatment period shall not affect continuation of treatment with ponatinib.
In case of SCT at some time after completion of treatment cycle 1, treatment with ponatinib will be terminated.

## Reference therapy, dose and mode of administration, batch number

Not applicable.

## Criteria for evaluation:

<u>Efficacy:</u>

The primary endpoint was to evaluate the proportion of patients who achieve molecular remission/MRD response after one cycle of treatment with ponatinib in patients with a molecular failure after consolidation 1. Both patients responded to therapy and MRD levels decreased.

<u>Safety:</u>

The 2 patients tolerated the medication. One SAE occurred (infection – not suspected to be related with ponatinib.

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Statistical methods

Not applicable.

Summary – Conclusions:

Only 2 patients were enrolled in the study, therefore the significance of the study results are severely limited. In both patients, a MRD response could be seen, no severe toxicities occurred. Further studies are needed to assess the efficacy, safety and tolerability of ponatinib in the setting of PH+ALL therapy.

Conclusions:

The GMALL-MOLACT2-PONA study has to be stopped prematurely. Only two patients were enrolled within July 2021 and April 2022. The medication was tolerated; the recruitment rate was proved to be too low to achieve the final objectives of the study in a reasonable time.
The reasons are manifold.
In the foreground are
1) protracted contract negotiations that have severely delayed the setup and
2) the very rare entity (molecular failure within Ph+ ALL) and
3) the limited number of centres combined with a low probability of patients being referred for the study.
We consider that the research question of the study, the initiation of therapy with the the well-tolerated TKI imatinib and intensification with ponatinib in the event of molecular persistence after consolidation 1 is not answered by any other study conducted worldwide.
It is planned to pursue this issue further, e.g. via the GMALL therapy recommendations and the GMALL registry.

**I hereby confirm that the data in the results report are collected properly and are correct.**

Date of report: 07.06.2023

Print name: PFEIFFER

Signature: