2. SYNOPSIS

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: Glivec and Tasigna		
Name of Active Ingredient: Imatinib and Nilotinib		

Title of Study: Imatinib continuation versus Nilotinib 300 mg twice daily in patients with chronic myeloid leukemia (CML) in chronic phase and major molecular response (MMR) without molecular response ≥ 4.5 log (MR4.5) receiving Imatinib at a dose of 400 to 800 mg daily. An open-label, randomised multicenter phase 3b study to determine the confirmed rate of molecular response ≥ 4 log (MR4) at two years

Protocol no. CAMN107ADE18T and EudraCT no. 2013-000077-68

Investigators: Coordinating Investigator was Prof. Dr. Nikolas von Bubnoff. The list of principal investigators of participated centres is provided in Appendix 16.1.4.

Study centres: A total of 18 centres participated in this study in Germany and 6 centres enrolled patients.

Publication (reference):

none

Study period (years):	Phase of development:
First patient in: 02 Apr 2014	Phase IIIb
Last patient out: 01 Aug 2018	

Objectives:

Primary Objective:

Goal of the study is to investigate whether in patients with CML in chronic phase and confirmed MMR without MR4.5 receiving Imatinib (400 to 800 mg daily) a switch to Nilotinib (300 mg twice daily) results in a higher proportion of patients with confirmed MR4 at two years of study treatment when compared with patients who continue receiving Imatinib (400 to 800 mg daily).

The secondary objectives are

- To determine the cumulative incidence of confirmed MR^4 after two years of study treatment
- To determine the cumulative incidence of MR^4 and $MR^{4.5}$ after one and two years of study treatment
- To determine the proportion of patients with MR^4 and $MR^{4.5}$ lasting for at least one year
- To determine the proportion of patients with MR^4 and $MR^{4.5}$ lasting for at least two years
- To determine the kinetics of BCR-ABL transcript levels over time
- To determine the proportion of patients with confirmed MR^4 two years after cross-over from Imatinib to Nilotinib in patients failing the primary endpoint in the Imatinib arm.
- To determine whether baseline clinical data are informative with respect to achievement of confirmed MR^4
- To investigate the predictive value of a previously developed mathematical model of CML treatment with respect to the patient-specific probability of reaching confirmed MR^4 under continuous Imatinib
- To collect data to establish a mathematical model regarding the prediction accuracy of the molecular relapse probability after treatment discontinuation

Trial Hypotheses:

In this trial, we seek to determine the proportion of patients with confirmed MR4 after two years of continuous administration of Imatinib versus Nilotinib in CP CML patients who have been treated

with Imatinib for at least 18 months and who have achieved MMR, but not MR4.5. Patients randomised in the Imatinib arm who do not achieve confirmed MR4 two years after randomisation will be offered a cross-over to Nilotinib. For these patients, the follow-up will be extended by two additional years. The subsequently projected DECLINEplus trial will examine investigational treatment discontinuation in patients previously treated within the DECLINE trial. The inclusion criteria for DECLINEplus will be established according to results of ongoing clinical trials investigating experimental treatment discontinuation in CML.

Methodology:

This phase IIIb trial was an open-label, randomised, multicenter trial conducted in 18 investigational sites.

Number of patients (planned and analysed):

Planned:	132
Screened:	28
Enrolled/Randomized/analysed:	16/14/14

Diagnosis and main criteria for inclusion:

Patients with chronic myeloid leukemia (CML) in chronic phase.

Main criteria for inclusion:

1. Signed written informed consent
2. Male or female patients aged ≥18 years (without upper limit of age)
3. ECOG performance status of 0 to 2
4. CML in chronic phase, with chronic phase defined as blasts < 15% in blood and/or bone marrow and peripheral blood basophils < 20% and platelets ≥ 100 G/L
5. Pretreatment with Imatinib with a treatment duration of at least 18 months at a dosage of 400 to 800 mg daily
6. Major molecular response (MMR) without molecular response ≥ 4.5 log ($MR^{4.5}$), i.e. BCR-ABL>0.0032% and ≤0.1% IS confirmed by central laboratory at screening will be required for randomisation
7. Patients must have a serum Creatinine of ≤ 1.5 x ULN, SGOT ≤ 1.5 x ULN, total bilirubin ≤ 1.5 x ULN (except known M. Gilbert), and Lipase ≤ 1.5 x ULN
8. Women of child-bearing potential

Main criteria for exclusion:

1. Any previous treatment for CML other than Hydroxyurea, Imatinib or Interferon alpha
2. Evidence of features of accelerated or blast phase at any time
3. Previous loss of hematologic or cytogenetic response
4. Concomitant medications known to be strong inducers or inhibitors of P450 Isoenzyme CYP3A4 (see Cytochrome P450 Drug Interaction under www.drug-interaction.com)
5. Finding of a secondary BCR-ABL resistance mutation at any time
6. History of intolerance to Imatinib that required treatment interruption longer than 4 weeks (cumulative) or dose reductions to less than 400 mg daily for longer than 4 weeks (cumulative) during the last 12 months before informed consent
7. Patients who had prior allogeneic, syngeneic, or autologous bone marrow transplant or stem cell transplant

8. Patients unwilling to or unable to comply with the planned therapeutic intervention or to comply with the study treatment visits including blood sample collection within the protocol
9. History of pancreatitis, chronic inflammatory diseases or autoimmune diseases
10. Patients who underwent solid organ transplantation
11. Impaired cardiac function
12. Known HIV and/or hepatitis B or C infection
13. Other malignancies within the past 3 years before informed consent except for adequately treated carcinoma of the cervix and basal or squamous cell carcinoma of the skin
14. Women who are pregnant or breast feeding
15. Male/female patients of reproductive potential unwilling to practice a highly effective method of birth control
16. History of noncompliance to medical regimens
17. Treatment with another investigational product during this study or during the last 30 days prior to informed consent

Investigational Product, dose and mode of administration, batch number:

Proprietary name:	**Glivec**
Name of substance:	Imatinib
Manufacturer:	Novartis Pharma GmbH
Dosage Form:	film-coated tablets
Route of Administration:	oral
Strength:	400mg
Dose:	1x 400mg to 800mg daily
Batch No.:	Imatinib was used according to label and will therefore not be supplied to the study centres.
Proprietary name:	**Tasigna**
Name of substance:	Nilotinib
Manufacturer:	Novartis Pharma GmbH
Dosage Form:	film-coated tablets
Route of Administration:	oral
Strength:	150mg
Dose:	2x 300mg daily
Batch No.:	S0058 (Exp. Date: 01.2019) S0028 (Exp. Date: 04.2018) S0045 (Exp. Date: 09.2016) S0017B (Exp. Date: 01.2016)

Duration of Treatment:

After enrollment, study treatment will be administered over a period of two years (primary endpoint: confirmed MR4 at two years) and for patients who achieve confirmed MR4 within two years extended for two additional years from the time point of confirmed MR4. Patients in arm A (Imatinib) who could not achieve MR4 within two years after randomisation will switch treatment from Imatinib 400 to 800 mg daily to Nilotinib 300 mg twice daily (cross-over). If these patients achieve MR4

within 2 years after treatment switch, treatment will be continued for additional 2 years as long as MR is stable. Thus, treatment duration will be at least 27 months (MR4 at baseline and conformation at 3 months after randomisation) and not longer than 72 months (MR4 at 48 months after randomisation for the cross-over patients). All patients will be followed with centrally performed peripheral blood qRT-PCR in 3 months intervals.

Criteria for evaluation:

Efficacy:

The primary endpoint of the study is proportion of patients with confirmed MR4 at two years of study treatment in both treatment arms. Confirmed MR4 at two years is defined as either BCR-ABL ≤ 0.01% IS at 21 and 24 months or BCR-ABL ≤ 0.01% IS at 24 months and confirmation within six weeks.

Secondary endpoints for the evaluation of efficacy were the following:

- Cumulative incidence of confirmed MR^4 after two years of study treatment. Confirmed MR^4 is defined as BCR-ABL ≤ 0.01% IS at two consecutive time points
- Cumulative incidence of MR^4 and $MR^{4.5}$ after one and two years of study treatment
- Proportion of patients with MR^4 lasting for at least one year, defined as BCR-ABL ≤ 0.01% IS in at least three out of four consecutive 3-monthly measurements with first and last measurement showing MR^4
- Proportion of patients with MR^4 lasting for at least two years, defined as BCR-ABL ≤ 0.01% IS in at least six out of eight consecutive 3-monthly measurements with first and last measurement showing MR^4
- Proportion of patients with $MR^{4.5}$ lasting for at least one year, defined as BCR-ABL ≤ 0.0032% IS in at least three out of four consecutive 3-monthly measurements with first and last measurement showing $MR^{4,5}$
- Proportion of patients with $MR^{4.5}$ lasting for at least two years, defined as BCR-ABL ≤ 0.0032% IS in at least six out of eight consecutive 3-monthly measurements with first and last measurement showing $MR^{4,5}$
- Kinetics of BCR-ABL transcript levels over time
- Proportion of patients with confirmed MR4 two years after cross-over from Imatinib to Nilotinib in patients failing the primary endpoint in the Imatinib arm (patients failing to achieve confirmed MR4 two years after randomisation and continued treatment with Imatinib)
- Analysis of baseline clinical data which are informative with respect to achievement of confirmed MR4
- Application of a previously developed mathematical model to predict the patient-specific probability of reaching confirmed MR4 under continuous Imatinib
- To establish a mathematical model to predict molecular relapse probability after treatment discontinuation (to be validated in DECLINEplus)
- Analysis of changes in the health-related Quality of Life (EORTC-QLQ-C30, EORTC-QLQ-CML24)
- Study drug compliance (patient diary)

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Safety:

Safety assessments will consist of evaluating adverse events (AEs) and serious adverse events (SAEs).

Statistical methods:

Sample size calculation:

We are planning a parallel group study comparing patients receiving experimental treatment (Nilotinib 300 mg twice daily) and receiving standard treatment (Imatinib 400 mg daily). Both groups are of equal size. Prior data indicate that the MR^4 rate under standard is 0.25 (Hughes, Lipton et al. 2011). If the true MR^4 rate for the experimental treatment is 0.5, a total of 66 per group will be needed to reject the null hypothesis that the MR^4 rates for experimental and control subjects are equal on a significance level of 5% with power of 80%. To this end a continuity-corrected two-sided chi-squared test is used to evaluate the null hypothesis "the MR^4 rates for experimental and control subjects are equal at two years after randomisation". The sample size calculation was performed with "Add plan V 4.0.3".

Sample size computations were also performed when considering the sample drawn from two subpopulations: Half of the sample is composed of patients with MMR at inclusion without MR4. The other half is composed of patients with MR4 at baseline. We supposed the MR4 rates of the first subpopulation to remain the same as above and considered different scenarios for the second subpopulation. Plausible values of MR^4 rates for this subpopulation could be 0.5 for the standard treatment and 0.8 for the experimental treatment. This would lead to a sample size of 58 patients per group. However given the uncertainty of these assumptions the sample size of 66 patients will be kept.

Definition of populations included in the analyses:

Patients with CML in first chronic phase and confirmed MMR without $MR^{4.5}$ receiving Imatinib at the standard dose of 400 to 800 mg daily for at least 18 months.

Changes in the Conduct of the Study:

V1.2, 11.06.2014 (non-substantial):

Extension of the recruitment period from 12 to 18 months; Clarification of the reference point e.g. in the inclusion and exclusion criteria and recording of adverse events; Correction of inconsistencies within the protocol (Synopsis vs. protocol); Correction of spelling mistakes

V2.1, 12.11.2014:

Adaption of Inclusion criteria No. 5 and No. 6 and Exclusion criteria No. 3

V3.0, 11.09.2015:

Previous restriction of imatinib dose of 400mg lifted; Simplification of inclusion criteria for molecular response (IC #6). Reformulation of the primary endpoint (and study title) because not all patients converted from MMR to MR4; Addition of a secondary endpoint. We have discussed the changes of the protocol with the responsible statistician also regarding the number of cases. No changes were required. Stratum "achievement of MMR within 12 months" changed to "MMR but not MR4 at inclusion" versus "patients with MR4 but not MR4.5 at inclusion". Correction of inconsistencies within the protocol. Extension of study duration. Another important change was the start of the accompanying research project for optimized patient information.

V4.0, 18.07.2016

Modification of the assessments in the flow chart based on a Healthcare Professional letter (Addition of HBV assessments)

SUMMARY - CONCLUSIONS:

EFFICACY RESULTS:

Primary endpoint:

The primary endpoint is the proportion of patients with confirmed MR4 at two years of study treatment in both treatment arms.

- In the Imatinib arm, 7 patients reached the 24 month visit. Two (28.6 %) had confirmed MR4 at two years.
- In the Nilotinib arm, 1 patient reached the 24 month visit. One (100 %) had confirmed MR4 at two years.

Secondary endpoints:

- Cumulative incidence of confirmed MR4 after two years of study treatment.

As the latest event occur 371 days after randomization, it is impossible to assess with reliability the cumulative incidence of confirmed MR4 after two years of treatment. At this time no patient is still at risk.

- Cumulative incidence of MR4 after one and two years of study treatment

As the latest event occur 261 days after randomization, it is impossible to assess with reliability the cumulative incidence of MR4 after one year or two years of treatment. At this time, no patient is at risk.

- Cumulative incidence of MR4.5 after one and two years of study treatment

Only one patient is at risk after one year of study treatment. No patient is at risk after 2 years of study treatment. Assessing the cumulative incidence of MR4.5 after one and two years of study treatment is not possible.

- Proportion of patients with MR4 lasting for at least one year

In 89% (8/9) and in 50% (1/2) of patients with at least four available BCL-ABL consecutive assessments in imatinib and nilotinib group respectively, the MR4 lasted for at least one year.

- Proportion of patients with MR4 lasting for at least two years

In 43% (3/7) and in 100% (1/1) of patients with at least eight available BCL-ABL consecutive assessments in imatinib and nilotinib group respectively, the MR4 lasted for at least two years.

- Proportion of patients with MR4.5 lasting for at least one year

In 33% (3/9) and in 50% (1/2) of patients with at least four available BCL-ABL consecutive assessments in imatinib and nilotinib group respectively, the MR4.5 lasted for at least one year.

- Proportion of patients with MR4.5 lasting for at least two years

In none of patients having had at least eight BCR-ABL consecutive assessments (7 in imatinib and 1 in nilotinib group) the MR4.5 lasted for at least two years.

- Kinetics of BCR-ABL transcript levels over time

Individual kinetics of BCR-ABL transcript levels over time are provided for each patient in Appendix.

- Proportion of patients with confirmed MR4 two years after cross-over from Imatinib to Nilotinib in patients failing the primary endpoint in the Imatinib arm (patients failing to

achieve confirmed MR4 two years after randomisation and continued treatment with Imatinib)

There are 3 patients failing the primary endpoint in the Imatinib arm who switched from Imatinib to Nilotinib. However none of them has a 2 year follow-up once they started the Nilotinib treatment.

- Analysis of baseline clinical data which are informative with respect to achievement of confirmed MR4

Not performed due to low number of recruited patients

- Application of a previously developed mathematical model to predict the patient-specific probability of reaching confirmed MR4 under continuous Imatinib

Not performed due to low number of recruited patients

- To establish a mathematical model to predict molecular relapse probability after treatment discontinuation (to be validated in DECLINEplus)

Not performed due to low number of recruited patients

- Analysis of changes in the health-related Quality of Life (EORTC-QLQ-C30, EORTC-QLQ-CML24)

Analysis of available data could not be performed due to low number of recruited patients.

- Study drug compliance (patient diary)

Noncompliance was documented in 8 patients and was in mainly due to intake error done by the patient or AEs. Intake errors lasted only one day except for one patient who took a half of nilotinib dose during 63 days.

SAFETY RESULTS:

The most frequently reported AEs (MedDRA PT level) in imatinib group were nausea and nasopharyngitis, followed by diarrhea, gastrooesophageal reflux disease, headache and vomiting. The most frequently reported AEs in nilotinib group were rash, headache, constipation and nausea.

The most often reported AEs judged by investigators to be related to imatinib were nausea and diarrhea. The most frequently reported AEs related to nilotinib were constipation, headache and rash.

There were 2 SAEs in 2 patients reported during the whole study. Both occurred in imatinib group and both were judged by the investigators as being not related to the IMP: in one patient an epileptic seizure occurred 566 days after randomisation and in another one a basal cell carcinoma was diagnosed on day 535 after randomisation; both SAEs resolved.

No deaths, no other significant AEs occurred during the study.

CONCLUSIONS:

The study was stopped due to insufficient patient recruitment, since only a minority of the patients available at the participating centers met the criteria required for inclusion, i.e. BCR-ABL ratio between BCR-ABL >0.0032% and ≤ 0.1% (IS) receiving Imatinib. Of note, study centers reported that some patients meeting the inclusion criteria refused participation since they did not want to modify their well-established therapy.

During trial conduct, no safety issues which could have an impact on the overall benefit-risk assessment of the study drug or the study program were observed. Upon premature termination of the trial, all patients were appointed to the end of study visit. Further therapy was discussed with

all patients and treating physicians to be performed according to standards of care (i.e. ELN and DGHO/Onkopedia) and marketing authorisation requirements. For patients receiving nilotinib, according to SmPC of nilotinib, discontinuation of treatment may be considered in eligible Philadelphia chromosome positive (Ph+) CML patients in chronic phase who have been treated with nilotinib for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy.

Efficacy and QoL endpoints were calculated as per protocol in both arms. However, due to low patient numbers, resulting data do not allow comparative analyses between the two arms.

List of sites participated in the trial:

The study was initiated in 18 study centers in Germany. Patients were enrolled from 6 active centers.12 centers did not enroll patients.

Site
Universitätsklinikum Freiburg, Medizinische Klinik I, Hämatologie/Onkologie Hugstetter Str. 55, 79106 Freiburg
Technische Universiät München Klinikum rechts der Isar, III. Medizinische Klinik und Poliklinik, Ismaninger Str. 22, 81675 München
Universitätsklinikum Ulm, Zentrum Innere Medizin Albert-Einstein-Allee 23, 89081 Ulm
Universitätsklinikum Hamburg-Eppendorf II. Medizinische Klinik und Poliklinik Onkologisches Zentrum, Martinistr. 52, 20246 Hamburg
Hämato-Onkologische, Überörtliche Gemeinschaftspraxis Pasing und Fürstenfeldbruck Bäckerstrasse 4, 81241 München
Internistische Schwerpunktpraxis Erlangen, oncosearch Nägelsbachstraße 49c, 91052 Erlangen
Universitätsklinikum Jena, Klinik für Innere Medizin III Erlanger Allee 101, 07747 Jena
Klinikum Mannheim GmbH Universitätsklinikum, III. Medizinische Klinik Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
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Gemeinschaftspraxis BAG Freiberg-Richter, Jacobasch, Illmer, Wolf Arnoldstr. 18, 01307 Dresden

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Gemeinschaftspraxis Hämatologie/Onkologie Hasselbachplatz 2, 39104 Magdeburg
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Onkologische Praxis Oldenburg Dres. Otremba, Reschke, Zirpel, Kühn Grüne Straße 11, 26121 Oldenburg
Praxis für Hämatologie/Onkologie Dres. Rudolph, Sengpiel, von Verschuer Henricistraße 40, 45136 Essen
Praxis Dr. Hauch Neuwerkstraße 51, 99084 Erfurt
Praxis Dr. Bruder / Dr. Heinrich / Prof. Bangerter Halderstraße 29, 86150 Augsburg

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23 Nov 2020