# Study Title:

**A phase I/II, randomized, open-label, multi-centre study of BIBF 1120 + reirradiation (R-RT) versus reirradiation in the treatment of patients with first or second progression of glioblastoma**

***Name(s) of the investigational medicinal product:*** BIBF 1120

***Indication:*** Glioblastoma multiforme

***Clinical trial phase:*** I/II

**Short Title** / **Acronym:** NOA-12: BIBF1120 and R-RT in glioblastoma / NONK-3/NOA-12

**Eudra-CT Number: 2011-000921-61**

**Study start date – study end date**
First patient in: 21-Sept-2012 –Last patient follow up phone call: 22-Nov-2017

# Clinical Study Report

## Sponsor of the Clinical Trial:

Ruprecht-Karls-University Heidelberg
Medical Faculty, represented by: Prof. Dr. Wolfgang Wick
Im Neuenheimer Feld 672
D-69120 Heidelberg, Germany

## National Coordinating Investigator:

Prof. Dr. med. Wolfgang Wick
University Clinic Heidelberg
Department of Neurology
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**Version 1.0** / **Date: 25.09.2018**

# Synopsis

**Sponsor:**
Ruprecht-Karls-University Heidelberg
Medical Faculty, represented by: Prof. Dr. Wolfgang Wick
Im Neuenheimer Feld 672
D-69120 Heidelberg, Germany
Phone:
E-Mail:

**Investigational medicinal product:** Vargatef®, Ofev®

**Drug substance:** Nintedanib (BIBF 1120 ES)

**Registration:** ClinicalTrials.gov registration number: NCT01666600

**Study title:**

NONK-3

A phase I/II, randomized, open-label, multi-centre study of BIBF 1120 + reirradiation (R-RT) versus reirradiation in the treatment of patients with first or second progression of glioblastoma.

The synopsis refers to the latest protocol version (V1.5).

During study progress there has been three amendments with associated study protocol changes to the observational plan:

- Amendment 1 (version 1.3.1 from 04.05.2012): Changes requested by the IEC were implemented and discrepancies in the study protocol in the pharmacokinetics part were revised and corrected. One inclusion criterion was more precisely described. Protocol amendment 1 was approved on 24.05.2012 by the responsible IEC and on 23.05.2012 by the higher federal authorities.
- Amendment 2 (version 1.4 from 04.09.2012): The dose of the radiotherapy administered as standard of care was increased to 18 x 2,4 Gy. The second amendment was approved on 05.03.2013 by the responsible IEC and on 13.02.2013 by the higher federal authorities.
- Amendment 3 (version 1.5 from 25.10.2013): Upon amendment 3, maintenance therapy after radiotherapy with 2 x 200 mg BIBF 1120 per day was decided. The third amendment was approved on 30.12.2013 by the responsible IEC and by the higher federal authorities.
- Amendment 4: The approval of an updated Letter of authorization (LoA) to refer to the Investigational Medicinal Product Dossier (IMPD) in the context of the study 1199.93 was requested. The fourth amendmend was approved on 09.11.2015 by the higher federal authorities.

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**Study sites:**
**Phase I:** 1 site planned, 1 site active (Universitätsklinikum Heidelberg, Neuroonkologie)
**Phase II:** 15-20 sites planned; 10 sites active (Universitätsklinikum Heidelberg, Neuroonkologie; Universitätsklinikum Knappschaftskrankenhaus Bochum, Neurologie; Universitätsklinikum Münster, Klinik und Poliklinik für Neurologie; Universitätsklinikum Tübingen, Universitätsklinik für Radioonkologie; Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Neurologie; Klinikum der Universität München, Strahlentherapie und Radioonkologie; Universitätsklinikum Leipzig, Klinik für Strahlentherapie und Radioonkologie; Universitätsklinikum Köln, Klinik und Poliklinik für Neurologie; Universitätsklinikum Essen, Innere Klinik (Tumorforschung); Klinikum der J.-W. Goethe-Universität Frankfurt a.M., Neuroonkologie)

**Publication:** not applicable

| | |
|---|---|
| **First patient in:** 21-Sep-2012<br>**Last patient follow up phone call:** 22-Nov-2017 | **Phase: I/II** |

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**Drug substance:** Nintedanib (BIBF 1120 ES)

**Study objective(s):**

**Phase I**

- Maximal tolerated dose of BIBF 1120 in combination with reirradiation
- Safety and tolerability of BIBF 1120 in conjunction with radiotherapy
- Pharmacokinetic parameters of BIBF 1120 and its clinically relevant metabolites (if feasible) in plasma and cerebrospinal fluid

**Phase II**

**Primary Objective**

- Progression-free survival after 6 months (PFS6).

**Secondary Objectives**

- Safety and tolerability of BIBF 1120
- Progression-free survival
- Objective response rates (OR)
- Duration of response (DR) in responders
- Recurrence pattern analysis
- Overall survival
- Quality of life as determined by EOR-RTC QLQ-C15 PAL and the EOR-RTC brain module QLQ-BN 20.
- Cognitive function determined by mini-mental status examination (MMSE)

**Trial design:**

**Phase I:** One-armed, unicenter study for 6 patients
**Phase II:** Randomised, open-label, multi-centre study

**Methods:**

Upon obtaining signed informed consent, screening evaluations were performed to confirm eligibility and to obtain baseline safety data.

During the phase I study, three cohorts were defined with increasing dosage of BIBF 1120 along with reirradiation (R-RT) in order to assess the maximum tolerated dose (MTD). In a fourth cohort, the MTD was given to three further patients. During phase II, patients were randomized 2:1 in arm A (BIBF 1120 therapy + R-RT) or arm B (R-RT only) and treated as specified below.

During the treatment period visits, blood samples of patients in phase I were analyzed for steady-state pharmacokinetics (PK). During weekly visits, the dosing of BIBF 1120 was assessed for patients in treatment arm A. Furthermore, vital signs, Karnofsky Performance Index (KPI) and safety lab results were documented. Beyond, all patients had to attend 6-weekly visits and an end-of-study visit where MRI-assessment, physical/neurological examination, vital signs, safety lab, KPI, and Quality of life (QoL) were documented. Abdominal ultrasound, 12-lead electrocardiogram (ECG;once) and urine analysis were performed 12-weekly and during an end-of-study visit. All adverse events (AEs) and serious AEs (SAEs) were followed until trial completion, defined as the end of trial visit. Adverse events of special interest as defined in the study protocol had to be reported in the same timeline as SAEs.

During the follow-up period, physical/neurological examination, vital signs, KPI, concomitant medication and AEs were assessed after 28 days; blood sampling and urine analysis were additionally conducted after 90 days. In case of potential adverse events or abnormal relevant safety parameters persisting after trial completion, further visits might have been scheduled until resolution. Survival information was collected from all patients after the end of study until death of the patient by phone and was documented in the eCRF.

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**Number of patients (planned and analyzed)**

**Phase I:** 12 patients planned, 12 patients analyzed

**Phase II:** 28 to 83 patients planned, 42 analyzed

According to the step 1 analysis (described below) that was conducted on 12.01.2017 after inclusion of 19 patients into the treatment arm A, less than three patients had a PFS of 6 months. Therefore, recruitment was stopped on 08.02.2017 and the study was terminated as designated in the study protocol. Patients upon BIBF 1120 therapy could have been treated onwards if they wished.

**Diagnosis and key inclusion criteria:**

Male and female patients with a recurrence / progression of glioblastoma either not being eligible for tumor resection or having macroscopic residual tumor after resection of the recurrence AND

- Diagnosis of glioblastoma must be proven histologically and progress must be documented by MRI. MRI images must not be older than 2 weeks before first dosing/start of R-RT
- Not more than two prior therapy regimens including one or two resections, one or two chemotherapies (one temozolomide-containing concomitant to radiotherapy) and one radiotherapy (R-RT) for the brain tumor
- Previous irradiation therapy of the primary tumor with a maximal dose of 60 Gy; at least 8 months since the end of preirradiation
- Candidate for reirradiation with recurrent tumor visible on MRIT1 (Gd) and with the largest diameter measuring 1 cm to 5 cm
- Informed consent
- Age ≥ 18 years, smoking or non-smoking, of any ethnic origin
- KPI ≥ 60%
- Neutrophile counts > 1500/µl / Platelet counts > 80.000/µl / Haemoglobin > 10 g/dl / Serum creatinine < 1.5-fold upper normal range / Bilirubin, AST or ALT < 2,5-fold upper normal range unless attributed to anticonvulsants / Alkaline phosphatase < 2,5- fold upper normal range
- Adequate contraception
- If on steroids, stable or decreasing treatment with steroids within 5 days before treatment start

**Investigational medicinal product (dosage, method of administration, batch number)**
BIBF 1120 ES, the applied BIBF 1120 ES batch numbers can be found in the appendix of the synopsis.
*Phase Ia (parallel to reirradiation (18 x 2 Gy)*

First cohort: 2 x 100 mg BIBF1120 per day p.o. in the first 3 patients

Second cohort: 2 x 150 mg BIBF1120 per day p.o. for patients 4-6 if no DLT occured in cohort 1

Third cohort: 2 x 200 mg BIBF1120 per day p.o. for patients 7-9 if no DLT occured in cohort 2

If at least one DLT occurred the next lower dose level should be used to treat another 3 patients.

- *Phase Ib*

2 x MTD BIBF 1120 was given parallel to 18 x 2.4 Gy reirradiation for 3 further patients.

If no DLT occured this dose was carried forward to phase II.

After the combination therapy maintenance treatment was administered with 2x200 mg BIBF1120 per day unless dose modifications were necessary.

- *Phase II*

Arm A: 2 x MTD BIBF1120 per day p.o. parallel to reirradiation.

After the combination therapy maintenance treatment was performed with 2x200 mg BIBF1120 per day unless dose modifications were necessary due to DLT.

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**Duration of treatment:**
According to the study protocol, the treatment consisted of R-RT at 5/days a week and R-RT + BIBF 1120 continuously in 18 cycles. Thereafter, BIBF 1120 could be administered as maintenance therapy until the onset of progression, death or unacceptable toxicities and according to the patients' wish.
The maximum treatment time during phase I with R-RT and BIBF 1120 was 30 days, with a mean of 25.5 days. Patients in phase II received R-RT and BIBF 1120 for a maximum of 29 days. During maintenance therapy, the maximum duration of treatment was 355 days within the first administration cycle, with a mean of 51.6 days.

**Reference therapy**

Reference treatment was radiotherapy as standard of care and was carried out on an out-patient or in-patient basis at the discretion of the Investigator.

**First reference drug:** n.a.
**Second reference drug:** n.a.

**Unblinding:** n.a.

**Efficacy/clinical pharmacology evaluation:**
During the phase I part, pharmacokinetic parameters of BIBF 1120 and its clinically relevant metabolites (if feasible) in plasma and cerebrospinal fluid were assessed and analyzed. Plasma exposure to BIBF 1120 was in the range of variability determined in a meta-analysis examining data from various cancer indications. Low CSF levels were only measureable in dose group 2. It remains to be investigated whether radiotherapy or the glioblastoma itself disintegrated the blood brain barrier resulting in measureable CSF concentrations.
The primary objective of the phase II study was the PFS after 6 months. After 6 months, the PFS6 rate was 34.8% (95%-CI: 17.6-52.7) vs. 26.3% (95%-CI: 6.4-52-2) of patients in arm A (BIBF 1120 + R-RT) vs. B (R-RT onlyThe median PFS of patients in arm A was 4 months (95%-CI: 2.4-6.3) vs. 3.4 months (95%-CI: 1.9-6.0) for patients allocated to arm B. The difference between the treatment arms was not significant (p=0.1528). Only 2 responders, defined as patients with a confirmed PFS time of at least 6 months, were identified in arm A. Of those 2 responders, 1 had a best response (CR+PR), resulting in an ORR of 0% (95%-CI: not calculable). Median overall survival (OS) for patients in arm A and B was 10.9 months (95%-CI 8.4-19) and 12.7 months (95%-CI: 8.5-20.8), respectively. The difference between the treatment arms was not significant as indicated by a p-value of 0.8666. As the interesting response rate of 30% (i.e. at least 3 patients with a PFS of 6 months) was not reached, the study was terminated as defined in the study protocol.
Generally, most domains of QoL declined during the course of the study, with a global health status and physical functioning deterioration and increase of symptom scores such as fatigue, pain, appetite loss at study end, the latter being especially apparent in control arm B. There was no clear influence of the treatment arms on the functional scores. Several QLQ-BN 20 items were negatively affected within the course of the study, with no clear differentiated impact on the single treatment arms. Especially future uncertainty, motor dysfunction, communication deficit, hair loss, weakness of legs were more obviously negatively changed in patients of arm B compared to arm A. With regard to the MMSE test, the patient scores were within the normal range suggestive of a normal cognitive function.

**Safety evaluation:**

**Phase I**

Overall, the phase I part of this trial showed that BIBF 1120 can be safely administerd in combination with radiotherapy in patients with first or second progression of glioblastoma. One dose-limiting toxicity occurred during the concurrent treatment of BIBF 1120 with radiotherapy, therefore, the MTD was set to 2x 150 mg daily.

A total of 182 treatment emergent adverse events (TEAEs) occurred in 12 patients. The most common TEAEs were "Lymphocyte count decreased" (10.4%), "Alanine aminotransferase increased" (7.1%), "Headache" (6%), "Gamma-glutamyltransferase increased" (5.5%), "Fatigue" (5%) and "Aspartate aminotransferase increased" (5%). Regarding the outcomes, 108 cases (59.3%) were recovered/resolved,

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2 (1.1%) were recovered with sequelae, 28 (15.4%) were not recovered/resolved, 2 (1.1%) were not recovered at death, 35 (19.2%) led to a change in toxicity/grade/sensitivity/seriousness, 6 (3.3%) were not recovered at study end and 1 (0.6%) outcome was unknown at study end. In the majority of cases (77.5%), the causality was not related to study medication. The dose was not changed upon 122 events (76%), whereas dose reduction was applied consequent to 8 events. No TEAE was the reason for the end of treatment. Concomitant medication to treat the TEAE was administered in 74 cases (40.7%).

**Phase II**

Of 42 patients enrolled in the phase II study, all patients experienced a total of 435 TEAEs (323 in arm A and 112 in arm B). The most common TEAEs in treatment arm A were “Diarrhea” (9%), “Nausea” (5.3%), “Alanine aminotransferase increased” (5.6%) and “Gamma-glutamyltransferase increased” (5.3%). In arm B, “Fatigue” (9.8%), “Alopecia” (8%), “Hyperglycemia (7.1%) and Seizure (7.1%) were most commonly documented. Of 323 documented TEAEs in arm A, 215 were considered as related to BIBF 1120 therapy in 20 of 27 patients allocated to arm A. Of all TEAEs that occurred in arm A, 188 (58.2%) were recovered/resolved and 84 (22.9%) were not recovered/resolved. 25 led to a change in toxicity/grade/severity or seriousness. Fatal TEAEs were reported for 5 patients, and 10 TEAEs were still ongoing at study end. Of 112 TEAEs documented in arm B, 56 (50%) were recovered/resolved and 28 (25%) were not recovered/resolved.14 (12.5%) led to a change in toxicity/grade/severity or seriousness, 4 (3.6%) had a fatal outcome and 2 (1.8%) were ongoing at end of study. The dose was reduced consequently to 16 events (5%) in arm A; 11 events in arm A and 1 event in arm B were the reason for end of treatment. Concomitant medications/therapies were applied due to 131 TEAEs in arm A and 43 TEAEs in arm B.

**Statistical methods:**
**Phase II**
The optimal two-stage design of Simon was applied to the BIBF1120 + R-RT treatment arm assuming a non-interesting 6-months PFS rate of $p_0$ = 15%, a 6-months PFS target rate of interest of $p_1$ = 30%, first-type error probability $\alpha$ = 0.05 and a second-type error probability of $\beta$ = 0.20. This design required 19 patients in the first step and 36 patients in the potential second step (55 patient overall). A control group of patients treated with R-RT alone in half the size of the investigational arm were included by random allocation of patients in 2:1 ratio in favor of the investigational arm. For the primary analysis, the decision criteria of the two stage Simon design were applied to test the hypotheses on the 6-months PFS rate in the BIBF1120 + R-RT treatment arm. As the target response rate of 30% had not been reached, the study was terminated as defined in the study protocol.
In explorative analyses the Kaplan-Meier estimate of the PFS function were calculated within both treatment groups. The 6-month PFS rates, the median PFS and the corresponding 95%-confidence intervals were derived from the Kaplan-Meier estimates.

**Summary of results:**

**Efficacy:**
According to the planned interim step I analysis, analysis the efficacy of BIBF 1120 combined with R-RT was unsatisfactory.
**Tolerability:**
Administration of BIBF 1120 showed good tolerability and no unexpected safety issues occurred during the study.
**Conclusion(s):**
After analysis of the first 19 patients with recurrent glioblastoma treated with BIBF 110 and R-RT during this study, an unsatisfactory efficacy (PFS6 rate below 15%) became aware. Therefore the further recruitment was stopped and the study was terminated according to the study protocol.

**Date of report:** 25.09.2018

**List of Signatures of the *LKP* [National Coordinating Investigator], the Sponsor, and the Biostatistician, and, if applicable, of Other Authors**

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By signing this Clinical Study Report, the undersigned authors agree with the contents of this Clinical Study Report. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable legislation.

**Sponsor (Representative)**

**National Coordinating Investigator**

**Biostatistician**

[redacted]

## List of Study Sites and Principal Invesigators

| Investigator | Principal Investigator | Street | Postal Code | City |
|---|---|---|---|---|
| Universitätsklinikum Heidelberg, Radiologische Universitätsklinik, Klinische Radiologie und Poliklinik | [redacted] | Im Neuenheimer Feld 400 | 69120 | Heidelberg |
| Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkologie | [redacted] | Schleusenweg 2-16 | 60528 | Frankfurt |
| Klinikum rechts der Isar, Neurochirurgische Klinik | [redacted] | Ismaninger Straße 22 | 81675 | München |
| Universitätsklinikum Essen, Innere Klinik und Poliklinik | [redacted] | Hufelandstraße 55 | 45122 | Essen |
| Universitätsklinikum Hamburg-Eppendorf, Klinik für Neurochirurgie | [redacted] | Martinistraße 52 | 20246 | Hamburg |
| Knappschaftskrankenhaus Bochum, Klinik für Neurologie | [redacted] | In der Schornau 23-25 | 44892 | Bochum |
| Universitätsklinik Köln, Zentrum für Neurochirurgie | [redacted] | Kerpener Straße 62 | 50937 | Köln |
| Universitätsklinikum Leipzig, Klinik und Poliklinik für Strahlentherapie und Radioonkologie | [redacted] | Stephanstr. 9a | 04103 | Leipzig |
| Westfälische Wilhelms-Universität Münster, Klinik für Neurologie | [redacted] | Albert-Schweitzer-Campus 1 | 48149 | Münster |
| Universitätsklinik Tübingen, Universitätsklinik für Radioonkologie | [redacted] | Hoppe-Seyler-Str. 3 | 72076 | Tübingen |

## List of BIBF1120 Batch numbers

E07655-001L02
E07655-019L01
E007655-0080L003
E007655-0174L001
E007655-0224L001
E07655-002L02
E007655-008L004
E007655-0174L002