

Afatinib as first-line treatment in patients with *EGFR*-mutated non-small cell lung cancer in routine clinical practice

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Abstract

Background: Lung cancer is a leading cause of cancer-related death in Germany and worldwide. Non-small cell lung cancer (NSCLC) comprises ~80% of lung cancer diagnoses; in White patients, around 10% of NSCLC cases are epidermal growth factor receptor mutation-positive (*EGFR*m+). Head-to-head clinical trials have demonstrated superior efficacy with second-/third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) versus first-generation EGFR TKIs in *EGFR*m+ NSCLC. Data from routine clinical practice are necessary to confirm that clinical trial findings are transferable to real-world populations.

Methods: In NCT02047903, a prospective non-interventional study in Germany, patients with *EGFR*m+ NSCLC received first-line afatinib until disease progression or intolerable adverse events. Key objectives were progression-free survival (PFS) rate at 12 months, objective response rate (ORR) and overall survival (OS). Safety/tolerability was also assessed.

Results: Of 152 patients, 106 (69.7%) were female, 20 (13.1%) patients had an uncommon *EGFR* mutation and 51 patients (33.6%) had brain metastases. A starting dose of <40 mg was received by 39 (25.7%) patients. Overall, the 12-month PFS rate was 50.2% while the median PFS was 12.2 months. The ORR was 74.6% and the median OS was 30.4 months. In patients with brain metastases and uncommon mutations, the median PFS was 10.5 and 10.7 months, and the ORR was 77.3% and 83.3%, respectively. Treatment effectiveness was similar in patients with a starting dose of <40 mg (median PFS: 16.4 months; ORR, 81.3%) and a starting dose of 40 mg (median PFS: 10.8 months; ORR, 72.1%). Adverse drug reactions were manageable and consistent with the known afatinib safety profile.

Conclusion: The results support clinical trial data for afatinib in routine clinical practice, including in patients generally excluded from clinical trials. Outcomes were positive in patients with uncommon *EGFR* mutations and in those with brain metastases. Treatment benefit was also seen in patients receiving a <40 mg afatinib starting dose, supporting patient-tailored dosing.

Keywords: afatinib, *EGFR* mutation, first-line, non-interventional study, non-small cell lung cancer

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Introduction

Lung cancer is a leading cause of cancer-related death in Germany and worldwide.^{1,2} In 2020, approximately 65,000 new cases of lung cancer

were diagnosed in Germany.² Approximately 80% of lung cancer diagnoses are non-small cell lung cancer (NSCLC).^{3,4} Epidemiological studies indicate that approximately 30–40% of Asian patients

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and approximately 10–20% of White patients with NSCLC have epidermal growth factor receptor mutation-positive (*EGFRm+*) tumours.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the first-line treatment choice for *EGFRm+* NSCLC.⁵ Five EGFR TKIs are currently indicated to treat patients with *EGFRm+* NSCLC in Europe: the first-generation reversible EGFR TKIs, gefitinib and erlotinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation irreversible EGFR TKI, osimertinib.^{6–10} In addition, combinations of bevacizumab or ramucirumab with erlotinib are approved as first-line treatments for *EGFRm+* NSCLC.^{11–13}

Head-to-head clinical trials have demonstrated that second- and third-generation EGFR TKIs confer superior outcomes to first-generation EGFR TKIs in patients with *EGFRm+* NSCLC;^{14–16} however, no prospective studies have compared the efficacy of second- and third-generation TKIs. Therefore, questions remain regarding which TKI is most appropriate in individual patients with respect to specific *EGFR* mutation type, disease characteristics, demographics and likely availability of subsequent targeted treatment options following disease progression.¹⁷

In the LUX-Lung clinical trial programme, first-line afatinib demonstrated significant improvement of progression-free survival (PFS) *versus* platinum-based chemotherapy,^{18–20} and gefitinib.¹⁴ Notably, in prespecified analyses of LUX-Lung 3 and 6, afatinib conferred significant overall survival (OS) benefit *versus* platinum-based doublet chemotherapy in patients with a deletion in exon 19 (Del19) mutation.^{16,21} In LUX-Lung 7, there was a trend towards improved OS *versus* gefitinib.²² In addition, in LUX-Lung 2, 3 and 6, afatinib demonstrated clinical benefit in patients with baseline brain metastases¹⁸ and with the uncommon mutations G719X, L861Q and S768I.²³ In Germany, afatinib is indicated for the treatment of NSCLC patients with tumours harbouring any activating *EGFR* mutation.⁸

While randomised controlled trials provide key information regarding the efficacy and safety of a drug, they do not fully identify the effectiveness of a drug in clinical practice; many patients encountered in everyday clinical practice often fail to meet the inclusion criteria required for trial

participation.²⁴ For example, a 2016 database search of patients with NSCLC in the US revealed that only ~7% (56/759 patients) were enrolled into a clinical trial.²⁵ Collection of real-world data is therefore important to assess whether clinical trial findings can be extrapolated to everyday clinical practice. Indeed, real-world studies are increasingly recognised by regulatory bodies as an important source of information to monitor the effectiveness and safety of approved drugs and to support market approval applications for agents in development.^{26,27} Studies in routine clinical practice also provide an opportunity to assess the activity of specific therapeutic sequences, such as afatinib followed by osimertinib.

GIDEON is a non-interventional study of patients with *EGFRm+* NSCLC who received first-line afatinib in routine clinical practice in Germany [ClinicalTrials.gov identifier: NCT02047903]. The study objectives were to prospectively investigate the effectiveness, safety and effect on quality of life (QoL) of afatinib with a primary endpoint of PFS rate at 12 months. The analysis included patient subgroups under-represented in clinical trials, such as those with uncommon mutations, brain metastases and patients who received a non-standard starting dose of afatinib. In addition, outcomes of patients who received sequential afatinib and osimertinib were assessed.

Methods

Patients

The GIDEON study enrolled adult patients who were EGFR TKI-naïve with locally advanced and/or metastatic *EGFRm+* NSCLC and received afatinib as a first-line therapy. Any activating *EGFR* mutation was permitted; *EGFR* mutation status was determined by local laboratories (Supplemental material A). Patients were excluded if they had: a contraindication for afatinib; participated in another clinical trial within the past 30 days; prior systemic chemotherapy (however, (neo-)adjuvant chemotherapy and (neo-)adjuvant radiotherapy were permitted); or undergone previous treatment with an EGFR TKI.

The trial was conducted in accordance with the principles of the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the Declaration of Helsinki. GIDEON was performed in compliance with §4.23 and §67.6 of the German Drug Law (*Arzneimittelgesetz*), and

with recommendation of the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*). The study was submitted to the ethics committee of the Technical University of Dresden (IORG0001076) on 2nd October 2013 and was accepted on 7 October 2013. All patients provided written consent for study participation. Close external monitoring was conducted *via* site visits, whereby the number of visits was dependent on patient recruitment and need of conductance; a total of 98 monitoring visits were performed.

Trial design

Enrolment was planned to start in April 2014 and to last for approximately 2 years. Patients were treated with afatinib according to their usual treatment routine as per local regulation until disease progression, death or intolerable adverse events (AEs), and were followed-up for 2 years. Each patient underwent a maximum observation period of 3 years from the date of study enrolment. All study visits and treatments followed routine clinical practice and treatment decisions were made independently of study participation by the attending physician.

Baseline patient characteristics, treatment details and AEs were recorded by the study investigators using electronic case report forms (eCRFs). The contract research organisation, Alcedis GmbH, was contracted for the development of the electronic data capture system, quality control, verification of the data collection, data analysis and data transfer to Boehringer Ingelheim Pharma GmbH & Co.KG. Statistical analyses were performed by Alcedis and Syneos Health.

Patient evaluation

The primary objective was the PFS rate at 12 months, as assessed by study investigators according to their routine clinical standards. PFS was calculated from the start of therapy until progression or death, whichever came first. The date progression was first observed was documented by the attending physician. Patients without documented progression and who were not known to have died were censored on the day following their last examination.

Secondary objectives included: objective response rate [ORR; complete response (CR) + partial response (PR), %]; disease control rate (DCR;

CR + PR + stable disease, %); and PFS (months), as defined previously. Responses are reported as documented by the treating physician. Responses were unconfirmed.

AEs were reported by the study investigators *via* the eCRF. AEs were defined as any deleterious, pathological or unintentional changes in anatomical, physiological or metabolic functions, as indicated by physical signs, symptoms and/or changes in laboratory values that occurred during the course of the study, whether or not related to a drug. This definition of AE included the worsening of pre-existing diseases or events, intervening diseases and drug interactions. Progression was not considered an AE. Treatment-emergent AEs (TEAEs), serious AEs and adverse drug reactions (ADRs) were also assessed. TEAEs were defined as all AEs occurring between the start of treatment and 30 days after permanent discontinuation of therapy (or at study completion). Serious AEs were defined as any AEs that: were acutely life threatening; required or prolonged hospitalisation; resulted in death, permanent or serious health worsening; resulted in malignant disease or congenital malformation to newborns; or were medically significant. ADRs were defined as those AEs causally related to the study drug by investigator assessment.

Other objectives included median OS, 1- and 2-year survival rates, and documentation of QoL and tumour-related symptoms. OS was calculated from start of therapy until the day following the reported date of death. Patients not known to have died were censored on the day following their last examination. Afatinib dose modifications were also documented. In order to record QoL and symptom control, patients were asked to fill out the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30²⁸ and QLQ-LC13²⁹ every 8 weeks (before or during each study visit), and at the end of treatment.

All consenting patients with ≥ 1 documented administration of afatinib were included in the treated set (TS) and were included in the safety analysis. All consenting patients with ≥ 1 documented administration of afatinib and whom did not violate any inclusion/exclusion criterion were included in per protocol set (PPS).

Statistical analyses

Sample size was determined based on the results of the pivotal LUX-Lung 3 study, which

demonstrated a 47% 12-month PFS rate in patients treated with afatinib. To confirm this rate with a margin of error of $\pm 8\%$, a total of 150 patients was deemed necessary. PFS rate at 12 months was calculated *via* Kaplan–Meier methodology; 95% confidence intervals (CIs) were calculated using Greenwood’s variance estimator.

Patient-reported QoL responses were transformed to a 0–100 scale and analysed in line with EORTC scoring algorithms.²⁸ A higher score represented a higher level of symptoms, and improvement or worsening were defined as a ≥ 10 point decrease or ≥ 10 point increase from baseline, respectively. In a previous study, for patients who indicated ‘little’, ‘moderate’ or ‘very much’ change, the mean change in scores was approximately 5–10, 10–20 and >20 , respectively.³⁰ A 10-point change may therefore represent a small/moderate change. Kaplan–Meier estimates of time to symptom worsening were calculated in order to assess symptom control.

Exploratory subgroup analyses, including those assessing outcomes according to *EGFR* mutation type, presence of brain metastases and afatinib starting dose were undertaken. All data are shown in a descriptive manner and testing for statistical significance within and between patient groups was not performed.

Results

Patients

Between 24 March 2014 and 30 December 2016, 161 patients were enrolled from 41 sites in Germany. Database lock was 14 March 2019. Nine patients were ineligible for treatment (Figure 1); therefore, 152 (94.4%) patients were included in the TS. Of these, six patients did not meet or violated inclusion/exclusion criteria, meaning 146 (96.1%) patients were included in the PPS.

Overall, 106 (69.7%) patients were female, median age was 67 years (range: 38–89) and 139 (91.4%) had lung adenocarcinoma (Table 1). Over half ($n=98$; 64.5%) of patients had tumours with an *EGFR* Del19 mutation and 34 (22.4%) had the L858R mutation. A total of 20 patients (13.2%) had uncommon exon 18–21 mutations and these are detailed in Supplemental Figure S1. At screening, most patients ($n=150$, 98.7%) had stage IV disease and 51 (33.6%) patients had

brain metastases. According to the Tumour, Node and Metastases classification,³¹ most patients were T4 ($n=39$, 25.7%) or T2a ($n=33$, 21.7%), N2 ($n=47$, 30.9%) or N3 ($n=44$, 28.9%), and M1b ($n=93$, 61.2%) or M1a ($n=57$, 37.5%). Prior therapy had been received by 28 (18.4%) patients in the TS, most frequently surgery ($n=20$, 13.2%), (neo-)adjuvant chemotherapy ($n=14$, 9.2%) and (neo-)adjuvant radiotherapy ($n=12$, 7.9%). Of the 51 patients with brain metastases, four and three patients received neo-adjuvant and adjuvant radiotherapy, respectively, prior to initiating afatinib. During afatinib treatment, osseous radiotherapy, whole-brain radiotherapy and stereotactic brain radiotherapy were documented for five (3.3%), four (2.6%) and three (2.0%) patients, respectively. Other radiotherapy (not further specified) was recorded for one (0.7%) patient.

At baseline, 65 (42.8%) patients had Eastern Cooperative Oncology Group performance status (ECOG PS) 1, and 73 (48.0%) had ECOG PS 0. Four (2.6%) patients had ECOG PS 2, three (2.0%) patients had ECOG PS 3 and seven (4.6%) patients were not assessed. A total of 64 (42.1%) patients were non-smokers, 47 (30.9%) were ex-smokers and 10 (6.6%) were current smokers.

Treatment exposure

In total, 152 patients received at least one dose of afatinib, with 39 (25.7%) patients receiving a starting dose of <40 mg (30 mg: $n=33$; 20 mg: $n=6$), and 113 (74.3%) patients receiving a starting dose of 40 mg. A starting dose of <40 mg was more common in patients aged ≥ 70 years than those aged <70 years ($n=25$, 37.9% and $n=14$, 16.3%, respectively) and in patients without brain metastases *versus* those with brain metastases ($n=29$, 28.7% and $n=10$, 19.6%, respectively). A total of 50 (32.9%) patients permanently discontinued afatinib treatment during the study for reasons other than disease progression or death. The reasons reported for these discontinuations were: AEs/serious AEs ($n=24$, 48.0%), patient wishes/withdrawal of informed consent ($n=16$, 32.0%), patient lost to follow-up ($n=4$, 8.0%) and other ($n=6$, 12.0%; Figure 1). At the time of data cut-off, five patients were still receiving afatinib treatment.

Median duration of therapy for the TS was 10.7 months (range: 0.4–48). Afatinib dose was modified in 94 (61.8%) patients, with 91 (59.9%)

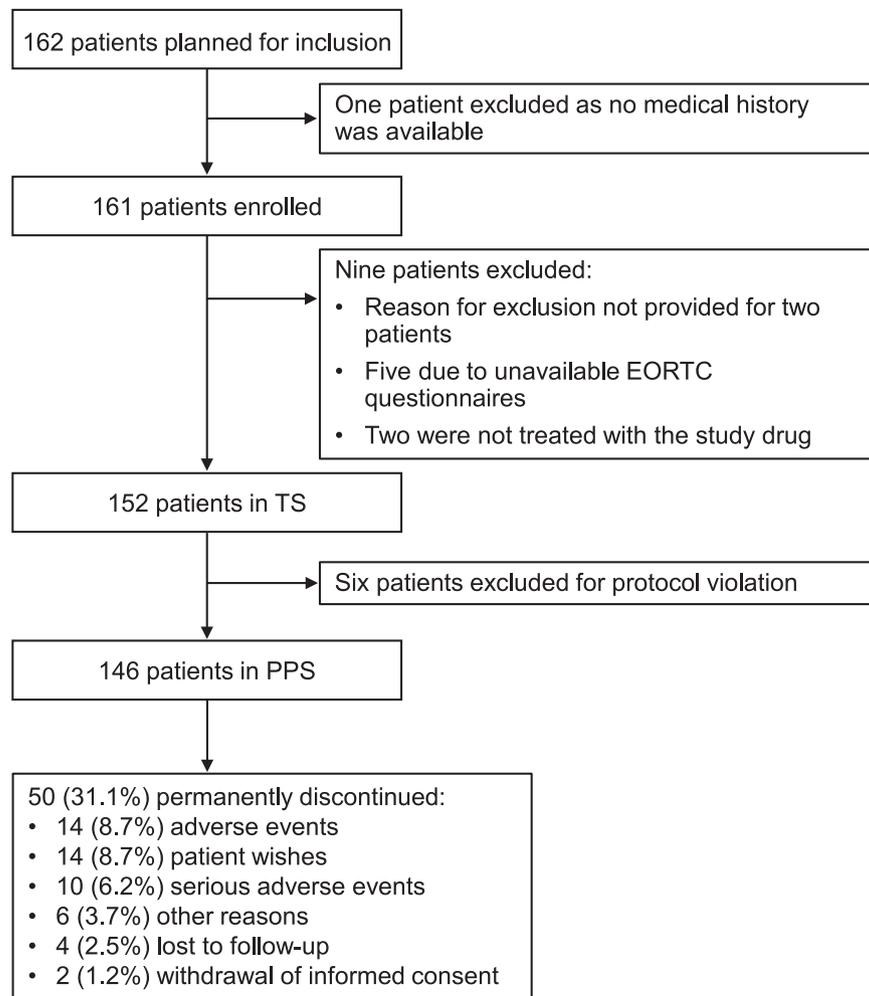


Figure 1. Study flow chart.

EORTC, European Organisation for Research and Treatment of Cancer; PPS, per-protocol set; TS, treated set.

receiving at least one dose reduction and 26 (17.1%) having at least one dose increase.

Effectiveness

The overall one-year PFS rate was 50.2% (Table 2). In patients harbouring Del19, L858R or uncommon exon 18–21 mutations, one-year PFS rate was 53.7%, 45.5% and 40.2%, respectively. The one-year PFS rate was 58.6% in patients receiving an afatinib starting dose of <40 mg and 47.2% in patients receiving 40 mg. In patients without brain metastases and those with brain metastasis, 55.9% and 39.4% achieved one-year PFS, respectively.

Median PFS was 12.2 months (95% CI: 10.5–16.0 months; Figure 2a); 118 (81.4%) patients

progressed or died (progressed: $n=102$, 70.3%; died: $n=16$, 11.0%), and 27 (18.6%) were censored. Of censored patients, 19 (11.8%) had a regular end to observation following 24 months of follow-up. Patients with Del19, L858R or uncommon exon 18–21 mutations had a median PFS of 13.1 months (95% CI: 10.6–17.3), 10.1 months (95% CI: 8.1–16.8) and 10.7 months (95% CI: 3.6–17.6; Figure 2b), respectively. PFS and best response for patients in the PPS with uncommon mutations are provided in Supplemental Figure S1. Median PFS was 14.9 months (95% CI: 10.6–18.4) in patients without brain metastases and 10.5 months (95% CI: 9.1–12.7; Figure 2c) in patients with brain metastases. For patients receiving a starting dose of <40 mg afatinib ($n=38$), median PFS was 16.4 months (95% CI: 10.3–20.1); for those with a starting dose of 40 mg

Table 1. Patient baseline disease and demographic characteristics.

| GIDEON (N= 152) | Patients (TS), n (%) |
|--------------------------------|----------------------|
| Sex | |
| Male | 46 (30.3) |
| Female | 106 (69.7) |
| Median age, years (range) | 67 (38–89) |
| Age category, years | |
| <65 | 61 (40.1) |
| ≥65–<70 | 25 (16.4) |
| ≥70–<75 | 24 (15.8) |
| ≥75 | 42 (27.6) |
| Tumour histology | |
| Adenocarcinoma | 139 (91.4) |
| Mixed tumour SCLC/NSCLC | 5 (3.3) |
| Squamous cell carcinoma | 1 (0.7) |
| Large cell carcinoma | 1 (0.7) |
| Mixed tumour: adeno-squamous | 1 (0.7) |
| Not determined | 5 (3.3) |
| Stage (UICC7) | |
| IV | 150 (98.7) |
| Other | 2 (1.3) |
| ECOG PS | |
| 0 | 73 (48.0) |
| 1 | 65 (42.8) |
| ≥2 | 7 (4.6) |
| Missing | 7 (4.6) |
| Brain metastases | |
| Yes | 51 (33.6) |
| No | 101 (66.4) |
| EGFR mutation status | |
| Del19 | 98 (64.5) |
| L858R | 34 (22.4) |
| Uncommon exon 18–21 mutations* | 20 (13.2) |

(continued)

Table 1. (continued)

| GIDEON (N= 152) | Patients (TS), n (%) |
|--|----------------------|
| Starting afatinib dose | |
| 40 mg | 113 (74.3) |
| <40 mg [†] | 39 (25.7) |
| Smoking status | |
| Smoker | 10 (6.6) |
| Ex-smoker | 47 (30.9) |
| Non-smoker | 64 (42.1) |
| Not specified | 31 (20.4) |
| *Not including T790M mutations. [†] n = 33 patients (21.7%) received a 30 mg starting dose; n = 6 (4.0%) received a 20 mg starting dose. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; TS, treated set; UICC7, Union for International Cancer Control 7th edition. | |

(n = 107), median PFS was 10.8 months (95% CI: 9.8–14.4; Figure 2d). In *post hoc* subgroup analysis of patients with brain metastases, median PFS was 9.9 months (95% CI: 1.7–11.1) for those receiving a starting dose of <40 mg afatinib (n = 10) and 10.7 months (95% CI: 8.3–16.7) for those receiving a starting dose of 40 mg afatinib (n = 38); see Supplemental Figure S2.

Tumour response data were available for 118 patients in the PPS; the overall ORR was 74.6% (n = 88) and the DCR was 91.5% (n = 108). ORR was 74.7% (n = 59), 70.4% (n = 19) and 83.3% (n = 10) in patients with tumours harbouring Del19, L858R and other exon 18–21 mutations, respectively. Best responses for patients with uncommon mutations are reported in Supplemental Figure S1. Of nine patients in the PPS with G719X mutations, response data were available for seven patients (ORR: 85.7%, n = 6; DCR: 85.7%, n = 6), including one patient with both G719A and L747V mutations (best response: PR). Patients with an afatinib starting dose of <40 mg and those receiving 40 mg had an ORR of 81.3% (n = 26) and 72.1% (n = 62), respectively. ORR was 77.3% (n = 34) in patients with brain metastasis and 73.0% (n = 54) in those with no brain metastases.

Median OS was 30.4 months (95% CI: 23.6–39.0 months; Figure 3a). During follow-up for

OS, 69 patients died (47.6%) and 76 patients were censored (52.4%). Reasons for censoring included: regular end of study ($n=46$, 31.7%); lost to follow-up ($n=14$, 9.7%); patient's wish ($n=8$, 5.5%); withdrawal of informed consent ($n=5$, 3.4%); missing ($n=2$, 1.4%); and early closure of study centre ($n=1$, 0.7%). Patients with Del19, L858R or other exon 18–21 mutations had a median OS of 33.9 months, 23.8 months and 23.6 months, respectively (Figure 3b).

The median OS was 32.6 months (95% CI: 24.3–46.1) in patients without brain metastases and 23.8 months [95% CI: 18.3–not reached (NR)] in those with brain metastases (Figure 3c). Patients who received an afatinib starting dose of <40 mg had a median OS of 32.2 months (95% CI: 20.2–NR) and those receiving 40 mg had a median OS of 27.4 months (95% CI: 23.1–46.1) (Figure 3d). Overall survival rates were 79.1% at 12 months and 57.7% at 24 months. In unplanned subgroup analyses, in patients with brain metastases receiving a starting dose of <40 mg afatinib ($n=10$), median OS was 20.2 months (95% CI: 6.8–NR); in patients receiving a starting dose of 40 mg

Table 2. Progression-free survival rate at 12 months.

| GIDEON (N=152) | Patients, n | PFS rate, % (95% CI) |
|------------------------------|-------------|----------------------|
| Total* | 145 | 50.24 (41.6–58.3) |
| <i>EGFR</i> mutation status | | |
| Del19 | 94 | 53.65 (42.7–63.4) |
| L858R | 34 | 45.54 (28.3–61.3) |
| Uncommon exon 18–21 mutation | 17 | 40.18 (16.6–62.9) |
| Brain metastases | | |
| Yes | 48 | 39.38 (25.4–53.0) |
| No | 97 | 55.91 (45.1–65.4) |
| Starting dose | | |
| 40 mg | 107 | 47.18 (37.1–56.6) |
| <40 mg | 38 | 58.63 (41.0–72.6) |

*Data were available for 145 out of 146 patients included in the PPS. One patient was not included as the entered date of the event (progressive disease or death) preceded the start date of therapy. CI, confidence interval; *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; PPS, per-protocol set.

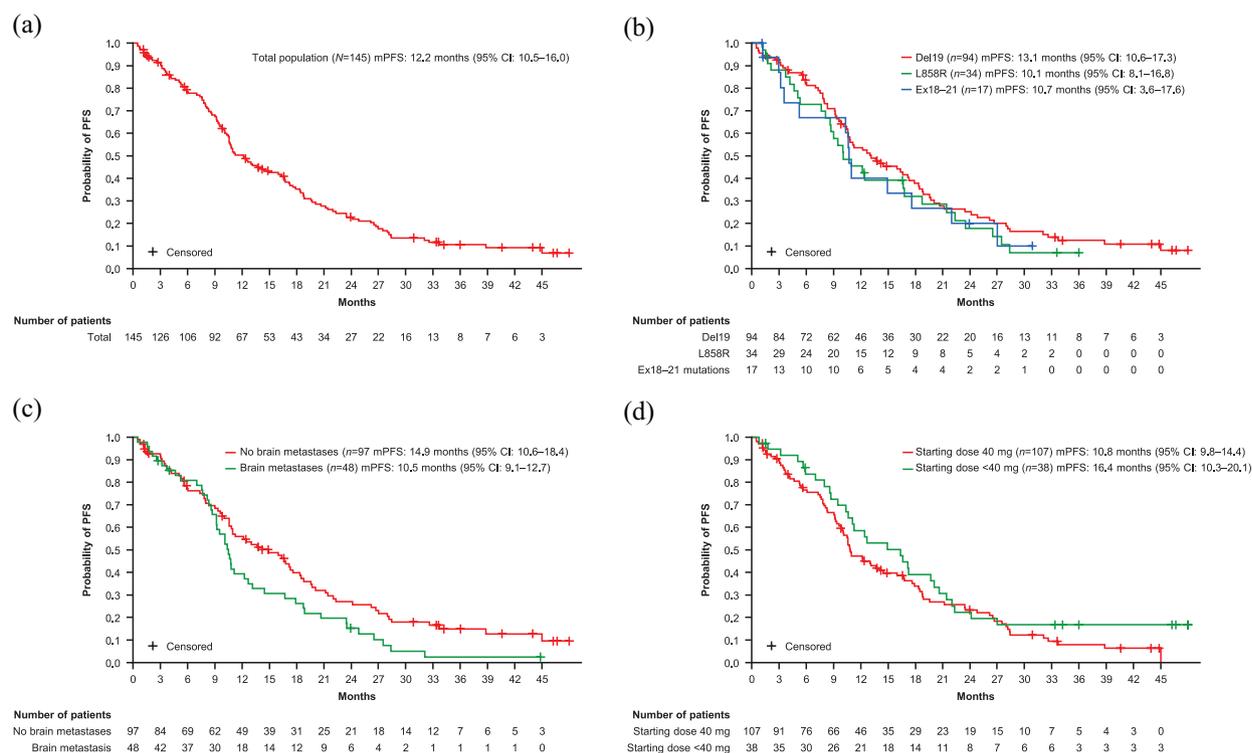


Figure 2. Progression-free survival in the PPS. (a) PFS in the total population. (b) PFS according to *EGFR* mutation type. Red: Del19, green: L858R, blue: uncommon exon 18–21 mutations. (c) PFS in patients without brain metastases (red) and with brain metastases (green). (d) PFS in patients with a starting dose of 40 mg afatinib (red) and <40 mg afatinib (green). CI, confidence intervals; Del19, exon 19 deletion; *EGFR*, epidermal growth factor receptor; Ex18–21, Exon 18–21; mPFS, median progression-free survival; PFS, progression-free survival; PPS, per-protocol set.

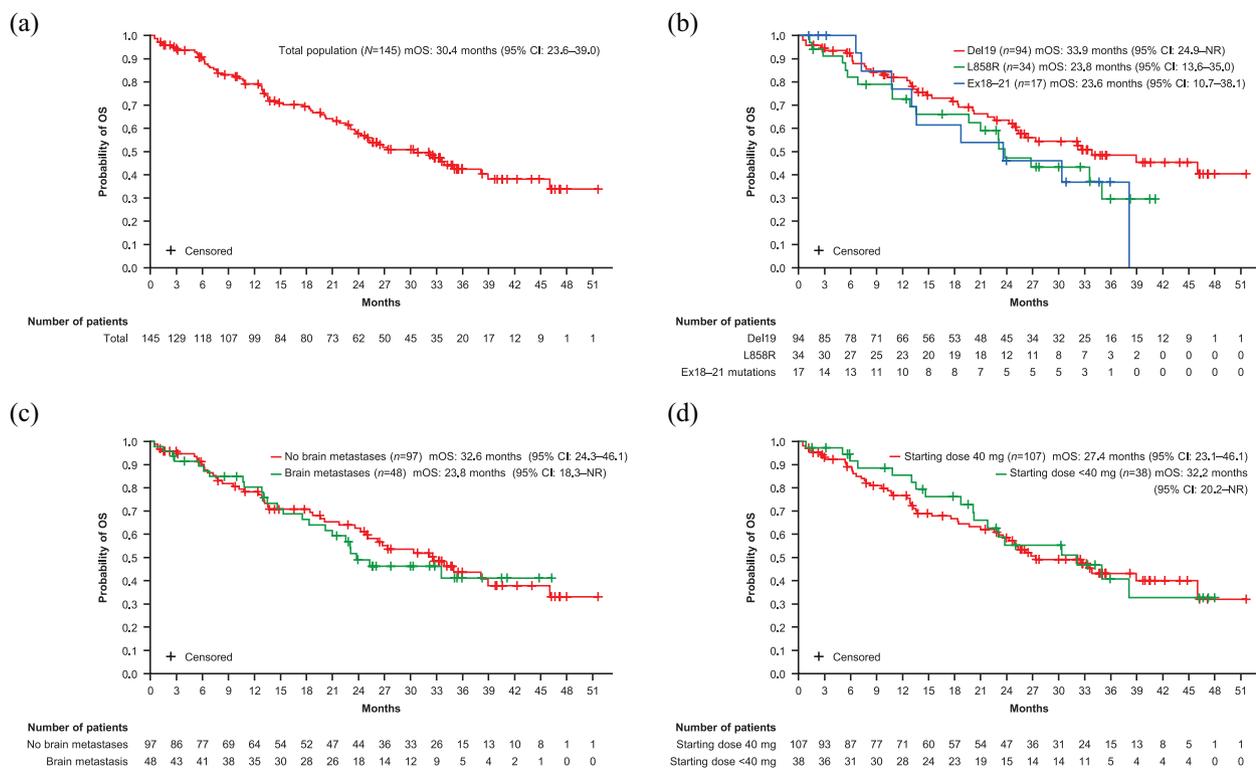


Figure 3. Overall survival in the PPS. (a) OS in the total population. (b) OS according to *EGFR* mutation type. Red: Del19, green: L858R, blue: uncommon exon 18–21 mutations. (c) OS in patients without brain metastases (red) and with brain metastases (green). (d) OS in patients with a starting dose of 40 mg afatinib (red) and <40 mg afatinib (green). CI, confidence intervals; Del19, exon 19 deletion; *EGFR*, epidermal growth factor receptor; Ex18–21, exon 18–21; mOS, median overall survival; NR, not reached; OS, overall survival; PPS, per-protocol set.

afatinib ($n=38$), median OS was 33.6 months (95% CI: 18.3–NR, Supplemental Figure S3).

The median time to worsening of cough ($n=119$), dyspnoea ($n=118$) and pain ($n=119$) was 33.9 months (95% CI: 17.9–NR), 22.2 months (95% CI: 13.7–NR) and 18.3 months (95% CI: 9.2–23.7), respectively (Supplemental Table S2). Of 35 patients who returned the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires, at both the start and end of therapy, the most commonly improved symptom was dyspnoea (improvement in 19 [54.3%] patients); a further four (11.4%) patients had stable dyspnoea. Of other recorded symptoms, cough ($n=30$, 85.7%), shortness of breath ($n=29$, 82.9%), pain in chest ($n=26$, 74.3%) and global health status ($n=25$, 71.4%) most frequently improved or remained stable (Supplemental Table S3). Of patients who received a starting dose of <40 mg ($n=12$), global health status improved in five (41.7%) patients, remained stable in three (25.0%) patients and worsened in four (33.3%) patients. Of patients who received a starting dose of 40 mg ($n=23$),

global health status improved in 11 (47.8%) patients, remained stable in six (26.1%) patients, and worsened in six (26.1%) patients.

Subsequent therapy

After first-line afatinib therapy, 30 patients (19.7%) received subsequent osimertinib. For two of these patients, little further detail was provided. Of the remaining 28 patients (18.4%), 19 patients received osimertinib in a second-line setting and nine received osimertinib in an at least third-line setting (Supplemental Figure S4). Of the 28 patients with detailed records, 20 (71.4%) had a Del19 mutation, seven (25.0%) had the L858R mutation and one (3.6%) patient had an exon 18 point mutation (G719C). The ORR for patients receiving osimertinib was 21.4% ($n=6$ with PR). The median time from start of afatinib therapy to progression on osimertinib was 32.2 months. Median 1- and 2-year survival rates following the start of afatinib treatment were 100% and 89.3%, respectively. Overall, 10 patients (35.7%) experienced progressive disease

as a best response, and 18 patients (64.3%) experienced progressive disease within follow-up.

Safety

In total, 150 (98.7%) patients experienced a TEAE and 146 patients (96.1%) experienced an ADR. The majority of ADRs were grade 2 or 3, and the majority of (any grade) ADRs were gastrointestinal disorders or skin and subcutaneous tissue disorders (Table 3). The most frequent ADRs were (any grade/grade 3): diarrhoea ($n=126$, 82.9%/ $n=21$, 13.8%), acneiform dermatitis ($n=57$, 37.5%/ $n=11$, 7.2%) and paronychia ($n=39$, 25.7%/ $n=1$, <1%). Sixty-five patients (42.8%) experienced a serious TEAE and 30 patients (19.7%) experienced a serious ADR. In total, 54 patients (35.5%) experienced a TEAE or serious TEAE that led to discontinuation of afatinib. The most common TEAEs leading to discontinuation were diarrhoea ($n=7$, 4.6%), vomiting ($n=4$, 2.6%), stomatitis ($n=3$, 2.0%), dyspnoea ($n=3$, 2.0%) and dermatitis acneiform ($n=3$, 2.0%), which were all Grade ≤ 3 . Overall, two (1.3%) patients died as a result of a drug-related TEAE; these were pneumonia and death (not otherwise specified).

A total of 91 (59.9%) patients received a dose reduction, 71 (78.0%) of whom received an afatinib starting dose of 40 mg. Overall, 111 (98.2%) patients with a 40 mg starting dose, and 39 (100%) patients with a <40 mg starting dose experienced a TEAE; 49 (43.4%) and 16 (41.0%) patients, respectively, experienced a serious TEAE. A higher proportion of patients discontinued the study drug due to TEAEs or serious TEAEs in the 40 mg starting dose group ($n=28$, 24.8% and $n=15$, 13.3%, respectively) than in the <40 mg group ($n=8$, 20.5% and $n=3$, 7.7%, respectively).

Discussion

In this non-interventional study, the effectiveness of afatinib was similar to that observed in previous randomised controlled trials.¹⁶ Afatinib was also effective in several patient subgroups generally excluded from clinical trials. For example, although patients with brain metastases are represented in some trials of EGFR TKIs (including the LUX-Lung studies¹⁸), they are frequently ineligible for trials in lung cancer.³² Overall, effectiveness was not negatively impacted by a reduced afatinib starting dose and this finding supports the importance of patient-tailored dose

adaptations to manage toxicities. The tolerability profile was consistent with that observed in the LUX-Lung programme and no unexpected safety signals were identified.¹⁶ Health-related QoL was generally maintained or improved with afatinib, with dyspnoea, cough and pain most frequently improving or remaining stable. Therefore, this study supports the use of afatinib as a first-line treatment option in patients with *EGFR*m+ NSCLC.

Patient demographics and clinical characteristics were generally comparable with those reported in previous real-world studies of afatinib in the treatment of *EGFR*m+ NSCLC,^{27,33–35} and the LUX-Lung trials (Supplemental Table S4).^{14,20,36} Of note, however, a higher proportion of patients in the GIDEON study had Del19 mutations (64%) than in some previous real-world studies (range: 58–80%)^{27,33–35} and the LUX-Lung trials (49–58%).^{14,36} This may reflect prescribing decisions based on the significant OS benefit observed with afatinib *versus* chemotherapy in patients with Del19 mutations in the LUX-Lung 3 and 6

Table 3. The 10 most frequently reported adverse drug reactions by MedDRA system organ class, preferred term, and grade in the TS.

| GIDEON (N=152) | Any grade*, n (%) | Grade 3, n (%) |
|--|-------------------|----------------|
| Gastrointestinal disorders | | |
| Diarrhoea | 126 (82.9) | 21 (13.8) |
| Stomatitis | 28 (18.4) | 5 (3.3) |
| Nausea | 19 (12.5) | 5 (3.3) |
| Vomiting | 13 (8.6) | 2 (1.3) |
| Skin and subcutaneous tissue disorders | | |
| Dermatitis acneiform | 57 (37.5) | 11 (7.2) |
| Rash maculo-popular | 27 (17.8) | 5 (3.3) |
| Alopecia | 17 (11.2) | 0 (0.0) |
| Pruritus | 16 (10.5) | 0 (0.0) |
| Infections and infestations | | |
| Paronychia | 39 (25.7) | 1 (0.7) |
| General disorders and administration site conditions | | |
| Fatigue | 13 (8.6) | 1 (0.7) |

*None of the 10 most common adverse events were Grade >3. TS, treated set.

studies.³⁷ German guidelines were adapted in 2015 to recommend afatinib for patients with Del19 soon after these findings were published,³⁸ which may have influenced prescribing decisions during the last years of the recruitment period for GIDEON. Other demographic differences between GIDEON and the LUX-Lung studies were a higher median age (67 years compared with 58–63 years), and higher proportions of patients with ECOG PS of 0 (48% compared with 20–40%) and brain metastases (34% compared with 12–16%).^{14,18} In addition, GIDEON recruited patients with ECOG PS ≥ 2 . These demographic differences reflect the clinical practice setting of the GIDEON study.

In this study, the 12-month PFS rate was 50.2% and median PFS was 12.2 months; these results are consistent with those observed in afatinib-treated patient groups in LUX-Lung 3, 6 and 7 (12-month PFS rate: 47–51%; median PFS: 11.0–11.1 months).¹⁶ The ORR (74.6%) was higher than previously observed in LUX-Lung 3, 6 and 7 studies (56–70%), and other observational studies.^{16,33,39} Notably, median OS (30.4 months) was longer than observed in LUX-Lung 3, 6 and 7 (22.1–28.2 months, Supplemental Table S4).^{16,23} This may have been driven by the higher proportion of patients with Del19 mutations in GIDEON.³⁷

In general, PFS was consistent across patient subgroups and comparable to LUX-Lung outcomes, irrespective of mutation type.^{19–21} Preclinical data indicate that afatinib displays inhibitory activity against a wide range of *EGFR* mutations;⁴⁰ furthermore, as the most extensively studied second-generation *EGFR* TKI, afatinib has proven clinical activity against uncommon *EGFR* mutations in clinical trials.^{41,42} One-year PFS rate and median OS appeared similar between patients with L858R or uncommon mutations, though in patients with Del19 mutations, PFS rate was slightly higher and there was a trend towards longer OS when compared with the other mutation subgroups. A similar trend was observed for OS in the LUX-Lung 3 and LUX-Lung 6 studies.³⁶ In GIDEON, ORR (74.6%) and disease control rate (91.5%) were consistent between patient groups regardless of *EGFR* mutation type, supporting previous observations.^{41,42}

In this study, some patients (25.7%) received a starting dose below the standard dose of 40 mg afatinib daily. Previous analyses suggest that response and PFS rates are similar between

patients who receive <40 mg or 40 mg afatinib starting doses.^{27,43} In the present study, the proportion of patients with disease control and the 2-year survival rate were comparable between the two dose groups. ORR, PFS and one-year PFS rate were numerically higher in the <40 mg dose group. These differences may reflect the small sample size of patients receiving a <40 mg dose ($n=38$) and/or selection bias. Alternatively, a <40 mg dosing schedule could have greater tolerability, thus enabling patients to remain on treatment for longer without negatively impacting effectiveness.⁴⁴ Indeed, we noted a higher discontinuation rate due to TEAEs in the 40 mg dosing group than in the <40 mg group. In GIDEON, reasons for receiving a starting dose of <40 mg were not collected; however, patients starting on 40 mg were more likely to have brain metastases or be below 70 years of age at baseline, relative to patients with a starting dose of <40 mg. These findings suggest that physicians may have striven to improve tolerability in vulnerable patients, but effectiveness may have been prioritised in patients with brain metastases.

The afatinib dose was modified in 61.8% of patients, with the most common modification being dose reduction (59.9%). Dose modification occurred more frequently than observed in previous studies.^{19,20,27,33,34} This may be due to the patient population in GIDEON, as patients in routine clinical practice are more likely to have existing comorbidities and therefore require frequent dose monitoring. Moreover, clinicians are likely to use a more adaptive approach when treating patients in routine clinical practice, compared with in the clinical trial setting, taking into account patient and treatment experience, and knowledge of clinical trial results. For example, the RealGiDo study suggested that dose adjustments of afatinib did not compromise effectiveness but did reduce the frequency and intensity of ADRs.²⁷ Likewise, analysis of LUX-Lung 3 and LUX-Lung 6 demonstrated that reducing the dose to <40 mg effectively mitigates treatment-related AEs without impacting on efficacy.⁴⁴ With this knowledge, clinicians may be more likely to tailor doses to be patient-specific.

In LUX-Lung 3 and LUX-Lung 6, ORRs in patients with brain metastases (70.0% and 75.0%, respectively) appeared similar to those observed in patients without brain metastases (60.2% and 67.0%).¹⁸ Similar ORRs were observed in GIDEON, for patients with and without brain

metastases (77.3% and 73.0%, respectively). In the same LUX-Lung studies, median PFS and OS were shorter in patients with brain metastases than without (PFS: LUX-Lung 3: 11.1 months *versus* 13.8 months, LUX-Lung 6: 8.2 months *versus* 11.1 months; OS: LUX-Lung 3: 19.8 months *versus* 33.6 months, LUX-Lung 6: 22.4 *versus* 23.6 months).¹⁸ Similarly, in GIDEON, median PFS and 12-month PFS rate were numerically lower in patients with metastatic brain disease (10.5 months and 39.4%) than in those without (14.9 months and 55.9%). Median OS also differed between patients with brain metastases and those without (23.8 months and 32.6 months, respectively), although for OS the Kaplan–Meier curves crossed at several time points, which was not observed for PFS. In GIDEON, 62.8% of patients with metastatic brain disease had at least one dose reduction, with 33.3% receiving a final dose of 40 mg afatinib. However, consistent with a previous study,⁴⁵ a <40 mg afatinib starting dose ($n = 10$) in patients with brain metastases appeared to have a negative effect on clinical outcomes compared with the approved 40 mg dose ($n = 34$). This could indicate that the approved dose is required to ensure pharmacologically active concentrations of afatinib in the central nervous system (CNS), but very low numbers of patients in this unplanned subgroup analysis limit generation of firm conclusions. Based on case studies, it may be that pulsatile dosing regimens could maximise CNS penetration of afatinib⁴⁶ but more data are required.

Health-related QoL was generally maintained or improved with afatinib treatment, with dyspnoea, cough and pain most frequently improving or remaining stable. Long-term changes in QoL measures were similar between patients receiving an afatinib starting dose of <40 mg compared with 40 mg. However, a low proportion of patients returned questionnaires at both the start and end of therapy, restricting possible analyses. The QoL findings for the overall GIDEON population are consistent with those from the LUX-Lung programme, in which afatinib generally improved lung-cancer-related symptoms for patients with *EGFR*m+ NSCLC, relative to chemotherapy.⁴⁷

In this study, 30 (19.7%) patients went on to receive osimertinib. While this is higher than observed in LUX-Lung 7 (10.3%), it may still underestimate the proportion of patients who could potentially access osimertinib treatment following disease progression on afatinib. The

low uptake of osimertinib likely reflects its restricted access in Germany during the GIDEON recruitment period. The small number of patients, prevalence-incidence bias and limited follow-up restricts interpretation of the effectiveness data in this subgroup. As osimertinib is now reimbursed in Germany and T790M testing becomes more routine, it is expected that the proportion of patients who receive osimertinib following progressive disease on afatinib would have increased since this study.⁴⁸ Nevertheless, as a prospective evaluation on this topic is still required, an investigator-initiated phase IV study was recently initiated: the on-going AFAMOSI trial [ClinicalTrials.gov identifier: NCT04413201] investigates the use of sequential afatinib/osimertinib *versus* first line osimertinib.⁴⁹

Overall, ADRs observed in GIDEON were in line with the known safety profile of afatinib, with diarrhoea and acneiform dermatitis being the most frequently reported. No new safety signals for afatinib were identified. Therefore, this study provides further evidence of the manageable tolerability profile of afatinib in a clinical setting. ADRs occurred in 96.1% of patients, which is comparable to LUX-Lung 3, 6 and 7 (95–99%), but slightly higher than previously reported in the observational RealGiDo study (94.3%).^{14,19,20,27} Similar to prior studies, most ADRs were of gastrointestinal or dermatological system organ classes and were either Grade 2 (42.1%) or Grade 3 (35.5%).^{14,19,20,50} The most common ADR experienced was diarrhoea (82.9%), which was lower than previously reported in LUX-Lung 3, 6 and 7 (88–95%) and other observational studies.^{14,19,20,33,39,50} However, because of the non-interventional nature of the study, it may be that this AE was underreported by patients. There were lower rates of discontinuation due to TEAEs, most notably, serious TEAEs, among patients who received a starting dose of <40 mg compared with 40 mg.

This study has a number of weaknesses and should be interpreted with caution; the data presented do not necessarily reflect clinical experience outside of Germany. In some cases, outcome and safety data were underreported as interventions followed routine clinical practice (in these cases, patients were excluded from analyses). Regarding PFS evaluation, this was reported by investigators and there was no central review of response, meaning that PFS results were not independently evaluated. In addition, information on mechanisms of

acquired resistance to afatinib was not collected. Consequently, it is unknown whether all patients who developed the T790M resistance mutation went on to receive osimertinib as second-line treatment. Finally, caution should be taken when comparing GIDEON to other real-world studies due to differences in patient demographics and disease characteristics. For example, more patients received a starting dose of 40 mg afatinib (73.8%) compared with in other observational studies (49.6–57.3%).^{27,45,51}

Conclusion

Results from this prospective non-interventional study confirm the robust clinical data from pivotal randomised controlled trials of afatinib in the routine clinical setting, including in patient subgroups normally underrepresented in clinical trials, such as those with uncommon *EGFR* mutations and brain metastases. Overall, treatment benefit was observed in patients receiving <40 mg afatinib, supporting the use of patient-tailored dosing, with the possible exception of patients with brain metastases. Safety and tolerability were well-managed and consistent with results from the LUX-Lung programme, with no new safety signals identified.

Author contributions

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

Conflict of interest statement

This study was supported by Boehringer Ingelheim. Wolfgang Brückl has received honoraria for consulting from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Pfizer, Roche Pharmaceuticals and Takeda. Joachim Ficker has received speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, GSK, MSD, Novartis, Pfizer, Roche, and Sanofi-Aventis. Frank Griesinger has served on advisory councils or committees for Boehringer Ingelheim, Roche, and AstraZeneca; and has received honoraria, consulting fees, and grants or funds, from Boehringer Ingelheim, Roche, and AstraZeneca. Stefan Krüger has received honoraria, and grants or funds, from Boehringer Ingelheim. Justyna Rawluk has served on advisory councils or committees for AstraZeneca, BMS, MSD, Boehringer Ingelheim, Roche, and Takeda;

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Ethics approval

The study was submitted to the ethics committee of the Technical University of Dresden (IORG0001076) on 2nd of October 2013 and was accepted on 7th of October 2013. All patients provided written consent for study participation. The trial was conducted in accordance with the principles of the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the Declaration of Helsinki, in compliance with §4.23 and §67.6 of the German Drug Law (Arzneimittelgesetz), and with recommendation of the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte).

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Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested *via* this link:

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All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use <https://trials.boehringer-ingelheim.com> to request access to study data.

Supplemental material

Supplemental material for this article is available online.

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