Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Title of trial:	A 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of BIBF 1120 administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid on Forced Vital Capacity decline during one year, in patients with Idiopathic Pulmonary Fibrosis, with optional active treatment extension until last patient out.
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial, 92 recruiting centres in 25 countries worldwide
Publication (reference):	None
Clinical phase:	II
Objectives:	To investigate the efficacy and safety of 4 dose strategies of BIBF 1120 treatment for 52 weeks compared to placebo in patients with IPF.
Methodology:	Double-blind, placebo controlled, randomised, parallel design trial comparing 4 active arms to placebo over a 52 week treatment period. Progressive inclusion of upper dosages arms after Data Monitoring Committee review.
No. of subjects:	
planned:	entered: 400, 80 in each arm
actual:	enrolled: 679
	Treatment placebo: entered: 87 treated: 85 analysed (for primary endpoint): 83
	Treatment 50 mg qd: entered: 87 treated: 86 analysed (for primary endpoint): 85
	Treatment 50 mg bid: entered: 86 treated: 86 analysed (for primary endpoint): 86
	Treatment 100 mg bid: entered: 86 treated: 86 analysed (for primary endpoint): 85
	Treatment 150 mg bid: entered: 86 treated: 85 analysed (for primary endpoint): 84

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Diagnosis and main criteria for inclusion:	Idiopathic Pulmonary Fibrosis according ATS/ERS criteria <5 years, forced vital capacity **(**FVC) ≥50% of predicted, diffusing capacity of the lung for carbon monoxide (DL_{CO}, corrected for Hb) 30-79% of predicted. ATS/ERS radiological (and if available, histopathological) criteria confirmation centrally prior to randomisation.
Test product:	BIBF 1120 soft gelatine capsules
dose:	50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid
mode of admin.:	Per os
Reference therapy:	Placebo soft gelatine capsule
dose:	NA
mode of admin.:	Per os
Duration of treatment:	Duration of treatment: 52 weeks At the end of the 52 weeks treatment period patients have been proposed to enter an optional active blinded treatment phase until the overall end of the study.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary: annual rate of decline in FVC Secondary: changes in FVC at 6 and 12 months, survival (transplant-free), saturation of peripheral oxygen (SpO_2) at rest, arterial oxygen partial pressure (PaO_2), arterial carbon dioxyde partial pressure ($PaCO_2$), calculated alveolo-arterial oxygen gradient ($P(A\text{-}a)O_2$), diffusing capacity of the lung for carbon monoxide (DL_{CO}), 6-Minute Walk Test (6-MWT), forced expiratory volume in 1 second (FEV_1)/FVC, St George's Respiratory Questionnaire (SGRQ), Medical Research Council (MRC) dyspnoea scale, total lung capacity (TLC), residual volume (RV), thoracic gas volume (TGV), vital capacity (VC), inspiratory capacity (IC), exacerbations, time to progression, blood biomarkers, and other exploratory criteria. Pharmacokinetics: plasma concentrations of BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide.
Safety:	Vital signs, physical examination Clinical laboratory tests (haematology, clinical chemistry and urinalysis) Reporting of adverse events Body weight 12 lead electrocardiogram

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Statistical methods: Mixed linear regression model for primary endpoint

Analysis of covariance for other continuous endpoints, Log Rank Test and Cox regression model for time to event, ordinal logistic regression model for categorical endpoints and Cochran-Mantel-Haenszel test for responders endpoints.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Disposition of patients

A total of 679 patients were screened for the study. Of these, 432 were randomized after screening visit examinations and review of HRCT (and surgical biopsy, if available). A total of 4 patients were randomized but did not receive treatment. The efficacy endpoints are reported on the randomized set.

Overall, 316 (73.8%) completed the 52-week follow up phase. Twenty-four (28.2%), 24 (27.9%), 18 (20.9%), 14 (16.3%) and 32 (37.6%) patients discontinued prior to end of the 52 weeks treatment period, in the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups, respectively. Premature discontinuations were mainly due to adverse events. The mean exposure to study drug was by 1.1 months shorter in the BIBF 150 mg bid dose group compared to placebo during period 1.

The following analyses on efficacy and safety focus on the 52 weeks treatment period where active dose can be compared to placebo. After completion of the 52 weeks, patients were allowed to continue on their dose, and placebo patients were switched to 50 mg qd. Results from data collected during this optional treatment period until cut off date (10 June 2010) did not reveal new relevant aspects with regard to safety or efficacy, and are reported in the main part of this trial report.

Demographic data

Age (mean 65.1 y), gender (74.8% male) and ethnicity (79.0% Caucasian, 21.0 % Asian) were similar across the 5 treatment groups except that the percentage of Asian patients in the 150 mg bid dose group (28.2%) was numerically higher than in placebo (23.5%) and the other dose groups (50 qd: 20.9%, 50 mg bid: 16.3%, 100 mg bid: 16.3%). Mean FVC(%pred) was 81.7, 80.4, 79.8, 85.5 and 79.1, in the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups (total mean: 81.3%).

Primary endpoint:

The **annual rate of decline in FVC** (spirometry), difference compared to placebo, was [L/year] (95% CI): 0.016 (−0.086, 0.118), −0.020 (−0.119, 0.080), 0.028 (−0.071, 0.128), and 0.131 (0.027, 0.235) in the 50 mg qd,

50 mg bid, 100 mg bid, and 150 mg bid dose groups. It reached nominal statistical significance for the 150 mg bid dose when compared to placebo (adjusted difference=0.131 L/year; hierarchical testing procedure specified in the TSAP as a sensitivity analysis: p=0.0136; closed testing procedure as per protocol: p=0.0639), showing a meaningful reduction of the annual rate of decline.

Secondary endpoints:

Forced Vital Capacity (FVC) [spirometry]

For the randomized set, the adjusted mean for absolute change from baseline in FVC% pred (%) at 52 weeks, compared to placebo, was 1.43 (−1.15, 4.01), 1.10 (−1.48, 3.68), 2.86 (0.26, 5.46), and 4.97 (2.37, 7.56), and reached statistical significance for the 100 mg bid (p=0.0314) and 150 mg bid (p=0.0002) dose groups (95% CI).

For the FAS50 (at least 3 months uninterrupted treatment with at least 50% of planned drug intake), the adjusted mean for absolute change from baseline in FVC% pred (%) at 52 weeks, compared to placebo, was 1.60 (−1.20, 4.40), 1.33 (−1.37, 4.02), 2.85 (0.14, 5.56), and 5.00 (2.26, 7.75), and reached statistical significance for the 100 mg bid (p=0.0396) and 150 mg bid (p=0.0004) dose groups (95% CI).

A decrease of FVC by >10% or 200 mL was observed in 37 (44%), 35 (41.2%), 41 (47.7%). 30 (35.3%) and 20 (23.8%) of patients, in placebo and the 4 dose groups (p=0.0041 for the 150 mg bid dose group).

Nominal statistical significance was reached for all subsequent sensitivity analyses performed on FVC over the 52-week treatment period, for the 150 mg bid group.

FEV_1/FVC, as expected, decreased with each active treatment dose versus placebo (adjusted mean for absolute change from baseline compared to placebo: -1.77 and p=0.0099 for BIBF 100 mg bid; -1.67 and p=0.0152 for BIBF 150 mg bid).

Subgroup of Asian patients (FVC)

In the small subgroup of Asian patients, FVC difference [L] to placebo (19 patients) was 0.108 (-0.064, 0.280) for the 50 mg qd group (17 patients), -0.022 (-0.202, 0.159) for the 50 mg bid group (14 patients), 0.079 (-0.100, 0.257) for 100 mg bid group (14 patients) and 0.030 (-0.135, 0.195) for the 150 mg bid group (23 patients) (95% CI). Results of additional subgroup analyses on Asian patients regarding secondary endpoints, suggested non-significant trends towards improved lung function (e.g. FVC%pred), however without clear dose-ordering.

Total Lung Capacity (TLC) and Thoracic Gas Volume (TGV) [body plethysmography]

For the randomized set, the adjusted mean for absolute change from baseline in Total Lung Capacity (L) at 52 weeks, compared to placebo, was 0.022 (−0.178, 0.222), 0.140 (−0.051, 0.332), 0.158 (−0.034, 0.351), and 0.358 (0.160, 0.556), and reached statistical significance for the 150 mg bid (p=0.0004) dose group (95% CI). Similar results were seen for TGV (Thoracic Gas Volume).

Exacerbations

The incidence of patients with at least one exacerbation, divided by the total number of years at risk, was 0.1567, 0.1303, 0.1246, 0.0746 and 0.0244 for placebo and the 4 dose groups and thus was significantly reduced in the highest dose group (p=0.0150 for the 150 mg bid dose group) even though the total number of exacerbations was low (12, 10, 10, 6 and 2 patients with at least one exacerbation in the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups, respectively.

Survival

Overall survival was not significantly different between groups, but a lower number of deaths was observed in 50 mg bid (3 deaths) and 100 mg bid (4 deaths) groups compared to the placebo, 50 mg qd and 150 mg bid groups (9, 11 and 7 deaths). For on-treatment survival (based on fatal AEs), a dose-dependent decrease in the number of deaths was observed: 12, 10, 4, 5 and 1 patient died in the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups, respectively. The number of respiratory deaths, after blinded (with regard to treatment group) adjudication by an independent external committee, was 8 (9.2%), 9 (10,3%), 3 (3.5%), 2 (2.3%) and 2 (2.3%), in the randomized set over 52 weeks (placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups, respectively).

Oxygen saturation (SpO_2)

For the randomized set, the adjusted mean for absolute change from baseline in SpO_2 (%) at 52 weeks, compared to placebo, was 0.44 (−0.51, 1.39), 0.33 (−0.61, 1.27), 1.36 (0.41, 2.31), and 1.12 (0.17, 2.07), and reached statistical significance for the 100 mg bid (p= 0.0051) and 150 mg bid (p=0.0211) dose groups (95% CI).

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A decrease of SpO_2 by >4% was observed in 9 (11.0%), 4 (4.9%), 7 (8.1%), 5 (6.0%) and 3 (3.6%) patients (p=0.0317 for the 150 mg bid dose group compared to placebo).

St George's Respiratory Questionnaire (SGRQ)

For the randomized set, the adjusted mean for absolute change from baseline in SGRQ total score at 52 weeks, compared to placebo, was −0.79 (−5.22, 3.64), −3.28 (−7.63, 1.07), −3.98 (−8.35, 0.39) and −6.12 (−10.57, −1.67), and reached statistical significance for the 150 mg bid (p=0.0071) dose group (95% CI). The clinically important improvements were confirmed by the responder analysis on 4 points change for the 100 mg bid and 150 mg bid dose groups (p=0.0069 and p=0.0341).
For the 150 mg bid dose groups, the SGRQ domains "symptoms" and "activities" were statistically significantly different from placebo (p=0.0028 and p=0.0043). The "impact" domain showed a dose-dependent trend towards improvement with increasing doses (-4.35 points change in the 150 mg bid dose group), but did not reach statistical significance.

Other endpoints

For the following endpoints, no difference between any of the dose groups and placebo was observed. However, for none of these endpoints a statistically significant observation favouring placebo was made.

- Diffusion capacity of the Lung for CO (DLCO)
- 6-Minute Walk Test (6MWT)
- Partial pressure of oxygen (PaO_2) and oxygen gradient ($P(A\text{-}a)O_2$)
- Medical Research Council Questionnaire (MRC)
- Composite Physiologic Index (CPI)
- Progression-free Survival (PFS)
- Time to oxygen first intermittent/continuous supplementation (total only 14 patients)

Plasma biomarker results

Plasma biomarker assessment (KL-6, IL-8, TGFβ1, TGFβ2, TGFβ3) indicated slightly less increase of KL-6 and IL-8, over the 52 weeks, in the 150 mg bid dose group, compared to placebo.

Doses reductions

Dose reductions were more common in the 150 mg bid dose group compared to all other dose groups and placebo. In the randomized set, 7, 5, 7, 11 and 20 patients had a dose reduction during period 1 in the placebo, 50 mg qd, 50 mg bid, 100 mg bid, and 150 mg bid groups, respectively. Five, 4, 1, 10, 18 patients respectively, stayed on the reduced dose until discontinuation or until continuation into optional treatment. Twenty-two patients completed the trial with the reduced dose: 2, 4, 0, 9 and 7 patients in the placebo and rising dose groups. Two, 1, 6, 1 and 2 patients, respectively, reduced their dose only intermittently and returned to their initial dose by the end of period 1.

Pharmacokinetic results

The plasma concentrations of BIBF 1120 and its metabolites BIBF 1202 and BIBF 1202-glucuronide of all doses administered and at all time points collected showed moderate to high variability under steady state conditions. Visual inspection of individual and geometric mean plasma concentration-time profiles of all three analytes showed that steady state conditions were stable and already attained at the first blood collection (29 days of treatment) after multiple administration of BIBF 1120. At day 365 of treatment, BIBF 1120 gMean pre-dose plasma concentrations of 1.07, 2.12, 4.20 and 6.66 ng/mL were attained after multiple oral administration of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid of BIBF 1120. BIBF 1202 gMean pre-dose concentrations were in a similar range, while BIBF 1202 glucuronide gMean pre-dose concentrations were 7-9-fold higher as compared to BIBF 1120. Based on visual inspection, gMean BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide pre-dose plasma concentrations at steady state increased dose proportional up to the highest dose 150 mg BIBF 1120 administered twice daily.
An exploratory analysis of intrinsic factors showed that slightly higher gMean BIBF 1120 pre-dose concentrations were observed in patients with:

- moderate renal impairment (1.4-fold),
- an age older than 75 years (1.5-fold) and
- Asian ethnicity (1.3-fold)

as compared to patients with normal renal function, an age under 65 years or Caucasian ethnicity, respectively.
Furthermore, patients with homozygote UGT1A1 polymorphisms known to

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result in deficient glucuronidation by this transferase, showed 2-fold lower BIBF 1202-glucuronide pre-dose concentrations as compared to patients with wildtype UGT1A1, while the BIBF 1202 pre-dose concentration in plasma was not influenced by UGT1A1 polymorphisms. However, the BIBF 1202 pre-dose plasma concentration does not necessarily have to reflect BIBF 1202 concentration levels within the liver tissue, where a reduced UGT1A1 enzyme activity might translate into higher BIBF 1202 concentration levels within the cell. A population PK analysis will be conducted using the PK data of this trial and will analyse the influence of certain intrinsic factors in more detail to assess the clinical meaningfulness of the results observed here.

Safety results: **Adverse events**

The total number of patients with at least one AE was similar across treatment groups [N (%)]: 77 (90.6), 78 (90.7), 78 (90.7), 82 (95.3) and 80 (94.1) for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid. The number of patients with investigator defined drug-related AE [N (%)] increased with dose: 25 (29.4), 24 (27.9), 30 (34.9), 41 (47.7) and 55 (64.7) for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid. The number of patients with serious AE [N (%)] was 26 (30.6), 26 (30.2), 23 (26.7), 18 (20.9), 23 (27.1), and the number of patients with severe AE [N (%)] was 20 (23.5), 21 (24.4), 17 (19.8), 19 (22.1), and 19 (22.4) for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid.

The number of patients with gastrointestinal disorders [N (%)] increased in the two higher doses: 27 (31.8), 33 (38.4), 31 (36.0), 49 (57.0) and 63 (74.1) for the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups. Among the reports of gastrointestinal disorders [N (%), placebo vs. 150 mg bid], "nausea" [8 (9.4) vs. 20 (23.5)], "vomiting" [4 (4.7) vs. 11 (12.9)], "diarrhoea" [13 (15.3) vs. 47 (55.3)] and "upper abdominal pain" ([3 (3.5) vs. 10 (11.8)] were most frequently reported. The number of patients with serious gastrointestinal AE [N (%)] was 0 (0.0), 2 (2.3), 2 (2.3), 1 (1.2) and 4 (4.7) for the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups. Withdrawals due to gastrointestinal AE (driven by reports of "diarrhoea") were reported [N (%)] for 2 (2.4), 2 (2.3), 2 (2.3), 2 (2.3) and 14 (16.5) patients (placebo; 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups). The number of patients [N (%)] with "fatigue" [7 (8.2), 4 (4.7), 5 (5.8), 8 (9.3), 9 (10.6)], "pyrexia" [2 (2.4), 1 (1.2), 2 (2.3), 5 (5.8), 5 (5.9)], "abnormal hepatic function" [0 (0.0), 0 (0.0), 0 (0.0), 0 (0.0), 3 (3.5)], "investigations" [11 (12.9),

6 (7.0), 7 (8.1), 12 (14.0), 24 (28.2); difference for the highest dose group driven by reports of transaminase increases], “decreased appetite” [0 (0.0), 3 (3.5), 4 (4.7), 4 (4.7), 13 (15.3)], “weight decrease” [0 (0.0), 4 (4.7), 1 (1.2), 3 (3.5), 8 (9.4)], “headache” [5 (5.9), 7 (8.1), 9 (10.5), 8 (9.3), 11 (12.9)], and “psychiatric disorders” [4 (4.7), 10 (11.6), 7 (8.1), 7 (8.1), 7 (8.2), difference for the highest dose group driven by repors of “insomnia” and “sleep disorder”] was higher in the higher dose groups (placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid).

A serious neoplasm was detected in 1 patient in the placebo group versus 2, 2, 5 and 2 patients in the 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups. One patient in the 150 mg bid dose experienced a myelodysplastic syndrome (MDS) after 52 weeks treatment and died from immune failure. The MDS retrospectively had been pre-existant at baseline but only subclinically (elevated MCV). An additional risk factor for the MDS was previous therapy with azathioprime.

For the user-defined AE categories (UDAEC), differences between treatment groups were observed in the categories “selected liver enzyme increases”, “selected hepatobiliary dysfunctions” and “selected gastrointestinal disorders events”. The frequency of patients with “selected liver enzyme increases” [N(%)] was 2 (2.4), 0 (0.0), 3 (3.5), 1 (1.2), 10 (11.8), the frequency of patients with “selected hepatobiliary dysfunctions” [N (%)] was 4 (4.7), 0 (0.0), 5 (5.8), 3 (3.5), 19 (22.4), and the frequency of patients with “selected gastrointestinal disorders events” was 30 (35.3), 37 (43.0), 33 (38.4), 53 (61.6), 64 (75.3) for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid. No differences were seen for the UDAEC “thromboembolic events”, “cardiac events”, “skin and phototoxicity”, “hypertension”, “infection” and “bleeding events”.

Laboratory

For AST, the mean difference from baseline to last value on treatment [U/L] was 1, 1, -2, 1 and 5 for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid.
For ALT, the mean difference from baseline to last value on treatment [U/L] was 1, 1, 1, 0 and 7 for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid.
For GGT, the mean difference from baseline to last value on treatment [U/L] was 3, 2, -18, 1 and 59 for placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid. Transitions of AST from normal to high (maximum post baseline) occurred in 4, 8, 7, 8 and 22 patients (placebo, 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid). Transitions of ALT from normal to high (maximum post baseline) occurred

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in 6, 8, 10, 10 and 30 patients (placebo, 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid). Transitions of GGT from normal to high (maximum post baseline) occurred in 10, 13, 9, 16 and 34 patients (placebo, 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid). In the 150 mg bid dose group, 3 patients had an increase of AST to > 3x ULN, 4 patients had an increase of ALT to > 3x ULN, and 16 patients and an increase of GGT to > 3x ULN. No clinically significant increases of bilirubin (> 34 µmol/L) were observed. For all other laboratory parameters, no relevant or consistent differences between dose groups were observed.
In the 150 mg bid dose group, maximum on-treatment values of ALT (p=0.0018) and AST (p=0.0004) were significantly correlated with pre-dose steady state plasma levels of BIBF 1120.
For all other laboratory parameters, no relevant or consistent differences between dose groups were observed.

Vital signs, physical examination, weight, ECG

No relevant differences were observed between dose groups except for a decrease of weight in the 150 mg bid dose group (mean change from baseline at visit 9: -2.2 kg; maximum decrease of weight: -15 kg).

Summary:

Summary of efficacy

More patients discontinued early in the 150 mg bid dose group (37.6%), but less in the 100 mg bid dose group (16.3%), compared to placebo (28.2%). For the primary analysis, the slope of decline of FVC was included also from discontinued patients, but only based on their on-treatment evaluations provided they had at least two on-treatment FVC evaluations performed; missing values were not otherwise replaced. For the secondary analyses of FVC change from baseline, LOCF (last-observation-carried forward) was used for replacement of missing values, which, in a disease characterised by functional decline, may positively bias a treatment group with more or earlier discontinuations.
The primary endpoint, annual rate of decline of FVC, reached statistical significance for the 150 mg bid dose when compared to placebo (adjusted difference=0.131 L; p=0.0136), using the hierarchical testing procedure pre-specified in the TSAP as a sensitivity analysis. With the analysis as per protocol using the closed testing method for multiplicity correction, the overall protection of alpha was not achieved (p=0.0639).

The primary endpoint was supported by all secondary FVC analyses as well as

plethysmographic measurements of lung function, for the 150 mg bid dose. While the primary endpoint analysis was not statistically significant for any of the lower doses, an effect in lower dose groups, and ordinal dose-ordering could be observed in some of the secondary analyses of lung function (FVC secondary analyses, body plethysmography [TLC, TGV], and in several of these, significant differences to placebo were observed also for the 100 mg bid dose group (FVC, SpO_2). The robust effects on lung function were further supported by dose-dependent reduction of IPF exacerbation rates (p=0.0150 for the 150 mg bid dose group), as well as improvements in the SGRQ, reaching statistical significance at the 150 mg bid dose (6.12 points over placebo for total score, p=0.0071; odds ratio compared to placebo for responder analysis on 4 points change=2.20, p=0.0341 (worst case analysis)). The point difference for SGRQ was high in some domains, reaching 9.6 points in the 150 mg bid dose group for the "symptoms" domain.

No effects could be observed on DLCO, PaO_2, $PaAO_2$ and 6-MWT. None of the secondary endpoints favoured placebo. Plasma biomarker assessment (KL-6, IL-8, TGFβ1, TGFβ2, TGFβ3) indicated slightly less increase of KL-6 and IL-8, over the 52 weeks, in the active BIBF 1120 groups, compared to placebo. No statistically significant difference was observed for the other biomarkers between these two groups.

Overall survival was not different between treatment groups, however, for the randomized set over 52 weeks, a lower number of deaths was observed in 50 mg bid (3 deaths) and 100 mg bid (4 deaths) groups compared to the placebo, 50 mg qd and 150 mg bid groups (9, 11 and 7 deaths). Respiratory mortality as well as fatal adverse events numerically declined with increasing dose.

The incidence of exacerbations remained lower for the higher dose treatment groups, compared to lower dose groups, also for the total treatment period including optional treatment phase.

No significant effect, for the primary endpoint, was seen in the subgroup of Asian patients (90/432 patients). There were some non-significant trends towards improved lung function (e.g. FVC%pred), as well as improved patient-reported outcome (SGRQ) in the Asian subgroup, however, without clear dose-ordering. The number of patients treated per dose for the full year, in the subgroup of Asian patients may have been too low to allow comprehensive data analysis.

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Summary of safety

The mean duration of exposure to study medication was 10.6 months for placebo and 9.9, 11.0, 10.9 and 9.5 for the dose groups 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid, respectively, for the first 52 weeks period (period 1). It was by 1.1 months shorter in the BIBF 150 mg bid dose group compared to placebo. The following conclusions focus on period 1, where the period of observation was the same for all dose groups, and placebo comparison was available.

More patients prematurely discontinued the trial drug in the BIBF 150 mg bid group than in the other groups (32 (37.6%) versus 24 (28.2%), 24 (27.9%), 18 (20.9%), 14 (16.3%).

Overall, the proportions of patients with at least one AE or one serious AE were comparable among groups.

The frequency of patients with gastrointestinal AE increased with dose. In the 150 mg bid dose group, 16.5% of patients withdrew due to GI AE, however, in only 4.7% of patients in this dose group did the gastrointestinal AE fulfil a seriousness criterion.

Liver enzyme elevations were observed with increased frequency in the dose groups BIBF 1120 100 mg bid and, especially, 150 mg bid. However, clinically abnormal transaminase (AST and ALT) values were observed in only 3 patients (3.6%, AST) and 4 patients (4.8%, ALT) in this dose group. Bilirubin increases of clinical significance (increase by > 34µmol/L) were neither observed during the 52 weeks treatment period nor during the total treatment phase.

Aside from increased reporting of liver enzyme increases, hepato-biliary disorders (due to liver enzyme increases) and gastrointestinal disorders with increasing BIBF 1120 dose, no imbalances were seen in the user-defined adverse event category review (thromboembolic, cardiac, skin and phototoxicity, hypertension, infection, haemorrhagic and bleeding events).

Respiratory AEs (as well as serious respiratory AEs) and infectious AEs were reported from fewer patients with increasing dose of BIBF 1120. However, it has to be taken into consideration that exposure in this dose group, over the 52 weeks treatments phase, was by approximately 1 month shorter than for the placebo group.

Mortality was not different between treatment groups, however, for the

Conclusions:

randomized set over 52 weeks, a lower number of deaths was observed in 50 mg bid (3 deaths) and 100 mg bid (4 deaths) groups compared to the placebo, 50 mg qd and 150 mg bid groups (9, 11 and 7 deaths). Respiratory mortality as well as fatal adverse events numerically declined with increasing dose.

The frequency of patients with an AE leading to discontinuation was higher in the 150 mg bid dose group compared to placebo and the other dose groups. The difference to placebo was small (4 patients / 4.7%). The increase of discontinuations in the high dose was explained by gastrointestinal AE. On the other side, the frequency of patients with respiratory AE leading to discontinuation was lower with BIBF 1120 treatments compared to placebo.

No relevant changes in safety profile emerge when information collected from the optional treatment phase is included into the safety assessment.

Summary pharmacokinetic

The plasma concentrations of BIBF 1120 and its metabolites BIBF 1202 and BIBF 1202- glucuronide of all doses administered and at all time points collected showed moderate to high variability. Steady state conditions were already attained at the first PK visit (29 days of treatment) and were stable over the entire treatment period. BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide pre-dose plasma concentrations at steady state increased dose proportional with increasing dose.

In summary, treatment with BIBF 1120 150 mg bid over 52 weeks significantly reduced the decline of lung function in patients with IPF following the hierarchical testing procedure (sensitivity analysis). The signal was robust and was confirmed across different measures of lung function (FVC, TLC, TGV, SpO_2). The robustness of the observation was further supported by a meaningful reduction of the number of patients who experienced at least one exacerbation, and resulted in a significant and clinically relevant improvement of patient reported outcome measures. Lower doses of BIBF 1120 had no effect on the primary endpoint, however, for some secondary endpoints significant improvements versus placebo could be demonstrated also for the second highest dose, 100 mg bid. No effects were observed on diffusion capacity and 6-minute walk test. Overall survival was similar across treatment groups; however,

mortality was numerically highest in the placebo group and in the lowest dose group. A trend towards reduced frequency of respiratory deaths was observed with increasing doses.

Tolerability was overall acceptable. A steep increase of the number of patients with gastrointestinal AE ("diarrhoea", "nausea", "vomiting", "abdominal pain") was observed for the 150 mg bid dose group, compared to all other treatment groups, and resulted in a higher discontinuation rate in this treatment group compared to placebo. The frequency of liver enzyme elevations increased with increasing dose; however, no bilirubin increases and no cases of drug-induced liver failure were observed during the 52 weeks treatment period.

In overall conclusion, it is considered that BIBF1120 may confer clinical benefit for IPF patients, with acceptable safety. Boehringer Ingelheim interprets the data from this trial as supportive for proceeding with further clinical development of BIBF 1120 in IPF and has developed a Phase 3 program that includes two identical safety and efficacy trials (1199.32 and 1199.34) evaluating 150 mg bid and placebo for 52 weeks. The twin trials are planned to be conducted worldwide including Europe, Asia and the US.

Update following end of period 2

Overall, the mean duration of exposure was 16.8, 17.7, 18.6, 17.8 and 14.2 months in the placebo (switched to 50 mg qd at the beginning of period 2), 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid groups.

Efficacy

After the final DBL, very few modifications concerned data referring to the blinded 52-week treatment phase and consisted of minor changes in concomitant treatments (due to the use of an updated MedDRA version), changes in the time to censorship of few patients for the time to event criteria analysis and the availability of one additional vital status (explained by the update of the last contact date after the final DBL), and the correction of some DLCO values after an audit. The impact of these modifications on the results was minor and the conclusions raised about the efficacy at 52 weeks after the first DBL analysis remained the same.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2006-002875-42	
Name of active ingredient: BIBF 1120		**Page:** **15 of 16**	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 01 OCT 2014	**Trial No. / U No.:** 1199.30 / U11-1225-02	**Date of trial:** 14 Sep 2007 – 10 Jun 2010	**Date of revision** : 03 JAN 2012

Period 2 data were completed with the remaining data collected after the first cut off date until all patients had either withdrawn or switched to a different trial. Tables and figures describing the efficacy parameters measured over time were updated accordingly and did not show any new relevant information compared to the first analysis.

Pharmacokinetic

Pharmacokinetic data related to period 1 were updated after final DBL with the remaining blood samples received after the first database lock. The introduction of these additional blood samples in the analysis did not change any conclusions raised after the first DBL about pharmacokinetics.

Safety

The proportion of patients with at least one AE over time was similar between groups (greater than 90%). Overall, 175 patients (40.9%) experienced at least one serious AE.

The greater frequency of patients with drug-related AEs in the high dose group (69.4%) was driven by a greater proportion of related GI disorders (“Diarrhoea”, “Nausea”, “Vomiting”) in this group.

Overall, 144 patients (33.6%) had AEs that led to treatment discontinuation over time, mainly respiratory, gastrointestinal or infectious disorders. Gastrointestinal disorders leading to treatment discontinuation were more frequent in the 150 mg bid group compared to the others.

As it was observed after the first DBL, GI disorders reported over time were frequent (54.4% of patients) and increased with dose. This was mainly due to “Diarrhoea”, “Nausea” and “Vomiting”, the most frequent of them.

AEs in the SOC “Investigations” were more frequently reported in the BIBF 150 mg bid group than in the others over time.

Two serious cases of “hepatotoxicity” were reported during period 2 (one in the placebo group and one in the 150 mg bid dose group). Both patients recovered after trial drug was discontinued. In addition, one serious case of “hepatic enzyme increased” was reported in one patient of BIBF 50 mg bid group. The patient recovered after adequate treatment was administered without

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2006-002875-42	
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Disclosure Synopsis date: 01 OCT 2014	**Trial No. / U No.:** 1199.30 / U11-1225-02	**Date of trial:** 14 Sep 2007 – 10 Jun 2010	**Date of revision** : 03 JAN 2012

discontinuation of trial drug.

During the whole study duration, 51 on treatment fatal AEs were reported (16, 18, 4, 9, 4 in the placebo, BIBF 50 mg qd, BIBF 50 mg bid, BIBF 100 mg bid and BIBF 150 mg bid), including 19 during period 2 (4, 8, 0, 4, 3).

Overall, in the randomized set, 73 patients died during the whole study period irrespective whether they were on treatment or not (19, 20, 10, 10, 14 in the the placebo, BIBF 50 mg qd, BIBF 50 mg bid, BIBF 100 mg bid and 150 mg bid dose groups. Thirty nine of them died after 52 weeks of treatment.

Updated laboratory results and vital signs during period 2 were comparable to period 1. Body weight tended to decrease over time with increasing doses. Weight loss seemed to be associated with gastrointestinal disorders and decreased appetite.

In conclusion, efficacy data updated following end of period 2 were comparable to those observed after the first DBL. Weight decrease, potentially associated with gastrointestinal adverse events, may occur more often with higher doses of BIBF 1120. Overall, no new safety issue was identified.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for primary and secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Rate of decline in FVC (L/yr) at 12 months (Primary endpoint)	Table 15.2.1.1.1: 1
Absolute change from baseline in FVC% predicted (%) at 12 months (Secondary endpoint)	Table 15.2.1.2.1: 3
Absolute change from baseline in FVC (L) at 12 months (Secondary endpoint)	Table 15.2.1.3.1: 3
Relative change from baseline in FVC% predicted (%) at 12 months (Secondary endpoint)	Table 15.2.1.4.1: 3
Relative change from baseline in FVC (L) at 12 months (Secondary endpoint)	Table 15.2.1.5.1: 3
Change from baseline in FVC (L) by categories at 12 months (Secondary endpoint)	Table 15.2.1.6.1: 3
Change from baseline in FEV_1/FVC (%) at 12 months (Secondary endpoint)	Table 15.2.1.7: 3
Change from baseline in TLC (L) at 12 months (Secondary endpoint)	Table 15.2.8.1: 2
Change from baseline in TGV (L) at 12 months (Secondary endpoint)	Table 15.2.8.3: 2
Patients with at least one exacerbation (per patient−year) at 12 months (Secondary endpoint)	Table 15.2.9.1: 1
Survival at 12 months (Secondary endpoint)	Table 15.2.2.2: 3
AE Overall Summary	Table 15.3.2.1: 1

Table 15.2.1.1.1: 1 Rate of decline in FVC (L/yr) at 12 months* -
OC - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	83	85	86	85	84
Rate of decline					
Adjusted rate (SE)**	-0.190 (0.036)	-0.174 (0.037)	-0.210 (0.035)	-0.162 (0.035)	-0.060 (0.039)
95% Confidence interval	(-0.262, -0.119)	(-0.247, -0.102)	(-0.279, -0.141)	(-0.231, -0.093)	(-0.135, 0.016)
Comparison vs Placebo					
Adjusted difference (SE)**		0.016 (0.052)	-0.020 (0.051)	0.028 (0.051)	0.131 (0.053)
95% Confidence interval		(-0.086, 0.118)	(-0.119, 0.080)	(-0.071, 0.128)	(0.027, 0.235)

Comparison	Observed p-value	p-value for conclusion	Significant for the trial
H0 15: Placebo = BIBF 150mg bid	0.0136	0.0639	No
H0 14: Placebo = BIBF 100mg bid	0.5736	0.8530	No
H0 13: Placebo = BIBF 50mg bid	0.6991	0.7920	No
H0 12: Placebo = BIBF 50mg qd	0.7558	0.8530	No
H0 11: Placebo = BIBF 100mg bid = BIBF 150mg bid	0.0359		
H0 10: Placebo = BIBF 50mg bid = BIBF 150mg bid	0.0088		
H0 9: Placebo = BIBF 50mg qd = BIBF 150mg bid	0.0290		
H0 8: Placebo = BIBF 50mg bid = BIBF 100mg bid	0.6241		
H0 7: Placebo = BIBF 50mg qd = BIBF 100mg bid	0.8530		
H0 6: Placebo = BIBF 50mg qd = BIBF 50mg bid	0.7823		
H0 5: Placebo = BIBF 50mg bid = BIBF 100mg bid = BIBF 150mg bid	0.0235		
H0 4: Placebo = BIBF 50mg qd = BIBF 100mg bid = BIBF 150mg bid	0.0639		
H0 3: Placebo = BIBF 50mg qd = BIBF 50mg bid = BIBF 150mg bid	0.0221		
H0 2: Placebo = BIBF 50mg qd = BIBF 50mg bid = BIBF 100mg bid	0.7920		
H0 1: Placebo = BIBF 50mg qd = BIBF 50mg bid = BIBF 100mg bid = BIBF 150mg bid	0.0474		

* Based on visits up to visit 9
Negative change indicates worsening
** Based on a MMRM with terms for treatment*time, gender*height, gender*age, patient effect, patient*time (patient effect and patient*time random, all other effects fixed) and a variance component variance-covariance matrix
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\fvc_mx.sas 26NOV2010

Table 15.2.1.2.1: 3 Adjusted mean (SE) for absolute change from baseline in FVC% pred (%) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84	85	86	85	84
Baseline					
Mean (SE)	81.2 (1.89)	80.4 (1.94)	79.8 (1.70)	85.7 (2.08)	79.3 (2.02)
Visit V9					
Mean (SE)	75.4 (1.94)	76.0 (2.19)	75.0 (1.90)	82.5 (2.14)	78.4 (2.32)
Change from baseline					
Mean (SE)	-5.86 (1.094)	-4.40 (0.872)	-4.80 (0.847)	-3.24 (0.952)	-0.92 (0.825)
Adjusted mean (SE)**	-6.00 (1.019)	-4.58 (1.029)	-4.90 (0.984)	-3.15 (1.004)	-1.04 (0.990)
95% Confidence interval	(-8.01, -4.00)	(-6.60, -2.55)	(-6.84, -2.97)	(-5.12, -1.17)	(-2.98, 0.91)
Comparison vs Placebo					
Adjusted mean (SE)**		1.43 (1.312)	1.10 (1.312)	2.86 (1.324)	4.97 (1.319)
95% Confidence interval		(-1.15, 4.01)	(-1.48, 3.68)	(0.26, 5.46)	(2.37, 7.56)
p-value		0.2774	0.4014	0.0314	0.0002

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.2 ctr\fvcpp_anc.sas 26NOV2010

Table 15.2.1.3.1: 3 Adjusted mean (SE) for absolute change from baseline in FVC (L) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84	85	86	85	84
Baseline					
Mean (SE)	2.8 (0.08)	2.8 (0.09)	2.7 (0.07)	2.9 (0.09)	2.7 (0.09)
Visit V9					
Mean (SE)	2.6 (0.08)	2.6 (0.09)	2.5 (0.08)	2.8 (0.09)	2.7 (0.09)
Change from baseline					
Mean (SE)	-0.22 (0.039)	-0.18 (0.033)	-0.18 (0.027)	-0.14 (0.036)	-0.05 (0.028)
Adjusted mean (SE)**	-0.23 (0.036)	-0.18 (0.036)	-0.19 (0.035)	-0.13 (0.035)	-0.06 (0.035)
95% Confidence interval	(-0.30, -0.16)	(-0.25, -0.11)	(-0.26, -0.12)	(-0.20, -0.06)	(-0.13, 0.01)
Comparison vs Placebo					
Adjusted mean (SE)**		0.04 (0.046)	0.03 (0.046)	0.09 (0.046)	0.17 (0.046)
95% Confidence interval		(-0.05, 0.13)	(-0.06, 0.13)	(0.00, 0.18)	(0.08, 0.26)
p-value		0.3644	0.4525	0.0471	0.0004

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1.2 ctr\fvc_anc.sas 26NOV2010

Table 15.2.1.4.1: 3 Adjusted mean (SE) for relative change from baseline in FVC% pred (%) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84	85	86	85	84
Baseline					
Mean (SE)	81.2 (1.89)	80.4 (1.94)	79.8 (1.70)	85.7 (2.08)	79.3 (2.02)
Visit V9					
Mean (SE)	75.4 (1.94)	76.0 (2.19)	75.0 (1.90)	82.5 (2.14)	78.4 (2.32)
Change from baseline					
Mean (SE)	-6.91 (1.276)	-5.99 (1.141)	-6.22 (1.006)	-3.27 (1.406)	-1.58 (1.115)
Adjusted mean (SE)**	-7.28 (1.321)	-6.37 (1.334)	-6.42 (1.277)	-3.47 (1.302)	-1.81 (1.283)
95% Confidence interval	(-9.88, -4.68)	(-8.99, -3.74)	(-8.93, -3.91)	(-6.03, -0.91)	(-4.33, 0.71)
Comparison vs Placebo					
Adjusted mean (SE)**		0.91 (1.702)	0.86 (1.702)	3.81 (1.716)	5.47 (1.710)
95% Confidence interval		(-2.43, 4.26)	(-2.49, 4.20)	(0.43, 7.18)	(2.11, 8.83)
p-value		0.5920	0.6155	0.0271	0.0015

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.1.9.2, Statdoc 6.1.4.1.2 ctr\fvcpp_anc.sas 26NOV2010

Table 15.2.1.5.1: 3 Adjusted mean (SE) for relative change from baseline in FVC (L) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84	85	86	85	84
Baseline					
Mean (SE)	2.8 (0.08)	2.8 (0.09)	2.7 (0.07)	2.9 (0.09)	2.7 (0.09)
Visit V9					
Mean (SE)	2.6 (0.08)	2.6 (0.09)	2.5 (0.08)	2.8 (0.09)	2.7 (0.09)
Change from baseline					
Mean (SE)	-7.58 (1.267)	-6.59 (1.131)	-6.90 (0.999)	-3.99 (1.400)	-2.24 (1.112)
Adjusted mean (SE)**	-7.96 (1.314)	-6.98 (1.327)	-7.16 (1.272)	-4.13 (1.285)	-2.52 (1.277)
95% Confidence interval	(-10.55, -5.38)	(-9.59, -4.37)	(-9.66, -4.66)	(-6.65, -1.60)	(-5.03, -0.01)
Comparison vs Placebo					
Adjusted mean (SE)**		0.99 (1.692)	0.80 (1.694)	3.84 (1.702)	5.44 (1.700)
95% Confidence interval		(-2.34, 4.31)	(-2.53, 4.13)	(0.49, 7.18)	(2.10, 8.78)
p-value		0.5601	0.6366	0.0246	0.0015

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.1.9.2, Statdoc 6.1.5.1.2 ctr\fvc_anc.sas 26NOV2010

Table 15.2.1.6.1: 3 Change from baseline in FVC (L) by categories at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84 (100.0)	85 (100.0)	86 (100.0)	85 (100.0)	84 (100.0)
Forced Vital Capacity at Visit V9					
Decrease > 10% or 200 mL	37 (44.0)	35 (41.2)	41 (47.7)	30 (35.3)	20 (23.8)
Change within <=10% AND <=200mL	41 (48.8)	44 (51.8)	39 (45.3)	46 (54.1)	52 (61.9)
Increase > 10% or 200 mL	6 (7.1)	6 (7.1)	6 (7.0)	9 (10.6)	12 (14.3)
Comparison vs Placebo					
Odds ratio**		0.911	1.136	0.657	0.415
95% Confidence interval		(0.506, 1.637)	(0.631, 2.045)	(0.363, 1.189)	(0.227, 0.757)
p-value		0.7543	0.6704	0.1649	0.0041

* Based on visit 9
Negative change indicates worsening
** Based on an ordinal logistic regression model with terms for treatment, baseline of corresponding continuous value, region (all effects fixed)
Odds ratio lower than 1 favors the treatment group over placebo
Source data: Appendix 16.1.9.2, Statdoc 6.1.6.1.2 ctr\fvc_lr.sas 26NOV2010

Table 15.2.1.7: 3 Adjusted mean (SE) for absolute change from baseline in FEV1/FVC (%) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	84	85	86	85	84
Baseline					
Mean (SE)	81.8 (0.62)	81.1 (0.69)	81.9 (0.63)	81.5 (0.75)	81.1 (0.80)
Visit V9					
Mean (SE)	82.9 (0.70)	81.0 (0.76)	81.9 (0.66)	81.0 (0.81)	80.7 (0.89)
Change from baseline					
Mean (SE)	1.15 (0.434)	-0.09 (0.463)	-0.06 (0.510)	-0.51 (0.572)	-0.41 (0.443)
Adjusted mean (SE)**	1.25 (0.529)	-0.10 (0.533)	0.00 (0.511)	-0.53 (0.516)	-0.42 (0.513)
95% Confidence interval	(0.21, 2.29)	(-1.15, 0.94)	(-1.00, 1.01)	(-1.54, 0.49)	(-1.43, 0.59)
Comparison vs Placebo					
Adjusted mean (SE)**		-1.35 (0.680)	-1.24 (0.680)	-1.77 (0.684)	-1.67 (0.683)
95% Confidence interval		(-2.69, -0.01)	(-2.58, 0.09)	(-3.12, -0.43)	(-3.01, -0.32)
p-value		0.0479	0.0685	0.0099	0.0152

* Based on visit 9
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.2, Listing 6.1.3 ctr\fevfvc_anc.sas 26NOV2010

Table 15.2.8.1: 2 Adjusted mean (SE) for absolute change from baseline in TLC (L) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	75	68	80	80	69
Baseline					
Mean (SE)	4.25 (0.128)	4.46 (0.138)	4.19 (0.105)	4.34 (0.122)	4.15 (0.133)
Visit V9					
Mean (SE)	3.99 (0.124)	4.18 (0.138)	4.08 (0.107)	4.22 (0.119)	4.27 (0.138)
Change from baseline					
Mean (SE)	-0.259 (0.0771)	-0.277 (0.0759)	-0.111 (0.0544)	-0.119 (0.0572)	0.122 (0.1003)
Adjusted mean (SE)**	-0.240 (0.0765)	-0.218 (0.0809)	-0.100 (0.0725)	-0.082 (0.0723)	0.118 (0.0774)
95% Confidence interval	(-0.390, -0.090)	(-0.377, -0.059)	(-0.242, 0.043)	(-0.224, 0.061)	(-0.034, 0.270)
Comparison vs Placebo					
Adjusted mean (SE)**		0.022 (0.1015)	0.140 (0.0974)	0.158 (0.0977)	0.358 (0.1008)
95% Confidence interval		(-0.178, 0.222)	(-0.051, 0.332)	(-0.034, 0.351)	(0.160, 0.556)
p-value		0.8288	0.1506	0.1059	0.0004

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.2, Listing 6.7.1 ctr\tlc_anc.sas 26NOV2010

Table 15.2.8.3: 2 Adjusted mean (SE) for absolute change from baseline in TGV (L) at 12 months* - LOCF - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number of analysed patients	73	64	78	78	66
Baseline					
Mean (SE)	2.51 (0.081)	2.65 (0.104)	2.43 (0.070)	2.42 (0.070)	2.54 (0.089)
Visit V9					
Mean (SE)	2.37 (0.087)	2.50 (0.094)	2.40 (0.076)	2.42 (0.067)	2.73 (0.095)
Change from baseline					
Mean (SE)	-0.139 (0.0709)	-0.153 (0.0946)	-0.031 (0.0497)	-0.002 (0.0381)	0.193 (0.0834)
Adjusted mean (SE)**	-0.137 (0.0657)	-0.075 (0.0707)	-0.035 (0.0622)	-0.016 (0.0623)	0.200 (0.0668)
95% Confidence interval	(-0.266, -0.008)	(-0.214, 0.064)	(-0.157, 0.088)	(-0.138, 0.107)	(0.068, 0.331)
Comparison vs Placebo					
Adjusted mean (SE)**		0.063 (0.0884)	0.103 (0.0839)	0.121 (0.0843)	0.337 (0.0874)
95% Confidence interval		(-0.111, 0.236)	(-0.062, 0.268)	(-0.044, 0.287)	(0.165, 0.509)
p-value		0.4792	0.2221	0.1510	0.0001

* Based on visit 9
Negative change indicates worsening
** Based on an ANCOVA with terms for treatment, baseline, region (all effects fixed)
Source data: Appendix 16.2, Listing 6.7.3 ctr\tgv_anc.sas 26NOV2010

Table 15.2.9.1: 1 Proportion of patients with at least one exacerbation (per patient-year) at 12 months* - OC - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Number (%) with at least one exacerbation	12 (13.8)	10 (11.5)	10 (11.6)	6 (7.0)	2 (2.3)
Total number of years at risk	76.58	76.72	80.24	80.38	81.84
Incidence of exacerbations rates	15.67	13.03	12.46	7.46	2.44
Comparison vs Placebo					
Risk ratio		0.83	0.80	0.48	0.16
95% Confidence interval		(0.36, 1.93)	(0.34, 1.84)	(0.18, 1.27)	(0.03, 0.70)
p-value**		0.6671	0.5926	0.1381	0.0150

* Based on data collected up to 365 days after randomisation
Rates ratio lower than 1 favors the treatment group over placebo
** Based on the statistic of ln(risk ratio) having a normal distribution N[0,[(1/number with at least one exacerbation in BIBF group) + (1//number with at least one exacerbation in BIBF placebo)]]
Risk ratio and incidence rate = 100*number of patient with at least one exacerbation/time at risk(days) and /time at risk(years), resp.
Time at risk starts at randomisation and ends on the day of either of exac. or, if no exac., last physical or phone contact
Source data: Appendix 16.2, Listing 6.9.1 ctr\nbexa12_cmh.sas 26NOV2010

Table 15.2.2.2: 3 Proportional hazard model for survival at 12 months* – OC - randomised set

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in Randomised set	87	87	86	86	86
Failure [N (%)]	9 (10.3)	11 (12.6)	3 (3.5)	4 (4.7)	7 (8.1)
Censored [N (%)]	78 (89.7)	76 (87.4)	83 (96.5)	82 (95.3)	79 (91.9)
Comparison vs Placebo					
Hazard ratio**		1.278	0.290	0.350	0.732
95% Confidence interval		(0.526, 3.102)	(0.078, 1.081)	(0.106, 1.154)	(0.271, 1.977)
p-value		0.5882	0.0653	0.0847	0.5383

* Based on data collected up to 365 days after randomisation
** Based on a Cox's regression model with terms for treatment, gender, age, height, region (all effects fixed)
Source data: Appendix 16.2, Listing 6.10.1 ctr\death12_surv.sas 26NOV2010

Table 15.3.2.1: 1 Adverse event overall summary - treated set

Treatment analysis: Treatment period 1 + 14d washout + TOTAL

	Placebo N (%)	BIBF 50 qd N (%)	BIBF 50 bid N (%)	BIBF 100 bid N (%)	BIBF 150 bid N (%)	Total N (%)
Number of patients	85 (100.0)	86 (100.0)	86 (100.0)	86 (100.0)	85 (100.0)	428 (100.0)
Patients with any AE	77 (90.6)	78 (90.7)	78 (90.7)	82 (95.3)	80 (94.1)	395 (92.3)
Patients with severe AEs	20 (23.5)	21 (24.4)	17 (19.8)	19 (22.1)	19 (22.4)	96 (22.4)
Patients with investigator defined drug-related AEs	25 (29.4)	24 (27.9)	30 (34.9)	41 (47.7)	55 (64.7)	175 (40.9)
Patients with other significant AEs (according to ICH E3)	9 (10.6)	6 (7.0)	11 (12.8)	10 (11.6)	24 (28.2)	60 (14.0)
Patients with AEs leading to discontinuation of trial drug	22 (25.9)	20 (23.3)	14 (16.3)	12 (14.0)	26 (30.6)	94 (22.0)
Patients with serious AEs	26 (30.6)	26 (30.2)	23 (26.7)	18 (20.9)	23 (27.1)	116 (27.1)
Fatal	12 (14.1)	10 (11.6)	4 (4.7)	5 (5.8)	1 (1.2)	32 (7.5)
Imm life-threatening	2 (2.4)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	4 (0.9)
Disability/incap.	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Req.hospitalisation	22 (25.9)	22 (25.6)	18 (20.9)	15 (17.4)	23 (27.1)	100 (23.4)
Prol.hospitalisation	2 (2.4)	0 (0.0)	0 (0.0)	4 (4.7)	0 (0.0)	6 (1.4)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (2.4)	2 (2.3)	2 (2.3)	4 (4.7)	3 (3.5)	13 (3.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 13.0