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Clinical Study Synopsis for Public Disclosure

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Module:		**Volume:** {hyperlink }	
Disclosure synopsis date: 01-OCT-2014	**Trial No. / U No.:** 1239.3 / U10-1013-01	**Dates of trial:** 18 MAY 2006 – 19 DEC 2008	**Date of revision:** Not applicable

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Title of trial:	A multi-centre 3-arm randomised phase II trial of BIBF 1120 versus BIBW 2992 versus sequential administration of BIBF 1120 and BIBW 2992 in patients with hormone-resistant prostate cancer
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study conducted in 9 centres in the UK
Publication (reference):	A phase II trial to compare BIBF 1120 or BIBW 2992 monotherapy vs. a combination of sequential administration of both medications in patients with hormone refractory prostate cancer (HRPC). Molife R, de Bono JS, Bell S, et al. American Society of Clinical Oncology, 2009 Genitourinary Cancers Symposium, Orlando, Florida, USA, 26-28 February 2009 (P09-04101)
Clinical phase:	II
Objectives:	To determine and compare the progression-free rate (PFR), as determined by prostate serum antigen (PSA) levels, bone metastases and radiographic criteria, after 12 weeks of treatment with study medication and to evaluate the safety of each of the treatment groups.
Methodology:	Randomised, open label, 2-stage, phase II design with 3 treatment arms: BIBF 1120 monotherapy (250 mg twice daily [b.i.d.]) versus BIBW 2992 monotherapy (40 mg once daily [q.d.]) versus a combination therapy of sequential alternating 7-day administration of BIBF 1120 250 mg b.i.d. and BIBW 2992 70 mg q.d. (ComBI 70 treatment group). After 3 patients had been treated with 70 mg BIBW 2992 q.d. as part of the ComBI 70 treatment schedule, a protocol amendment was introduced reducing the starting dose of BIBW 2992 for the sequential combination therapy to 40 mg BIBW 2992 q.d. (ComBI 40 treatment group). Patients treated with ComBI 40 were analysed separately from ComBI 70 patients. A screening period of up to 14 days was followed by randomisation and a continuous treatment period of up to 48 weeks (or until disease progression), and a follow-up period of 4 weeks.

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Methodology:	An interim analysis of efficacy was to be performed separately for each treatment group as soon as 15 patients had either been treated for 12 weeks or had experienced progressive disease (PD). If 2 or more of 15 patients had not experienced PD at 12 weeks, a further 20 patients were to be included in the treatment group (stage 2 of the trial design). The BIBF 1120 250 mg b.i.d. monotherapy treatment group was the only group to continue into stage 2 of the study.
No. of subjects:	
planned:	entered: up to 35 in each treatment arm
actual:	enrolled: 96 entered: 87 BIBF 1120 250 mg b.i.d. treatment group: entered: 47 treated: 46 analysed (for primary endpoint): 27 BIBW 2992 40 mg q.d. treatment group: entered: 21 treated: 20 analysed (for primary endpoint): 12 ComBI 70 treatment group (7-day alternating sequential combination therapy group with BIBF 1120 250 mg b.i.d. and BIBW 2992 70 mg q.d.): entered: 3 treated: 3 analysed (for primary endpoint): 0 ComBI 40 treatment group (7-day alternating sequential combination therapy group with BIBF 1120 250 mg b.i.d. and BIBW 2992 40 mg q.d.): entered: 16 treated: 16 analysed (for primary endpoint): 10 Analysed for pharmacokinetics (PK): 43 on BIBF 250 mg b.i.d. monotherapy; 18 on BIBW 40 mg q.d. monotherapy; 3 on ComBI 70; 16 on ComBI 40.
Diagnosis and main criteria for inclusion:	Patients with chemonaïve HRPC aged ≥18 years and with PD, defined as a minimum of 3 consecutive serum PSA measurements obtained at least 7 days apart within the 3 months before the start of trial, that documented progressively increasing values, and PSA values of >5ng/mL. Patients with progression of measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) or progression of bone disease also had to fit the criteria for PSA progression.

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Test product:	BIBF 1120 soft gelatine capsules
dose:	250 mg b.i.d., total dose: 500 mg/day, 28-day treatment cycle; if dose limiting toxicity (DLT) occurred the starting dose was to be reduced to 150 mg b.i.d.
mode of admin.:	oral
batch no.:	200 mg: 1243780001, 1283950001, 1298710001, 1308380001 50 mg: 1280210001, 1283930001, 1298730001

Test product:	BIBW 2992 tablets
dose:	40 mg q.d., 28-day treatment cycle; if DLT occurred the starting dose was to be reduced to 20 mg q.d.
mode of admin.:	oral
batch nos.:	20 mg: B061000903, B061000422, B050206

Test product:	BIBF 1120 soft gelatine capsules, BIBW 2992 tablets
dose:	28-day treatment cycles of sequential combination therapy with alternating 7-day treatments as follows: ComBI 70 treatment group BIBF 1120 250 mg b.i.d. on Days 1 to 7 and 15 to 21 BIBW 2992 70 mg q.d. on Days 8 to 14 and 22 to 28 If DLT occurred the starting doses were to be reduced to 150 mg BIBF 1120 b.i.d. (in case of transaminitis) or 40 mg BIBW 2992 q.d. (in case of skin toxicity). The starting dose of BIBW 2992 was reduced to with a protocol amendment: ComBI 40 treatment group BIBF 1120 250 mg b.i.d. on Days 1 to 7 and 15 to 21 BIBW 2992 40 mg q.d. on Days 8 to 14 and 22 to 28 If DLT occurred the starting doses were to be reduced to 150 mg BIBF 1120 b.i.d. (in case of transaminitis) or 20 mg BIBW 2992 q.d. (in case of skin toxicity).

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mode of admin.:	oral
batch nos.:	200 mg BIBF 1120: 1243780001, 1283950001, 1298710001, 1308380001 50 mg BIBF 1120: 1280210001, 1283930001, 1298730001 20 mg BIBW 2992: B061000903, B061000422, B050206 5 mg BIBW 2992: B061001815, B061000376 (ComBI 70 group only)
Duration of treatment:	48 weeks in the absence of disease progression
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the PFR at 12 weeks, with PFR defined as a composite endpoint for disease progression as follows: PSA progression (according to the Prostate-Specific Antigen Working Group [PSAWG] criteria), bone metastasis progression (development of new lesions on bone scan or of disease-related skeletal-related events [SREs]), or disease progression according to RECIST version 1.0. Note: new lesions in bone scans at 12 weeks were only considered as PD if accompanied by any other criteria for progression. The following secondary endpoints were assessed: disease progression based on primary endpoint at 24 and 48 weeks; time to PSA progression; tumour progression rate; time to progression; time to death (overall survival); PSA response and duration of response; overall objective tumour response and duration of response; BIBF 1120 and BIBW 2992 plasma concentrations.
Safety:	The following safety endpoints were assessed: monitoring of adverse events (AEs) according to United States National Cancer Institute (US-NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; Eastern Cooperative Oncology Group (ECOG) performance status; safety laboratory parameters; vital signs; body weight; chest X-ray; electrocardiogram (ECG).
Statistical methods:	Analyses were descriptive and exploratory. Time to PSA progression and time to death were analysed using survival analysis techniques: Kaplan-Meier estimates and confidence intervals (CI), calculated using Peto's variance estimate for CI.
SUMMARY – CONCLUSIONS:	
Efficacy results:	The clinical trial protocol specified the dose of BIBW 2992 for the sequential combination therapy group as 70 mg q.d.; however, this was amended to 40 mg q.d. because the higher dose was associated with a higher than expected

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Efficacy results (continued):

incidence of severe AEs in the first 3 patients treated. The lower BIBW 2992 dose sequential combination therapy group (ComBI 40) was analysed separately from the higher BIBW 2992 dose combination therapy group (ComBI 70). Data from the ComBI 70 treatment group were not included in analyses of efficacy.

Overall, approximately a third of patients on BIBF 1120 250 mg b.i.d. (33.3%) or BIBW 2992 40 mg q.d. (36.4%) and approximately two thirds of patients on ComBI 40 (60.0%) developed new bone lesions during the trial. One patient on BIBF 1120 250 mg b.i.d. reported SREs during the trial.

Following an interim analysis of efficacy (described above), only the BIBF 1120 250 mg b.i.d. monotherapy group was continued into stage 2 of the study.

There were no marked differences in demographic characteristics across the 4 treatment groups. Mean age ranged from 67.7 to 70.4 years, mean body mass index ranged from 27.8 to 28.9 kg/m^2, and almost all patients were white (97.6%). In total, 93.0% of patients were non-smokers, including 51.8% who had never smoked and 41.2% who were ex-smokers, and no patients were reported to drink alcohol to an extent that would interfere with the study assessments.

In total, 42 (49.4%) patients discontinued due to progressive disease. A further 28 (32.9%) discontinued due to AEs, 10 (11.8%) patients withdrew consent to participate in the trial, 4 (4.7%) patients discontinued due to other reasons, and 1 (1.2%) patient was withdrawn due to non-compliance.

In total, 7 patients (25.9%) on BIBF 1120 250 mg b.i.d. met the primary endpoint of the trial and were progression-free at 12 weeks compared with no patients on BIBW 2992 40 mg q.d. or ComBI 40. The differences between BIBF 1120 250 mg b.i.d. and the other trial medications were not statistically significant (vs. BIBW 2992 40 mg q.d., $p = 0.0577$; vs. ComBI 40, $p = 0.0863$).

One patient (3.7%) on BIBF 1120 250 mg b.i.d. and 1 patient (10.0%) on ComBI 40 showed a PSA response during the trial. The median time to PSA progression was similar in the BIBF 1120 250 mg b.i.d. and BIBW 2992 40 mg q.d. treatment groups (31.0 and 29.0 days, respectively) and longer in the ComBI 40 treatment group (57.0 days).

One patient on BIBF 1120 250 mg b.i.d. showed an unconfirmed objective response (RECIST partial response [PR]) compared with no patients on BIBW 2992 40 mg q.d. or on ComBI 40; the patient's maximum percentage reduction in tumour size was -32.1% and the duration of the response was 116 days.

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Efficacy results (continued):	The majority of patients (81.6%) showed no change in ECOG score during the trial; 8.2% of patients improved and 10.2% deteriorated. The patients who showed an overall improvement were: 3 (11.1%) patients in the BIBF 1120 250 mg b.i.d. group, 0 (0.0%) patients in the BIBW 2992 40 mg q.d. treatment group, and 1 (11.1%) patient in the ComBI 40 treatment group.
Clinical pharmacology results:	The PK data set and thereby the PK evaluation was limited because several PK samples were not received in the bioanalytical laboratory, or had to be excluded because the storage time was too long, or could not be evaluated as there was no time information recorded. The quality of the bioanalytical assays for the determination of BIBF 1120 and BIBW 2992 was good. BIBF 1120 250 mg b.i.d. monotherapy treatment group: The geometric mean (gMean) plasma concentrations at 1 and 3 hours post-dose were comparable between Day 8 and Day 15. Steady state was reached at latest on Day 8 and trough values were stable during the observed treatment duration with concentrations of 10.2 ng/mL at Day 8, 11.8 ng/mL at Day 15, and 11.8 ng/mL at Day 29. However, a high inter-patient variability was observed with geometric coefficient of variation (gCVs) ranging from 75.5 to 110%. BIBW 2992 40 mg q.d. monotherapy treatment group: The gMean plasma concentrations at 1 and 3 hours post dose were comparable between Day 8 and Day 15. Steady state was reached at latest on Day 8 and trough concentrations were stable at the observed treatment time with gMean values of 18.0 ng/mL at Day 8, 19.1 ng/mL at Day 15, and 18.2 ng/mL at Day 29. However, a high inter-patient variability was observed with gCVs ranging from 81.2 to 92.6%. BIBF 1120 and BIBW 2992 sequential combination therapy group (ComBI 40): The gMean plasma concentration of BIBF 1120 was 13.7 ng/mL (range 8.22 to 39.7 ng/mL) at 12 hours after the last dose on Day 14. The BIBW 2992 plasma concentrations 24 hours after the last 40 mg BIBW 2992 dose on Day 7 displayed a gMean value of 11.4 ng/mL (range 0.517 to 34.4 ng/mL). Plasma concentrations were moderately to highly variable with gCVs from 40.7 to 336% for BIBF 1120 and 33.8 to 216% for BIBW 2992.

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Safety results:

Treatment was continuous; it was described in terms of 28-day treatment cycles. The mean exposure time was 126.2 days (standard deviation [SD] 71.56) for all patients. The mean number of 28-day cycles initiated for all patients was 3.7 (SD 2.35) and 3.5 (SD 2.48) were completed. Mean exposure time was longer for BIBF 1120 250 mg b.i.d. patients (143.6 days) than for the other treatment groups (82.7 to 114.4 days). In total, 82.4% of patients were treated for at least 12 weeks. This percentage was highest for the ComBI 40 treatment group (93.8%) compared with 90.0% for BIBW 2992 40 mg q.d., 78.3% for BIBF 1120 250 mg b.i.d., and 33.3% for the ComBI 70 treatment group.

All patients reported at least 1 AE during the trial and at least 90% of patients in each group reported at least 1 drug-related AE. Based on the worst severity reported, there were no drug-related CTCAE grade 4 or 5 AEs. An overall summary of AEs by category of event is presented by treatment group in Table 1.

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Safety results (continued):

Table 1 Overall summary of adverse events - treated set

	BIBF 250 b.i.d. N = 46	BIBW 40 q.d. N = 20	ComBI 40 N = 16	ComBI 70 N = 3
Any AE	46 (100.0)	20 (100.0)	16 (100.0)	3 (100.0)
Drug-related AEs	42 (91.3)	20 (100.0)	15 (93.8)	3 (100.0)
Other sig. AEs (ICH E3)	15 (32.6)	5 (25.0)	3 (18.8)	2 (66.7)
AEs leading to discontinuation	19 (41.3)	5 (25.0)	4 (25.0)	2 (66.7)
Pre-specified sig. AEs [1]	8 (17.4)	4 (20.0)	2 (12.5)	0 (0.0)
Serious AEs	11 (23.9)	2 (10.0)	4 (25.0)	1 (33.3)
Fatal	0 (0.0)	1 (5.0)	1 (6.3)	0 (0.0)
Imm. life-threatening	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incapacity	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Req. hospitalisation	9 (19.6)	2 (10.0)	2 (12.5)	1 (33.3)
Prolongs hospitalisation	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.2)	0 (0.0)	1 (6.3)	0 (0.0)

sig. = significant; imm.= immediately; req. = requires

[1] CD4+ cell counts <200/µL, dose limiting increases in liver enzymes, rash, diarrhoea, nausea, vomiting, dyspnoea, visual impairment (e.g. blurred vision), decline in left ventricular ejection fraction, and decline in renal function, if considered related to trial medication, any DLT event, or an AE considered significant by the investigator.

The most commonly reported AEs in all treatment groups were gastrointestinal disorders (97.8% on BIBF 1120 monotherapy; 100% on BIBW 2992 monotherapy, 93.8% on ComBI 40, and 100% on ComBI 70) and, in particular, diarrhoea (76.1% on BIBF 1120 monotherapy; 100% on BIBW 2992 monotherapy, 93.8% on ComBI 40, and 66.7% on ComBI 70).

Drug-related AEs by treatment group

BIBF 1120 250 mg b.i.d. treatment group:

The most commonly reported AEs that were considered to be drug-related were gastrointestinal disorders (37 patients, 80.4%), including most commonly: diarrhoea (65.2%), nausea (54.3%), vomiting (32.6%), and constipation (10.9%). Other drug-related AEs with an incidence of >10% were: lethargy (19.6%),

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Safety results (continued):

increased alanine aminotransferase (ALT) (17.4%), fatigue (13.0%), and increased aspartate aminotransferase (AST) (10.9%). Drug-related AEs with a worst severity of CTCAE grade 3 reported by >1 patient were increased ALT (4 patients, 8.7%) and diarrhoea and increased AST, each reported by 3 (6.5%) patients.

BIBW 2992 40 mg q.d. treatment group:
The most commonly reported AEs that were considered to be drug-related were gastrointestinal disorders (100%). Drug-related AEs with an incidence of >10% were: diarrhoea (100%), epistaxis and rash (each reported by 40%), fatigue (25%), decreased appetite, lethargy, oral pain, and vomiting (each reported by 20%), and conjunctivitis, dry mouth, dry skin, dysgeusia, mouth ulceration, and nausea (each reported by 15%). The only drug-related AE with a worst severity of CTCAE grade 3 reported by >1 patient was diarrhoea (4 patients, 20%).

ComBI 40 treatment group:
The most commonly reported AEs that were considered to be drug-related were gastrointestinal disorders (93.8%). Drug-related AEs with an incidence of >10% were: diarrhoea (93.8%), lethargy (43.8%), nausea (37.5%), epistaxis, mouth ulceration, and rash (each reported by 31.3%), vomiting (25.0%), and constipation, dry skin, gastritis, increased ALT, increased AST, increased gamma glutamyl transferase (GGT), and rhinitis (each reported by 12.5%). The only drug-related AE with a worst severity of CTCAE grade 3 reported by >1 patient was diarrhoea (2 patients, 12.5%).

ComBI 70 treatment group:
All 3 patients (100%) reported drug-related AEs; the drug-related AEs were diarrhoea, epistaxis, mouth ulceration, nausea, vomiting (each reported by 2 patients [66.7%]), and abdominal distension, dermatitis acneiform, dry mouth, dry skin, dyschezia, dysgeusia, increased ALT, and increased GGT (each reported by 1 patient [33.3%]). The only drug-related AE with a worst severity of CTCAE grade 3 was diarrhoea, reported by 1 patient (33.3%).

Serious AEs (SAEs): Two SAEs were fatal: 1 patient on BIBW 2992 40 mg q.d. died due to progressive disease and 1 patient on ComBI 40 died due to unknown causes. Both deaths were considered to be unrelated to study medication. One immediately life-threatening SAE was reported for a patient on BIBF 1120 250 mg b.i.d.: deep vein thrombosis occurred on Day 43; the patient continued to be treated with study medication for a total of 107 days. There was 1 SAE

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Safety results (continued):

(ComBI 40 treatment group) that was considered to be possibly related to trial medication (a case of isolated thrombocytopenia with no evidence of myelosuppression that was coded as pancytopenia). The investigator later confirmed that this was a case of isolated thrombocytopenia with no evidence of myelosuppression and therefore did not constitute pancytopenia.

Other safety: With the exception of changes in liver enzymes, a known effect associated with BIBF 1120 therapy, there were no clinically significant changes in laboratory safety parameters during the course of the study. There were increases in mean AST and ALT in the BIBF 1120 250 mg b.i.d. treatment group (mean change from baseline to the last value on treatment: AST +26 U/L; ALT +29 U/L) compared with +4 U/L to -1 U/L for the other treatment groups over this period. A similar pattern was seen for GGT and lactate dehydrogenase values. There were no clinically significant changes in bilirubin values in any

treatment group. Possibly clinically significant increases in liver function tests were reported for up to half the patients in the BIBF 1120 250 mg b.i.d. group

(21 patients, 46.7% for GGT; 14 patients, 31.1% for ALT; 11 patients, 24.4% for AST; 2 patients, 4.4% for alkaline phosphatase). Percentages were lower for the BIBW 2992 40 mg q.d. treatment group (5.0 to 15.0%) and for the ComBI 40 group (12.5 to 37.5%). Almost all clinically significant abnormalities had resolved by the last value on treatment indicating that deteriorations in liver enzyme values were reversible and transient.

There were no clinically significant changes in vital signs, ECG, chest X-ray, or body weight from baseline to the last assessment.

Conclusions:

Like other anti-angiogenic therapies, BIBF 1120 showed potential antitumour activity in the indication HRPC in this phase II trial. Just over a quarter of patients treated with BIBF 1120 250 mg b.i.d. met the primary endpoint and were progression-free at 12 weeks compared with no patients on BIBW 2992 40 mg q.d. or ComBI 40. One patient on BIBF 1120 250 mg b.i.d. showed an unconfirmed objective response (partial RECIST response) compared with no patients on either BIBW 2992 40 mg q.d. or ComBI 40. The combination of BIBF 1120 and BIBW 2992 may have failed to show the same potential as BIBF 1120 monotherapy because it was administered using a sequential alternating schedule, interrupting treatment with BIBF 1120 every other week, which may have contributed to a rebound effect. A concomitant combination therapy schedule of BIBF 1120 and BIBW 2992 is currently under evaluation in various

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tumour types.

BIBF 1120 and BIBW 2992 monotherapies showed acceptable safety profiles that were consistent with previous studies and the listed AEs for BIBF 1120 and BIBW 2992. Combination therapy with BIBF 1120 and BIBW 2992 was associated with AEs listed for both BIBF 1120 and BIBW 2992. Reversible increases in hepatic enzymes occurred with BIBF 1120 therapy.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and results for primary and secondary endpoints of the trial.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Progression free rate at 12 weeks (Primary endpoint)	Table 15.2.1: 1
Progression free rate at 24 weeks (Secondary endpoint)	Table 15.2.1: 3
Progression free rate at 48 weeks (Secondary endpoint)	Table 15.2.1: 5
Summary of RECIST response at 12, 24, 36 and 48 weeks (Secondary endpoint)	Table 15.2.3: 3
Time to progression (Secondary endpoint)	Table 15.2.4: 1
Overall survival (Secondary endpoint)	Table 15.2.4: 2
Summary of PSA response (Secondary endpoint)	Table 15.2.2: 2
Objective RECIST response at 12, 24, 36, and 48 weeks (Secondary endpoint) Duration of RECIST Response (Secondary endpoint)	Table 15.2.3: 1
Adverse event overall summary (Secondary endpoint)	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	BIBF 250 bd N (%)	BIBW 40 od N (%)	ComBI 40 N (%)	ComBI 70 N (%)	Total N (%)
Enrolled					96
Not randomised					9
Entered/randomised	47	21	16	3	87
Not treated	1	1	0	0	2
Treated	46 (100.0)	20 (100.0)	16 (100.0)	3 (100.0)	85 (100.0)
Patient stopped trial medication for the following reason	46 (100.0)	20 (100.0)	16 (100.0)	3 (100.0)	85 (100.0)
Other adverse event	16 (34.8)	5 (25.0)	5 (31.3)	2 (66.7)	28 (32.9)
Non compliant with protocol	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (1.2)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	6 (13.0)	1 (5.0)	3 (18.8)	0 (0.0)	10 (11.8)
Other	4 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.7)
Progressive disease	20 (43.5)	13 (65.0)	8 (50.0)	1 (33.3)	42 (49.4)

Table 15.2.1: 1 Progression free rate at 12 weeks - mFAS

Treatment group	Progression free rate	95% Confidence interval	Comparison	P-value*
BIBF 250 bd	7 / 27 (25.9%)	(13.17 , 44.68)	BIBF - BIBW	0.0577
BIBW 40 od	0 / 12 (0.0%)	(0.00 , 24.25)		
ComBI 40	0 / 10 (0.0%)	(0.00 , 27.75)	BIBF - ComBI	0.0863

* Fisher's exact test

Table 15.2.1: 3 Progression free rate at 24 weeks - FAS

Treatment group	Progression free rate	95% Confidence interval
BIBF 250 bd	6 / 27 (22.2%)	(10.61 , 40.76)
BIBW 40 od	0 / 13 (0.0%)	(0.00 , 22.81)
ComBI 40	0 / 10 (0.0%)	(0.00 , 27.75)

Table 15.2.1: 5 Progression free rate at 48 weeks - FAS

Treatment group	Progression free rate	95% Confidence interval
BIBF 250 bd	5 / 27 (18.5%)	(8.18 , 36.70)
BIBW 40 od	0 / 13 (0.0%)	(0.00 , 22.81)
ComBI 40	0 / 10 (0.0%)	(0.00 , 27.75)

Table 15.2.3: 3 Summary of RECIST response at 12, 24, 36 and 48 weeks - FAS

RECIST evaluable	BIBF 250 bd	BIBW 40 od	ComBI 40	Total
Number of patients	12	8	7	27
12 weeks				
N [N (%)]	12 (100.0)	8 (100.0)	7 (100.0)	27 (100.0)
Complete response [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (unconfirmed) [N (%)]	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.7)
Stable disease [N (%)]	7 (58.3)	3 (37.5)	2 (28.6)	12 (44.4)
Progressive disease [N (%)]	1 (8.3)	4 (50.0)	3 (42.9)	8 (29.6)
Non-evaluable [N (%)]	3 (25.0)	1 (12.5)	2 (28.6)	6 (22.2)
Non-evaluable clinically progressive disease [N (%)]	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.7)
Non-evaluable clinically non-progressive disease [N (%)]	3 (25.0)	0 (0.0)	2 (28.6)	5 (18.5)
24 weeks				
N [N (%)]	6 (100.0)	1 (100.0)	1 (100.0)	8 (100.0)
Complete response [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (unconfirmed) [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease [N (%)]	1 (16.7)	1 (100.0)	1 (100.0)	3 (37.5)
Progressive disease [N (%)]	3 (50.0)	0 (0.0)	0 (0.0)	3 (37.5)
Non-evaluable [N (%)]	2 (33.3)	0 (0.0)	0 (0.0)	2 (25.0)
Non-evaluable clinically progressive disease [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-evaluable clinically non-progressive disease [N (%)]	2 (33.3)	0 (0.0)	0 (0.0)	2 (25.0)
36 weeks				
N [N (%)]	3 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)
Complete response [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (unconfirmed) [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease [N (%)]	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Progressive disease [N (%)]	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Non-evaluable [N (%)]	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)
Non-evaluable clinically progressive disease [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-evaluable clinically non-progressive disease [N (%)]	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)

Table 15.2.3: 3 Summary of RECIST response at 12, 24, 36 and 48 weeks - FAS

RECIST evaluable	BIBF 250 bd	BIBW 40 od	ComBI 40	Total
48 weeks				
N [N (%)]	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
Complete response [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (unconfirmed) [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Progressive disease [N (%)]	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
Non-evaluable [N (%)]	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
Non-evaluable clinically progressive disease [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-evaluable clinically non-progressive disease [N (%)]	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)

Table 15.2.4: 1 Time to progression - FAS

	BIBF 250 bd	BIBW 40 od	ComBI 40
Time to progression [days] *			
N	27	13	10
Censored	5	0	0
Median (95% CI)	31.0 (29.0, 84.0)	29.0 (29.0, 54.0)	57.0 (29.0, 78.0)
25th percentile	29.0	29.0	29.0
75th percentile	85.0	54.0	78.0

* Kaplan-Meier estimate

Table 15.2.4: 2 Time to death - FAS

	BIBF 250 bd	BIBW 40 od	ComBI 40
Time-to-death [days] *			
N	27	13	10
Censored	27	13	9
Median (95% CI)			
25th percentile			
75th percentile			

* Kaplan-Meier estimate

Table 15.2.2: 2 Summary of PSA response - FAS

	BIBF 250 bd	BIBW 40 od	ComBI 40
Number of patients	27	13	10
Summary, PSA response status [N (%)]			
N	27 (100.0)	13 (100.0)	10 (100.0)
Response	1 (3.7)	0 (0.0)	1 (10.0)
No response	26 (96.3)	13 (100.0)	9 (90.0)
Duration of PSA response [days]*			
N	27	13	10
Censored	27	13	10
Median	0	0	0
25th percentile	0	0	0
75th percentile	0	0	0

* Kaplan-Meier estimate

Table 15.2.3: 1 Objective RECIST response - FAS

RECIST evaluable	BIBF 250 bd	BIBW 40 od	ComBI 40	Total
Number of patients	12	8	7	27
12 weeks, Objective response [N (%)]				
N	12 (100.0)	8 (100.0)	7 (100.0)	27 (100.0)
Response - unconfirmed	1 (8.3)	0	0	1 (3.7)
No response	11 (91.7)	8 (100.0)	7 (100.0)	26 (96.3)
24 weeks, Objective response [N (%)]				
N	6 (100.0)	1 (100.0)	1 (100.0)	8 (100.0)
Response - unconfirmed	0	0	0	0
No response	6 (100.0)	1 (100.0)	1 (100.0)	8 (100.0)
36 weeks, Objective response [N (%)]				
N	3 (100.0)	0	0	3 (100.0)
Response - unconfirmed	0	0	0	0
No response	3 (100.0)	0	0	3 (100.0)
48 weeks, Objective response [N (%)]				
N	2 (100.0)	0	0	2 (100.0)
Response - unconfirmed	0	0	0	0
No response	2 (100.0)	0	0	2 (100.0)
Duration of RECIST response[1] [days]*				
N	12	8	7	27
Censored	11	8	7	26
Median	116.0	0	0	116.0
25th percentile	116.0	0	0	116.0
75th percentile	116.0	0	0	116.0

Objective response: Complete or Partial response
* Kaplan-Meier estimate
[1] Confirmed and non-confirmed responses

Table 15.3.2: 1 Adverse event overall summary - (all AEs) - treated set

Treatment analysis: Treatment for analysing AEs and labdata

	Screening N (%)	BIBF 250 bd N (%)	BIBW 40 od N (%)	ComBI 40 N (%)	ComBI 70 N (%)	Post Study N (%)
Common terminology criteria						
Grade 1	1 (1.2)	12 (26.1)	0 (0.0)	6 (37.5)	0 (0.0)	6 (7.1)
Grade 2	3 (3.5)	14 (30.4)	11 (55.0)	3 (18.8)	1 (33.3)	1 (1.2)
Grade 3	1 (1.2)	17 (37.0)	8 (40.0)	6 (37.5)	2 (66.7)	0 (0.0)
Grade 4	1 (1.2)	3 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5	0 (0.0)	0 (0.0)	1 (5.0)	1 (6.3)	0 (0.0)	0 (0.0)
NCI attribution category						
Missing	6 (7.1)	4 (8.7)	0 (0.0)	1 (6.3)	0 (0.0)	5 (5.9)
Unlikely	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Possible	0 (0.0)	17 (37.0)	4 (20.0)	3 (18.8)	1 (33.3)	0 (0.0)
Probable	0 (0.0)	22 (47.8)	12 (60.0)	11 (68.8)	0 (0.0)	0 (0.0)
Definite	0 (0.0)	3 (6.5)	4 (20.0)	1 (6.3)	2 (66.7)	0 (0.0)

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: 12.0