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Name of Company: Boehringer Ingelheim		Synopsis		 Boehringer Ingelheim																								
BI Proprietary Name: Not applicable		EudraCT No.: 2012-000081-37																										
BI Investigational Product: BI 655066		Page: 1 of 10																										
Report Date: 26 Mar 2015	Trial No. / Doc. No.: 1311.1 /c02434648-02	Dates of Trial: 25 Apr 2012 - 14 May 2014	Date of Revision: 12 Feb 2016																									
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Title of Trial:	Safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of single rising i.v. (Stage 1) and s.c. (Stage 2) doses of BI 655066 in male and female patients with moderate to severe psoriasis (randomised, double-blind, placebo-controlled within dose groups)																											
Coordinating Investigator:	[REDACTED]																											
Trial Sites:	Multicentre trial in 9 sites with enrolment (10 sites initiated) in 3 countries in 2 continents																											
Publications:	Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2015; epub ahead of print, available online 11 Mar 2015, doi: 10.1016/j.jaci.2015.01.018																											
Clinical Phase:	I																											
Objectives:	The primary objective of the current study was to investigate the safety and tolerability of BI 655066 in male and female patients with moderate to severe psoriasis following intravenous (iv) administration of single rising doses (Stage 1) and subcutaneous (sc) administration of single parallel doses (Stage 2). A secondary objective was to assess the clinical efficacy and pharmacokinetic (PK) of BI 655066 after a single dose.																											
Methodology:	A randomised, placebo-controlled within dose groups, double-blinded, single rising dose, and multicentre study. In Stage 1 (iv), 6 dose groups were enrolled sequentially in ascending order; in Stage 2 (sc), 2 dose groups were randomised in parallel. For both stages, dose level was known to investigators and patients. Sponsor trial and project teams were unblinded to Stage 2 treatment allocation.																											
No. of Patients:	<table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top;">Planned:</td> <td colspan="3">Entered: up to 38</td> </tr> <tr> <td></td> <td colspan="3">Stage 1 (iv): 4 patients per dose group (3 on BI 655066 and 1 on placebo)</td> </tr> <tr> <td></td> <td colspan="3">Stage 2 (sc): 7 patients per dose group (6 on BI 655066 and 1 on placebo)</td> </tr> <tr> <td style="vertical-align: top;">Actual:</td> <td colspan="3">Enrolled: 73</td> </tr> <tr> <td></td> <td colspan="3">Stage 1 (iv) BI 655066:</td> </tr> <tr> <td></td> <td>Entered: 18</td> <td>Treated: 18</td> <td>Analysed (for primary endpoint): 18</td> </tr> </table>				Planned:	Entered: up to 38				Stage 1 (iv): 4 patients per dose group (3 on BI 655066 and 1 on placebo)				Stage 2 (sc): 7 patients per dose group (6 on BI 655066 and 1 on placebo)			Actual:	Enrolled: 73				Stage 1 (iv) BI 655066:				Entered: 18	Treated: 18	Analysed (for primary endpoint): 18
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	Stage 1 (iv) BI 655066:																											
	Entered: 18	Treated: 18	Analysed (for primary endpoint): 18																									

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Actual (continued):	Stage 1 (iv) placebo: Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Stage 2 (sc) BI 655066: Entered: 13 Treated: 13 Analysed (for primary endpoint): 13 Stage 2 (sc) placebo: Entered: 2 Treated: 2 Analysed (for primary endpoint): 2			
Diagnosis:	Patients with chronic moderate to severe plaque psoriasis lasting ≥ 6 months with involvement of body surface area (BSA) $\geq 10\%$, psoriasis area and severity index (PASI) ≥ 12 , and static physician global assessment (sPGA) score of moderate and above.			
Main Criteria for Inclusion:	Patients had to be between 18 and 75 years old (inclusive) and had to have a body mass index (BMI) ≥ 18.5 and < 40 kg/m ² .			
BI Investigational Product 1:	BI 655066			
Dose:	0.01 mg/kg, 0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 3 mg/kg, and 5 mg/kg			
Mode of Admin.:	Intravenous (iv)			
Batch No.:	E1731F06			
BI Investigational Product 2:	BI 655066			
Dose:	0.25 mg/kg and 1 mg/kg			
Mode of Admin.:	Subcutaneous (sc)			
Batch No.:	E2744S02-1			
Comparator Product 1:	Placebo			
Dose:	Not applicable			
Mode of Admin.:	Intravenous (iv)			
Batch No.:	E1732F02			

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Comparator Product 2:	Placebo
Dose:	Not applicable
Mode of Admin.:	Subcutaneous (sc)
Batch No.:	E2746S01

Duration of Treatment:	A single administration followed by 24 weeks follow-up in Stage 1 (iv) and Stage 2 (sc) and an optional post-trial follow-up beyond 24 weeks for patients in Stage 2 (sc).
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Criteria for Evaluation:	<p>Efficacy / Clinical Pharmacology: The primary endpoints in this trial were safety endpoints and are described in the safety section below.</p> <p>Secondary endpoints of efficacy included the following clinical endpoints:</p> <ul style="list-style-type: none"> - psoriasis area and severity index (PASI) absolute score, percentage change from baseline and achievement of PASI₉₀ at Week 12 - PASI absolute score, percentage change from baseline and achievement of PASI₉₀ at Week 24 - static physician global assessment (sPGA) score and achievement of 1 or lower ('clear or almost clear') at Week 12 - sPGA score and achievement of 1 or lower ('clear or almost clear') at Week 24 <p>and the following pharmacokinetic parameters:</p> <ul style="list-style-type: none"> - maximum measured concentration (of analyte BI 655066) in plasma (C_{max}) - time from (last) dosing to the maximum measured concentration (of analyte BI 655066) in plasma (t_{max}) - area under the concentration-time curve (of analyte BI 655066) in plasma over the time interval from 0 extrapolated to infinity (AUC_{0-∞}) <p>Within the further endpoints (defined in the trial statistical analysis plan, revised) the follow-up of PASI90 during the 24 weeks follow-up and beyond was key for the evaluation of durability of clinical efficacy; the optional post-trial follow-up beyond 24 weeks for patients in Stage 2 (sc) was implemented by CTP amendment 7.</p>
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Safety:	<p>The primary endpoints were:</p> <ul style="list-style-type: none"> - number of patients with adverse events (AEs) - number of patients with significant changes from baseline laboratory measurements - number of patients with clinically relevant findings in vital signs - number of patients with clinically relevant findings in physical examination - number of patients with clinically significant abnormalities in electrocardiogram (ECG) results - number of patients with good and satisfactory assessment of global tolerability by investigator - number of patients without any symptoms at the drug administration site, as per local assessment of tolerability by investigator
Statistical Methods:	<p>Descriptive statistics for safety, efficacy, pharmacokinetic, and pharmacodynamic endpoints were calculated. Dose proportionality of BI 655066 was explored using a regression model. A 95% confidence interval for the slope was computed. Absolute bioavailability of the subcutaneous administration was estimated as the ratio of the geometric mean (gMean) of $AUC_{0-\infty}$ for the sc dose to that of the corresponding iv dose group.</p> <p>By clinical trial protocol (CTP) amendment 5, an unblinded interim analysis of PASI scores was added for project planning purposes for subsequent trials, after all patients in Stage 1 (iv) completed their 12 weeks follow-up visits. Investigators, patients, clinical research associates, and local clinical monitors remained blinded to treatment allocation and to the analysis results. There was no interim analysis performed on safety or other efficacy endpoints.</p> <p>By CTP amendment 6, an unblinded interim analysis of PASI scores, adverse events and local tolerability for all patients in Stage 2 (sc) was added for project planning purposes for subsequent trials. Investigators, patients, clinical research associates, and local clinical monitors remained blinded to treatment allocation and to the analysis results.</p>
SUMMARY - CONCLUSIONS:	

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Trial Patients and Compliance with Trial Protocol:	<p>A total of 73 patients were enrolled. Of these, 34 patients were not eligible for randomisation for various reasons. A total of 39 patients were entered, and all were treated (24 patients in Stage 1 [iv], and 15 patients in Stage 2 [sc]). All except 1 of these 39 patients completed the 24-week trial, 1 patient in Stage 1 discontinued early due to relocation. A total of 9 patients were followed-up beyond 24 weeks according to CTP amendment 7, and 5 of them completed this extended post-trial follow-up period.</p> <p>Key demographic data were as follows: For all 31 patients receiving BI 655066 (iv and sc) the median age was 45.0 years (minimum 24.0 years, maximum 61.0 years), 25 (80.6%) were male and all except 3 patients were White. For all 8 patients receiving placebo (iv and sc) the median age was 51.0 years (minimum 30.0 years, maximum 70.0 years), 6 (75%) were male and all were White. Considering the small numbers of patients treated in each iv and sc treatment group, there were no relevant differences in demographic and psoriasis characteristics at baseline.</p> <p>Each patient received a single dose of treatment. Treatment compliance was assured by administration of all trial medication under supervision of the investigator or a designee at the trial site. Important protocol violations (IPVs) were reported in the treated set for 6 (15.4%) of 39 patients in this trial. Patients' rights, safety and data integrity were considered being not compromised by these IPVs.</p>			
Efficacy / Clinical Pharmacology / Other Results:	<p><u>Clinical efficacy</u> <u>Psoriasis area and severity index (PASI)</u></p> <p>In Stage 1 (iv) and in Stage 2 (sc), improvements in PASI scores were observed as early as Week 2.</p> <p>In Stage 1 (iv), the median reduction in PASI score from baseline for 18 patients receiving BI 655066 was 92.6% at Week 12 (median PASI score 1.2) and 83.4% at Week 24 (median PASI score 2.5); for 6 patients receiving placebo, the median reduction in PASI score from baseline was 28.2% at Week 12 (median PASI score 12.3) and 18.3% at Week 24 (median PASI score 19.1). PASI₉₀ was met by 11 (61.1%) of 18 patients receiving BI 655066 at Week 12 and by 4 (23.5%) patients at Week 24. PASI₉₀ was met by none (0%) of 6 patients receiving placebo, neither at Week 12 nor at Week 24.</p> <p>In Stage 2 (sc), the median reduction in PASI score from baseline for 13 patients</p>			
Efficacy / Clinical	receiving BI 655066 was 90.6% at Week 12 (median PASI score 1.3) and 100%			

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Pharmacology / Other Results (continued):	<p>at Week 24 (median PASI score 0.0); for 2 patients receiving placebo only 1 patient was included in the analysis (i.e. no mean values available), the reduction in PASI score from baseline was 41.9% at Week 12 (PASI score 12.2) and 77.6% at Week 24 (PASI score 4.7). The PASI₉₀ response was achieved by 7 (53.8%) of 13 patients treated with BI 655066 at Week 12 and by 11 (84.6%) patients at Week 24. Neither (0%) of 2 patients treated with placebo met PASI₉₀ at Week 12 and Week 24.</p> <p>Durability of response measured by maintenance of PASI₉₀ in Stage 1 (iv) was reported for most BI 655066 doses up to Week 20. In Stage 2 (sc), PASI₉₀ was reported till the End-of-study Visit at Week 24. In the post-trial follow-up period, PASI₉₀ was reported up to 56 weeks for 1 patient treated with 0.25 mg/kg BI 655066 and up to 68 weeks for 1 patient treated with 1 mg/kg BI 655066.</p> <p><u>Static physician global assessment (sPGA)</u></p> <p>In Stage 1 (iv), 12 (66.7%) of 18 patients treated with BI 655066 had sPGA score 'moderate', 3 (16.7%) had 'marked', 2 (11.1%) had 'mild', and 1 (5.6%) patient had 'severe' at baseline. All 18 (100%) of 18 patients treated with BI 655066 shifted to a less severe sPGA score from baseline to Week 12. The majority, 14 (77.8%) of 18 patients shifted to 'clear' or 'almost clear', i.e. met the sPGA response 'clear or almost clear'. The 1 patient with 'severe' at baseline shifted to 'almost clear'. Two out of the 3 patients with 'marked' at baseline shifted to 'almost clear', and 1 shifted to 'mild'. Two (33.3%) of 6 patients treated with placebo shifted to a less severe sPGA score from baseline to Week 12, thereof 1 (16.7%) met the sPGA response 'clear or almost clear'. 2 (33.3%) patients treated with placebo showed no shift and 2 (33.3%) patients had data 'missing'.</p> <p>One patient discontinued after Week 12, this was taken into account for the total number of 17 patients analysed at Week 24. Eleven (64.7%) of 17 patients analysed receiving BI 655066 shifted to a less severe sPGA score from baseline to Week 24. Out of these 11 patients, 7 (63.6%) shifted to 'clear' or 'almost clear', i.e. met the sPGA response 'clear or almost clear'. The 1 patient with 'severe' at baseline had a sustained shift to 'almost clear' (as observed at Week 12). Two (33.3%) of 6 patients treated with placebo shifted to a less severe sPGA score from baseline to Week 24, but neither met the sPGA response 'clear or almost clear'. 1 (16.7%) patient treated with placebo showed no shift and 3 (50.0%) patients had data 'missing'.</p>
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Efficacy / Clinical Pharmacology / Other Results (continued):

In Stage 2 (sc), 9 (69.2%) of 13 patients treated with BI 655066 had sPGA score 'moderate', 2 (15.4%) had 'marked', 1 (7.7%) patient had 'mild', and 1 (7.7%) had 'severe'. At Week 12, all 13 (100%) patients treated with BI 655066 were reported with a shift in sPGA scores to 'clear' or 'almost clear', i.e. all patients met the sPGA response 'clear or almost clear'. The sPGA response observed at Week 12 was sustained until Week 24 by all patients treated with BI 655066. For the 2 patients treated with placebo, there was no shift observed and they did not achieve the sPGA response 'clear or almost clear', neither at Week 12 nor 24.

Pharmacokinetic

After iv infusion of BI 655066, plasma concentrations of BI 655066 decreased relatively rapidly. The gMean estimated half-life of BI 655066 after iv administration was 18 to 28 days. Increases in exposure were proportional with dose.

C_{max} , t_{max} , and $AUC_{0-\infty}$ were as follows:


Parameter	gMean (gCV%)		
	0.01 mg/kg N = 3	0.05 mg/kg N = 3	0.25 mg/kg N = 3
C_{max} [μ g/mL]	0.311 (8.76)	1.36 (27.7)	5.95 (10.6)
t_{max}^1 [day]	0.0833 (0.0674; 0.0833)	0.0430 (0.0417; 0.0833)	0.0938 (0.0833; 0.167)
$AUC_{0-\infty}$ [μ g·day/mL]	2.93 (24.7)	15.7 (55.6)	85.1 (14.1)
Parameter	gMean (gCV%)		
	1 mg/kg N = 3	3 mg/kg N = 3	5 mg/kg N = 3
C_{max} [μ g/mL]	12.3 (163)	66.2 (9.15)	110 (9.68)
t_{max}^1 [day]	0.0417 (0.0417; 0.167)	0.0833 (0.0417; 0.0833)	0.0833 (0.0417; 0.0833)
$AUC_{0-\infty}$ [μ g·day/mL]	167 (150)	952 (8.78)	1650 (24.1)

¹ median (min; max)

After sc injection of BI 655066, BI 655066 was absorbed slowly from the site of injection. The gMean estimated half-life of BI 655066 after sc administration was 22 to 28 days. Increases in exposure were proportional with dose.

C_{max} , t_{max} , and $AUC_{0-\infty}$ were as follows:


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Efficacy / Clinical Pharmacology / Other Results (continued):	Parameter	gMean (gCV%)	
		0.25 mg/kg	1 mg/kg
		N = 7	N = 6
	C_{max} [µg/mL]	0.960 (50.9)	5.73 (18.5)
	t_{max}^1 [day]	13.0 (2.00; 14.1)	5.00 (2.00; 10.0)
	$AUC_{0-\infty}$ [µg·day/mL]	41.6 (51.9)	219 (29.4)
¹ median (min; max) Positive anti-drug antibodies (ADA) results were detected in some of the predose samples and samples after intravenous administration of BI 655066. However, no ADA positive samples were detected after sc administration. It appeared that ADAs have the potential to influence the amount of BI 655066 detected in plasma. To further characterise positive ADA samples, a neutralising antibody (Nab) assay has been validated and will be used in future BI 655066 trials.			
<u>Biomarker</u> Treatment with BI 655066 resulted in significant changes over time in the molecular and protein profile observed in the skin and peripheral blood of patients with moderate to severe psoriasis as compared to placebo. These changes correlated with improvement in PASI scores at Week 12.			
Safety Results:	<u>Safety</u> <u>Adverse events</u> Treatment-emergent adverse events were reported for 20 (64.5%) of 31 patients treated with BI 655066 (iv and sc) and for 7 (87.5%) of 8 patients treated with placebo (iv and sc), and most AEs were of mild or moderate intensity. Most frequent AEs reported for patients receiving BI 655066 were headache in 3 (9.7%), nasopharyngitis in 2 (6.5%), and upper respiratory tract infection in 2 (6.5%) of 31 patients. The most frequent AE reported for patients receiving placebo was pruritus in 2 (25.0%) of 8 patients. With regard to the occurrence of AEs, there was neither a relevant difference between iv and sc administration nor evidence of dose-dependency of BI 655066. In total, 4 AEs were reported to be drug-related for 3 patients receiving BI 655066, consisting of a variety of individual AEs. All drug-related AEs were of mild and moderate intensity. AEs leading to treatment discontinuation were not applicable due to the single rising dose design; there were no AEs leading to trial discontinuation. Severe AEs were reported for 5 (16.1%) of 31 patients receiving BI 655066 (iv and sc) and for 3 (37.5%) of 8 patients receiving placebo (iv and sc). There were no deaths.		

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Safety Results (continued):	<p>Serious adverse events (SAEs) requiring hospitalisation were reported for 4 patients, all of them receiving BI 655066 (3 patients in Stage1 and 1 patient in Stage 2). None of the SAEs were assessed by the investigator to be drug-related.</p> <p><u>Clinical laboratory tests, vital signs, physical examination, and 12-lead ECG</u></p> <p>In clinical laboratory tests, measurements of vital signs, physical examination, and 12-lead ECG recordings, there were no treatment-related or dose-dependent findings observed.</p> <p>In Stage 1 (iv), 9 patients receiving BI 655066 and 1 patient receiving placebo were reported with clinically significant laboratory findings. In Stage 2 (sc), 9 patients receiving BI 655066 and 1 patient receiving placebo were reported with clinically significant laboratory findings. For the majority of these 20 patients in total, elevated values of total cholesterol and/or triglyceride were reported (9 patients in Stage 1 [iv] and 8 patients in Stage 2 [sc]). The review of individual patients' total cholesterol and triglyceride values showed no trends over time when comparing patients treated with placebo with those treated with BI 655066 nor any dose-related trend when evaluating data of patients treated with BI 655066.</p> <p>In Stage 1 (iv) and in Stage 2 (sc), there was no patient reported with any clinically relevant finding in the vital signs.</p> <p>In Stage 1 (iv) and in Stage 2 (sc), there were no clinically relevant ECG findings from baseline.</p> <p><u>Tolerability</u></p> <p>In Stage 1 (iv) the assessment of global tolerability by the investigator was 'good' for 18 (100%) patients receiving BI 655066 and 'good' or 'satisfactory' for 5 (83.3%) of 6 patients receiving placebo. In Stage 2 (sc) the global tolerability was assessed to be 'good' for all 13 (100%) patients receiving BI 655066 and for the 2 (100%) patients receiving placebo.</p> <p>The local tolerability of the intravenous trial drug administration was assessed to be well-tolerated for 18 patients receiving BI 655066 and for 6 patients receiving placebo. Occasional findings were reported for 3 patients in different BI 655066 treatment groups and at various times; 15 patients receiving BI 655066 were without any symptoms at the trial drug administration site.</p> <p>The local tolerability of the subcutaneous trial drug administration was assessed to be very well-tolerated. There was no finding for local tolerability, neither for the 13 patients receiving BI 655066 nor for the 2 patients receiving placebo.</p>
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Conclusions:	<p>Single doses of BI 655066 administered both intravenously and subcutaneously were assessed to be safe and well tolerated. BI 655066 showed a favourable clinical efficacy as early as Week 2 assessed by PASI, both administered iv and sc. PASI₉₀ response was mainly sustained up to Weeks 12 and 24. Additionally, the optional extended post-trial follow-up (implemented by CTP amendment 7) showed PASI₉₀ up to 68 weeks in 1 patient receiving 1 mg/kg BI 655066 sc. Assessments of sPGA were consistent with PASI. In Stage 2 (sc), all patients receiving BI 655066 achieved ‘clear or almost clear’ at both Weeks 12 and 24, compared with no patients receiving placebo.</p> <p>After iv and sc administration of BI 655066, the gMean estimated half-life of BI 655066 was 18 to 28 days. Increases in exposure were proportional with dose. The estimated bioavailability after sc administration was 73%.</p> <p>Treatment with BI 655066 resulted in significant changes over time in the molecular and protein profile observed in the skin and peripheral blood of patients with moderate to severe psoriasis as compared to placebo. These changes correlated with improvement in PASI scores at Week 12.</p>
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