Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-000687-22	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 APR 2014	**Trial No.** 1220.46 **Doc No.:** c01958457-02	**Dates of trial:** 09 JAN 2013 – 22 MAR 2013	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of BI 201335 (capsule) compared to three different oral solutions of BI 201335 following oral administration in healthy male and female volunteers (an open-label, randomised, single-dose, four-way crossover study)
Principal Investigator:	[redacted]
Trial site:	Department of Translational Medicine, Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published.
Clinical phase:	I
Objectives:	The primary objective was to investigate the relative bioavailability of 2 different doses of BI 201335 (faldaprevir) capsules vs. equivalent doses of 3 different oral solutions (OS) per dose. A secondary objective was to compare the confidence intervals (CIs) with the standard bioequivalence acceptance interval.
Methodology:	Randomised, open-label, four-way crossover design. A single dose of test or reference treatment was administered in each trial period and a washout period of at least 14 days separated each administration of trial medication.

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No. of subjects:

planned: entered: 56

actual: entered: 56 (20 subjects in the 40 mg dose group and 36 subjects in the 120 mg dose group)

Treatment A: 40 mg faldaprevir soft gelatine capsule (SGC)
treated: 20 analysed (for primary endpoint): 19

Treatment B: 40 mg faldaprevir oral solution 383 (OS1)
treated: 20 analysed (for primary endpoint): 19

Treatment C: 40 mg faldaprevir oral solution 412 (OS2)
treated: 20 analysed (for primary endpoint): 20

Treatment D: 40 mg faldaprevir oral solution 384 (OS3)
treated: 20 analysed (for primary endpoint): 18

Treatment E: 120 mg faldaprevir SGC
treated: 36 analysed (for primary endpoint): 35

Treatment F: 120 mg faldaprevir oral solution 383 (OS1)
treated: 36 analysed (for primary endpoint): 35

Treatment G: 120 mg faldaprevir oral solution 412 (OS2)
treated: 36 analysed (for primary endpoint): 36

Treatment H: 120 mg faldaprevir oral solution 384 (OS3)
treated: 36 analysed (for primary endpoint): 35

Diagnosis and main criteria for inclusion: Healthy male and female volunteers aged 18 to 55 years, with body mass index (BMI) from 18.5 to 29.9 kg/m^2.

Test products: Faldaprevir oral solution 383 (OS1, Treatments B, F)
Faldaprevir oral solution 412 (OS2, Treatments C, G)
Faldaprevir oral solution 384 (OS3, Treatments D, H)

dose: 40 mg (Treatments B, C, D)
120 mg (Treatments F, G, H)

mode of admin.: Oral (under fed conditions, i.e. following a high-fat breakfast)

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Test products (cont.):	
batch no.:	B121002859 (oral solution 383, OS1, Treatments B, F) B121002861 (oral solution 412, OS2, Treatments C, G) B121002860 (oral solution 384, OS3, Treatments D, H)
Reference therapy:	Faldaprevir SGC (Treatments A, E)
dose:	40 mg (1 capsule of 40 mg, Treatment A) 120 mg (3 capsules of 40 mg, Treatment E)
mode of admin.:	Oral (under fed conditions, i.e. following a high-fat breakfast)
batch no.:	B121003646
Duration of treatment:	Single dose of either test or reference product in each of 4 treatment periods separated by washout phases of at least 14 days between drug administrations
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints were $AUC_{0-\infty}$, C_{max}, and AUC_{0-tz} for faldaprevir. Other endpoints were t_{max}, CL/F, V_z/F, $t_{½}$, λ_z, and MRT_{po} as well as a palatability assessment of the oral solutions.
Safety:	Adverse events (AEs), clinical laboratory assessments, vital signs (blood pressure and pulse rate), and electrocardiograms (ECG)
Statistical methods:	To assess the relative bioavailability of the SGC vs. each of the 3 OS formulations, point estimates of the ratio of geometric means (gMeans) for treatments of $AUC_{0-\infty}$, C_{max}, and AUC_{0-tz} and their 2-sided 90% CIs were calculated. The statistical model used was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were based on the residual error from ANOVA. Descriptive statistics were calculated for all other parameters (further pharmacokinetic parameters, safety parameters, and palatability assessments).

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Of the 56 subjects who were entered in the trial and treated, 54 subjects (96.4%) completed the planned observation time. Two subjects (3.6%) withdrew from the trial due to an AE; they did not participate in trial periods D and E, respectively. Two subjects (3.6%) completed the trial after interrupting temporarily due to AEs; they did not participate in trial periods A and H, respectively. The study medication was not completely administered to 1 subject in trial period B; therefore, this period was excluded from PK evaluation for this subject. All other subjects received all planned doses of medication.

The treated set comprised 28 male (50.0%) and 28 female (50.0%) subjects. Fifty-five subjects were of White race and 1 was Black. The mean age of the 40 mg dose group was 40.9 years (SD 6.5, range 26 to 50 years) and mean BMI was 24.0 kg/m^2 (range 19.3 to 29.4 kg/m^2). The mean age of the 120 mg dose group was 36.6 years (SD 9.2, range 20 to 51 years) and mean BMI was 24.0 kg/m^2 (range 19.5 to 29.0 kg/m^2). No subject reported relevant medical history or baseline conditions.

For both 40 and 120 mg doses, gMean values for C_{max}, $AUC_{0-\infty}$ and AUC_{0-tz} (primary endpoints) were similar between the 3 OS formulations but were lower than the matching SGC formulation. Other pharmacokinetic parameters (t_{max} and $t_{1/2}$) were similar between OS and SGC formulations.

A supra-proportional increase in systemic exposure with faldaprevir was observed with the 120 mg dose when compared with the 40 mg dose, regardless of formulation.

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Clinical pharmacology results (cont.):

Summary (gMean±%gCV) of pharmacokinetic parameters of faldaprevir

Treatment	N	$AUC_{0-\infty}$ [ng·h/mL]	AUC_{0-tz} [ng·h/mL]	C_{max} [ng/mL]
OS1 40 mg	19	3400±28.5	2600±32.9	65.4±39.0
OS2 40 mg	20	3350±28.4	2520±38.3	64.0±40.4
OS3 40 mg	18	3420±30.4	2550±34.3	69.7±28.1
SGC 40 mg	19	3960±32.3	3020±29.4	86.4±36.0
OS1 120 mg	35	13 900±38.8	12 900±39.4	481±47.1
OS2 120 mg	36	14 500±38.3	13 400±38.0	488±52.1
OS3 120 mg	35	14 100±36.0	13 100±37.0	485±48.4
SGC 120 mg	35	15 000±34.5	14 200±35.2	625±47.3

OS = oral solution, SGC = soft gelatine capsule

Bioavailability of faldaprevir in each of the OS formulations (test treatments) was investigated relative to the SGC reference treatment. For both the 40 and 120 mg dose groups, there were no relevant differences in the primary endpoints of C_{max}, $AUC_{0-\infty}$, and AUC_{0-tz} when comparing the OS1, OS2, and OS3 formulations. The 40 mg OS formulations obtained approximately 70% of the SGC peak exposure (C_{max}) and approximately 80% of the SGC total exposure ($AUC_{0-\infty}$, AUC_{0-tz}). For all 3 parameters, the upper limit of the 90% CI was within the bioequivalence acceptance range of 80 to 125%; however, the lower limit of the 90% CI extended below the lower boundary.

The 120 mg OS formulations obtained approximately 70% of the SGC peak exposure (C_{max}) and approximately 90% of the SGC total exposure ($AUC_{0-\infty}$, AUC_{0-tz}). The 90% CIs for the calculated relative bioavailabilities determined from the adjusted gMean $AUC_{0-\infty}$ and adjusted gMean AUC_{0-tz} were contained in the standard bioequivalence acceptance interval (80 to 125%). The 90% CIs for the calculated relative bioavailability determined from the adjusted gMean C_{max} were not contained in standard bioequivalence acceptance interval.

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Safety results:	Overall, a total of 33 of 56 subjects (58.9%) reported treatment-emergent AEs during the trial. AEs which the investigator considered related to the trial medication were reported by 5 of 20 subjects (25%) in the 40 mg dose group and by 6 of 36 subjects (16.7%) in the 120 mg dose group. One subject in each dose group reported an AE that led to the discontinuation of the trial medication and was thus classified as an 'other significant AE' (according to ICH E3). The investigator did not consider these AEs to be drug-related. One subject (5%) in the 40 mg dose group and 4 subjects (11.1%) in the 120 mg dose group reported AEs of severe intensity. No subject reported significant AEs (pre-specified) in either dose group. There were no deaths or other serious AEs. Headache was the most frequently reported AE by preferred term. It was reported by 6 out of 20 subjects (30.0%) in the 40 mg dose group and by 10 out of 36 subjects (27.8%) in the 120 mg dose group. There were no clinically relevant findings in the clinical laboratory evaluation, 12-lead ECG, or vital signs. Comparing across treatment periods, there were no notable differences in AE frequency, AE intensity, or relationship of AEs to trial medication. An increase in AE frequency was not observed in the higher dose group. In both dose groups, most subjects rated the taste of all 3 oral solutions as 'acceptable' or better and most subjects would accept taking all 3 oral solutions for chronic use.
Conclusions:	Relative bioavailability of a single 40 mg dose of the OS formulations was reduced by approximately 20 to 30% when compared with the SGC. Similarly, the relative bioavailability of a single 120 mg dose of the OS formulations was reduced by approximately 10 to 20% when compared with the SGC. The relative bioavailability (90% CIs) of AUC exposures fell within the 80 to 125% range for each OS vs SGC when dosed at 120mg but fell below this range when dosed at 40 mg. Consideration may need to be given to adjusting the OS dose in order to achieve similar concentrations between OS and SGC. Administration of a single dose of either 40 or 120 mg faldaprevir was safe and well tolerated by the healthy subjects in this trial. All 3 oral solutions had acceptable or better palatability.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the trial synopsis. They complement patient disposition results, results for the primary endpoints of the trial, and safety data.

Results for	presented in
Patient Disposition	
40 mg Faldaprevir Group	Table 15.1.1: 1
120 mg Faldaprevir Group	Table 15.1.1: 2
Adjusted Geometric Mean and Statistical Analysis Compared with Soluble Gel Capsule (SGC) Reference: $AUC_{0-\infty}$ of Faldaprevir on Day 1	
40 mg Faldaprevir Group-	
OS1 40 mg	Table 15.5.1.1: 1
OS2 40 mg	Table 15.5.1.1: 3
OS3 40 mg	Table 15.5.1.1: 5
120 mg Faldaprevir Group-	
OS1 120 mg	Table 15.5.2.1: 1
OS2 120 mg	Table 15.5.2.1: 3
OS3 120 mg	Table 15.5.2.1: 5
Adjusted Geometric Mean and Statistical Analysis Compared with Soluble Gel Capsule (SGC) Reference: C_{max} of Faldaprevir on Day 1	
40 mg Faldaprevir Group-	
OS1 40 mg	Table 15.5.1.2: 1
OS2 40 mg	Table 15.5.1.2: 3
OS3 40 mg	Table 15.5.1.2: 5
120 mg Faldaprevir Group-	
OS1 120 mg	Table 15.5.2.2: 1
OS2 120 mg	Table 15.5.2.2: 3
OS3 120 mg	Table 15.5.2.2: 5

continued…

concluded…

Results for	**presented in**
Adjusted Geometric Mean and Statistical Analysis Compared with Soluble Gel Capsule (SGC) Reference: $AUC_{0\text{-}tz}$ of Faldaprevir on Day 1	
40 mg Faldaprevir Group-	
OS1 40 mg	Table 15.5.1.3: 1
OS2 40 mg	Table 15.5.1.3: 3
OS3 40 mg	Table 15.5.1.3: 5
120 mg Faldaprevir Group-	
OS1 120 mg	Table 15.5.2.3: 1
OS2 120 mg	Table 15.5.2.3: 3
OS3 120 mg	Table 15.5.2.3: 5
AE Summary	
40 mg Faldaprevir Group	Table 15.3.2: 1
120 mg Faldaprevir Group	Table 15.3.2: 2

Table 15.1.1: 1 Trial completion − 40 mg group − treated set

	ADBC N (%)	BACD N (%)	CBDA N (%)	DCAB N (%)	Total N (%)
Number of randomised subjects	5	5	5	5	20
Not treated	0	0	0	0	0
Number of treated subjects	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	20 (100.0)
Completed planned observation time	5 (100.0)	4 (80.0)	5 (100.0)	5 (100.0)	19 (95.0)
Not completed planned observation time	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.0)
Discontinued due to					
Adverse event	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.0)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow−up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn for further participation (not due to adverse event)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment: A = 40mg SGC, B = 40mg OS1, C = 40mg OS2, D = 40mg OS3

Source data: Appendix 16.2.1, Listing 1 s15\et_disp.sas 22MAY2013

Table 15.1.1: 2 Trial completion − 120 mg group − treated set

	EHFG N (%)	FEGH N (%)	GFHE N (%)	HGEF N (%)	Total N (%)
Number of randomised subjects	10	8	9	9	36
Not treated	0	0	0	0	0
Number of treated subjects	10 (100.0)	8 (100.0)	9 (100.0)	9 (100.0)	36 (100.0)
Completed planned observation time	10 (100.0)	8 (100.0)	8 (88.9)	9 (100.0)	35 (97.2)
Not completed planned observation time	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.8)
Discontinued due to					
Adverse event	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.8)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow−up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn for further participation (not due to adverse event)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment: E = 120mg SGC, F = 120mg OS1, G = 120mg OS2, H = 120mg OS3

Source data: Appendix 16.2.1, Listing 1 s15\et_disp.sas 22MAY2013

Table 15.5.1.1: 1 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS1 (T1) : 40mg SGC (R1), PK set
AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS1 (T1) N	40mg OS1 (T1) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS1 (T1) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
19	3330.265	19	4032.699	82.58	1.067	73.694	92.540	19.7	0.3157

Table 15.5.1.1: 3 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS2 (T2) : 40mg SGC (R1), PK set
AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS2 (T2) N	40mg OS2 (T2) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS2 (T2) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
20	3354.878	19	4025.580	83.34	1.073	73.651	94.302	22.2	0.2860

Table 15.5.1.1: 5 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS3 (T3) : 40mg SGC (R1), PK set
AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS3 (T3) N	40mg OS3 (T3) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS3 (T3) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
18	3386.694	19	4035.795	83.92	1.069	74.689	94.284	19.6	0.2411

Table 15.5.2.1: 1 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS1 (T4) : 120mg SGC (R2), PK set AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS1 (T4) N	120mg OS1 (T4) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS1 (T4) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	13986.05	35	15054.46	92.90	1.03	88.94	97.04	10.5	0.0000

Table 15.5.2.1: 3 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS2 (T5) : 120mg SGC (R2), PK set AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS2 (T5) N	120mg OS2 (T5) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS2 (T5) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
36	14485.32	35	15031.27	96.37	1.03	91.55	101.43	12.7	0.0000

Table 15.5.2.1: 5 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS3 (T6) : 120mg SGC (R2), PK set AUCinfpred [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS3 (T6) N	120mg OS3 (T6) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS3 (T6) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	14154.22	35	14987.07	94.44	1.03	89.88	99.24	12.0	0.0000

Table 15.5.1.2: 1 Adjusted by-treatment geometric means and relative bioavailability comparison 40mg OS1 (T1) : 40mg SGC (R1), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

40mg OS1 (T1) N	40mg OS1 (T1) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS1 (T1) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% – 125%
19	64.586	19	87.200	74.07	1.073	65.442	83.826	21.5	0.8538

Table 15.5.1.2: 3 Adjusted by-treatment geometric means and relative bioavailability comparison 40mg OS2 (T2) : 40mg SGC (R1), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

40mg OS2 (T2) N	40mg OS2 (T2) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS2 (T2) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% – 125%
20	64.037	19	87.447	73.23	1.087	63.325	84.683	26.2	0.8478

Table 15.5.1.2: 5 Adjusted by-treatment geometric means and relative bioavailability comparison 40mg OS3 (T3) : 40mg SGC (R1), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

40mg OS3 (T3) N	40mg OS3 (T3) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS3 (T3) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]		Intra-indiv. gCV [%]	p-value for ratio outside interval 80% – 125%
						[%]	[%]		
18	68.779	19	87.323	78.76	1.079	68.935	89.994	22.7	0.5798

Table 15.5.2.2: 1 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS1 (T4) : 120mg SGC (R2), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

120mg OS1 (T4) N	120mg OS1 (T4) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS1 (T4) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	488.240	35	623.560	78.30	1.056	71.420	85.840	22.5	0.6527

Table 15.5.2.2: 3 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS2 (T5) : 120mg SGC (R2), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

120mg OS2 (T5) N	120mg OS2 (T5) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS2 (T5) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
36	491.406	35	626.517	78.43	1.074	69.543	88.463	30.4	0.6086

Table 15.5.2.2: 5 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS3 (T6) : 120mg SGC (R2), PK set Cmax [ng/mL] for BI 201335 ZW (PLASMA)

120mg OS3 (T6) N	120mg OS3 (T6) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS3 (T6) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	489.843	35	627.269	78.09	1.073	69.348	87.937	29.4	0.6337

Table 15.5.1.3: 1 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS1 (T1) : 40mg SGC (R1), PK set
AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS1 (T1) N	40mg OS1 (T1) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS1 (T1) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
19	2552.970	19	3112.521	82.02	1.044	75.979	88.546	13.1	0.2875

Table 15.5.1.3: 3 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS2 (T2) : 40mg SGC (R1), PK set
AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS2 (T2)		40mg SGC (R1)		Ratio	gSE	90%		Intra-	p-value for ratio
N	gMean	N	gMean	40mg OS2 (T2) : 40mg SGC (R1) [%]		Confidence interval [%]	[%]	indiv. gCV [%]	outside interval 80% - 125%
20	2523.099	19	3117.496	80.93	1.048	74.582	87.826	14.5	0.4037

Table 15.5.1.3: 5 Adjusted by-treatment geometric means and relative bioavailability
comparison 40mg OS3 (T3) : 40mg SGC (R1), PK set
AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

40mg OS3 (T3) N	40mg OS3 (T3) gMean	40mg SGC (R1) N	40mg SGC (R1) gMean	Ratio 40mg OS3 (T3) : 40mg SGC (R1) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
18	2489.970	19	3128.004	79.60	1.035	74.839	84.669	10.2	0.5557

Table 15.5.2.3: 1 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS1 (T4) : 120mg SGC (R2), PK set AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS1 (T4) N	120mg OS1 (T4) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS1 (T4) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	13013.14	35	14207.61	91.59	1.03	87.53	95.84	11.0	0.0000

Table 15.5.2.3: 3 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS2 (T5) : 120mg SGC (R2), PK set AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS2 (T5) N	120mg OS2 (T5) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS2 (T5) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	90% Confidence interval [%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
36	13384.60	35	14181.46	94.38	1.03	89.76	99.24	12.4	0.0000

Table 15.5.2.3: 5 Adjusted by-treatment geometric means and relative bioavailability comparison 120mg OS3 (T6) : 120mg SGC (R2), PK set AUClast [ng*h/mL] for BI 201335 ZW (PLASMA)

120mg OS3 (T6) N	120mg OS3 (T6) gMean	120mg SGC (R2) N	120mg SGC (R2) gMean	Ratio 120mg OS3 (T6) : 120mg SGC (R2) [%]	gSE	90% Confidence interval [%]	[%]	Intra-indiv. gCV [%]	p-value for ratio outside interval 80% - 125%
35	13133.11	35	14134.69	92.91	1.03	88.42	97.63	12.0	0.0000

Table 15.3.2: 1 Adverse event overall summary − treated set

Dose group: 40 mg

	40mg SGC N (%)	40mg OS1 N (%)	40mg OS2 N (%)	40mg OS3 N (%)	On treatment N (%)
Number of subjects	19 (100.0)	20 (100.0)	20 (100.0)	19 (100.0)	20 (100.0)
Subjects with any AE	3 (15.8)	2 (10.0)	8 (40.0)	6 (31.6)	12 (60.0)
Subjects with severe AEs	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)
Subjects with investigator defined drug−related AEs	2 (10.5)	0 (0.0)	2 (10.0)	2 (10.5)	5 (25.0)
Subjects with other significant AEs (according to ICH E3)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)
Subjects with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)
Subjects with significant AEs (pre−specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life−threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

A subject may be counted in more than one seriousness criterion.
Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 15.1
AEs occurring up to date of end−of−study visit + 1 day were assigned to treatment

Table 15.3.2: 2 Adverse event overall summary − treated set

Dose group: 120 mg

	120mg SGC N (%)	120mg OS1 N (%)	120mg OS2 N (%)	120mg OS3 N (%)	On treatment N (%)
Number of subjects	35 (100.0)	36 (100.0)	36 (100.0)	35 (100.0)	36 (100.0)
Subjects with any AE	6 (17.1)	7 (19.4)	8 (22.2)	11 (31.4)	21 (58.3)
Subjects with severe AEs	2 (5.7)	1 (2.8)	0 (0.0)	1 (2.9)	4 (11.1)
Subjects with investigator defined drug−related AEs	1 (2.9)	2 (5.6)	3 (8.3)	3 (8.6)	6 (16.7)
Subjects with other significant AEs (according to ICH E3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.8)
Subjects with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.8)
Subjects with significant AEs (pre−specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life−threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

A subject may be counted in more than one seriousness criterion.
Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 15.1
AEs occurring up to date of end−of−study visit + 1 day were assigned to treatment