Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Faldepravir		**EudraCT No.:** 2009-012429-12	
Name of active ingredient: BI 201335		**Page:** 1 of 11	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 JUL 2013	**Trial No. / U No.:** 1220.9 / U13-1974-01	**Date of trial:** 18 JAN 2010 – 17 MAR 2010	**Date of revision:** Not applicable

Title of trial:	An open label fixed sequence Phase I study to investigate the effect of BI 201335 mediated UGT1A1 inhibition on the multiple oral dose pharmacokinetics of raltegravir (Isentress®) in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial sites:	[redacted] Germany [redacted]
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate the effect of UGT1A1 inhibition by single and multiple oral doses of BI 201335 on the single and multiple oral dose pharmacokinetics of raltegravir and to investigate safety and tolerability
Methodology:	Open label fixed-sequence intra-individual comparison in healthy male and female volunteers.
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 24 entered: 24 treated: 24 analysed (for primary endpoint): 24
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥ 21 and ≤ 50 years, BMI range: ≥ 18.5 and ≤ 29.9 kg/m^2

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Test product:	BI 201335 240 mg soft gelatine capsules Raltegravir (Isentress®) 400 mg film covered tablet
dose:	BI 201335: 480 mg loading dose, followed by 240 mg on day 6 (4-0-2) 240 mg b.i.d. on days 7 to 14 (2-0-2) 240 mg q.d. on day 15 (2-0-0) Raltegravir: 400 mg b.i.d. on day 1 to day 14 (1-0-1) 400 mg q.d. on day 15 (1-0-0)
mode of admin.:	Oral administration with 240 mL water
batch no.:	BI 201335: 08JM-214 Raltegravir: NK14080
Reference therapy:	Not applicable
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	BI 201335: 10 days for each subject Raltegravir: 15 days for each subject

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Criteria for evaluation:

Efficacy / pharmacokintic:	Primary endpoints: • Raltegravir pharmacokinetic parameters: C_{max} and $AUC_{0-\infty}$ Secondary endpoints: • Raltegravir pharmacokinetic parameters: AUC_{0-tz}, t_{max}, λz, $t_{1/2}$, MRT_{po}, CL/F, V_z/F
Safety:	Physical examination, vital signs (BP and PR), 12-lead ECG, laboratory tests, adverse events, assessment of tolerability by investigator
Statistical methods:	For the primary analyses, point estimators (geometric means) of the median intrasubject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% confidence intervals (CIs) were derived. For the secondary analyses, descriptive statistics and tabular and graphical displays were used to summarize and evaluate the secondary endpoints.

SUMMARY – CONCLUSIONS:

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Clinical pharmacology results:

The bioanalytical work at the Lab21 site in Cambridge, UK, including method validation and sample analysis, for the analytes raltegravir and raltegravir glucuronide were audited by the sponsor). At the conclusion of the audit it was determined that the data were not reportable as GCP compliant due to a number of compliance and documentation issues found in the validation and sample reports.

BI 201335:

The noncompartmental pharmacokinetics of BI 201335 in plasma after 3 and 19 doses of BI 201335 240 mg (study days 7 and 15, respectively) are summarized in the following table. Steady-state plasma BI 201335 concentrations appear to be achieved after 7-9 days of dosing

Study Day		C_{max} [ng/mL]	AUC_{0-12} [ng·h/mL]	C_{12} [ng/mL]	t_{max} [h]
7	N	24	24	24	24
	gMean	15700	135000	8210	3.10
	gCV [%]	34.3	35.7	45.0	38.9
	Mean	16600	144000	8970	3.30
	CV [%]	39.8	39.3	46.7	32.1
	SD	6610	56500	4190	1.06
	Min	8440	60000	2740	1.33
	Median	15600	136000	8510	3.03
	Max	40400	346000	23900	5.02
		$C_{max,ss}$ [ng/mL]	$AUC_{0-12,ss}$ [ng·h/mL]	$C_{12,ss}$ [ng/mL]	$t_{max,ss}$ [h]
15	N	23	23	23	23
	gMean	32800	322000	22300	2.78
	gCV [%]	35.2	38.9	46.0	33.9
	Mean	34500	341000	24100	2.92
	CV [%]	30.7	31.3	33.9	29.2
	SD	10600	107000	8140	0.852
	Min	11200	96100	5230	1.47
	Median	34000	357000	26100	2.98
	Max	64500	600000	41200	4.10

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Raltegravir

After 3 doses of BI 201335 NA (480 mg loading dose, then 240 mg q12h), steady-state raltegravir geometric mean $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 49%, 59% and 113%, respectively, relative to raltegravir alone; arithmetic mean half-life was unchanged (2.50 h vs. 2.45 h). With continued dosing of BI 201335 NA to steady-state, raltegravir geometric mean $C_{max,ss}$ was now unchanged, and $AUC_{0-12,ss}$ and $C_{12,ss}$ increased 19% and 56%, respectively, relative to raltegravir alone; arithmetic mean half-life increased approximately 39% (3.40 h vs. 2.45 h).

	$C_{max,ss}$ [nmol/L]	$AUC_{0-12,ss}$ [µmol·h/L]	$C_{12,ss}$ [nmol/L]	$t_{max,ss}$ [h]	$t_{1/2,ss}$ [h]	$CL/F_{,ss}$ [L/h]	$Vz/F_{,ss}$ [L]
Day 5 (raltegravir 400 mg alone)							
N	24	24	24	24	24	24	24
gMean	2100	7.62	92.5	3.82	2.16	118	367
gCV [%]	88.6	74.9	178	70.0	55.0	74.9	134
Mean	2820	9.39	200	4.43	2.45	145	559
CV [%]	85.6	66.0	170	48.4	53.5	63.1	85.8
SD	2420	6.19	340	2.15	1.31	91.2	480
Min	685	2.64	18.2	0.517	0.885	36.7	58.1
Median	1860	7.55	72.0	5.00	2.06	119	397
Max	9510	24.5	1640	10.0	5.90	341	1770
Day 7 (raltegravir 400 mg after 3 doses of BI 201335 NA)							
N	24	24	24	24	24	24	24
gMean	3120	12.1	197	4.51	2.16	74.6	232
gCV [%]	123	104	172	43.1	57.8	104	185
Mean	4860	16.2	387	4.90	2.50	107	477
CV [%]	103	68.9	146	44.7	60.4	91.2	130
SD	5030	11.2	566	2.19	1.51	97.8	619
Min	642	2.67	28.0	2.02	1.01	21.1	39.6
Median	3140	14.1	240	4.91	2.22	63.6	232
Max	21000	42.7	2690	11.9	6.04	337	1980

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Day 15 (raltegravir 400 mg with steady-state BI 201335 NA)

N	23	23	23	23	23	23	23
gMean	2110	9.05	144	3.70	2.72	99.4	390
gCV [%]	73.5	70.7	117	52.8	66.5	70.7	139
Mean	2680	11.1	242	4.15	3.40	119	614
CV [%]	86.8	71.3	141	49.9	94.7	59.4	99.8
SD	2330	7.91	342	2.07	3.22	70.6	613
Min	741	2.96	35.9	1.50	1.36	30.0	60.3
Median	1800	8.87	96.6	4.05	2.29	101	491
Max	11000	30.0	1530	9.98	16.7	304	2790

Raltegravir-glucuronide

After 3 doses of BI 201335 NA (480 mg loading dose, then 240 mg q12h), steady-state raltegravir-glucuronide geometric mean $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 18%, 45% and 209%, respectively, relative to raltegravir alone; arithmetic mean half-life was increased approximately 59% (3.59 h vs. 2.26 h). Relative to raltegravir alone, the geometric mean metabolite-to-parent ratios (raltegravir-glucuronide: raltegravir) for $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ at steady-state decreased approximately 20% and 8%, and increased approximately 44%, respectively.

With continued dosing of BI 201335 NA to steady-state, raltegravir-glucuronide geometric mean $C_{max,s}$s was now unchanged (2% increase), and $AUC_{0-12,ss}$ and $C_{12,ss}$ increased 41% and 138%, respectively, relative to raltegravir alone; arithmetic mean half-life was increased approximately 46% (3.31 h vs. 2.26 h). Relative to raltegravir alone, the geometric mean metabolite-to-parent ratios (raltegravir-glucuronide: raltegravir) for $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ at steady-state was now unchanged (2% increase), and increased 18% and 52%, respectively.

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	$C_{max,ss}$ [nmol/L]	$AUC_{0-12,ss}$ [µmol·h/L]	$C_{12,ss}$ [nmol/L]	$t_{max,ss}$ [h]	$t_{1/2,ss}$ [h]	Ratio $C_{12,ss,M/P}$	Ratio $C_{max,ss,M/P}$	Ratio $AUC_{\tau,ss,M/P}$
Day 5 (raltegravir 400 mg alone)								
N	24	24	24	24	24	24	24	24
gMean	1250	5.58	95.8	4.89	1.94	1.04	0.593	0.731
gCV [%]	64.8	61.0	212	48.0	49.1	50.3	38.4	32.0
Mean	1490	6.51	206	5.35	2.26	1.16	0.634	0.765
CV [%]	65.3	60.4	123	39.9	86.0	52.9	38.7	30.4
SD	971	3.93	253	2.13	1.94	0.613	0.245	0.233
Min	429	2.07	10.1	2.00	1.10	0.383	0.301	0.370
Median	1170	5.60	82.8	5.98	1.83	1.06	0.593	0.727
Max	4090	16.9	869	10.0	11.0	3.31	1.37	1.30
Day 7 (raltegravir 400 mg after 3 doses of BI 201335 NA)								
N	24	24	24	24	24	24	24	24
gMean	1480	8.09	296	---	3.09	1.50	0.473	0.670
gCV [%]	78.3	74.9	154	---	54.4	40.3	50.1	32.3
Mean	1820	9.78	487	5.51	3.59	1.61	0.527	0.704
CV [%]	61.1	57.1	91.9	53.9	70.1	35.8	50.5	33.4
SD	1110	5.59	448	2.97	2.52	0.576	0.266	0.235
Min	443	2.41	56.8	0	1.73	0.627	0.193	0.367
Median	1540	10.3	320	5.43	2.62	1.59	0.466	0.651
Max	4060	20.1	1690	11.9	12.1	2.87	1.19	1.33
Day 15 (raltegravir 400 mg with steady-state BI 201335 NA)								
N	23	23	23	23	23	23	23	23
gMean	1270	7.84	228	---	3.05	1.58	0.602	0.866
gCV [%]	62.4	57.2	103	---	40.7	43.1	28.4	24.7
Mean	1510	8.99	344	3.91	3.31	1.70	0.624	0.890
CV [%]	68.0	55.4	115	69.5	47.1	39.5	26.5	23.1
SD	1030	4.98	396	2.72	1.56	0.674	0.165	0.206
Min	488	2.86	84.2	0	1.62	0.716	0.304	0.526
Median	1160	7.24	173	3.97	3.12	1.54	0.640	0.920
Max	4950	22.0	1530	8.03	8.20	2.82	0.962	1.21

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Effect of UGT1A1 genotype and BI 201335 on raltegravir

For subjects with wild type UGT1A1 genotype (N=4), steady-state raltegravir $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 27%, 38% and 14% relative to raltegravir alone, respectively, when co-administered with BI 201335 NA on day 7 (3rd dose of BI 201335). When co-administered with steady-state BI 201335 NA on day 15, $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 48%, 79% and 80% relative to raltegravir alone, respectively.

For subjects with possibly reduced UGT1A1 activity (N=14), steady-state raltegravir $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 58%, 64% and 145% relative to raltegravir alone, respectively, when co-administered with BI 201335 NA on day 7 (3rd dose of BI 201335). When co-administered with steady-state BI 201335 NA on day 15, raltegravir $C_{max,ss}$ decreased 12%, $AUC_{0-12,ss}$ was unchanged (3% increase) and $C_{12,ss}$ increased 41%, relative to raltegravir alone.

For subjects with reduced UGT1A1 activity (N=6), steady-state raltegravir $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{12,ss}$ increased approximately 43%, 61% and 134% relative to raltegravir alone, respectively, when co-administered with BI 201335 NA on day 7 (3rd dose of BI 201335). When co-administered with steady-state BI 201335 NA on day 15, $C_{max,ss}$ was unchanged (3% increase), and $AUC_{0-12,ss}$ and $C_{12,ss}$ increased 24% and 75%, respectively, relative to raltegravir alone.

Effect of BI 201335 NA on raltegravir pharmacokinetics

With the third dose of BI 201335 (Day 7), raltegravir $AUC_{0–12,ss}$, $C_{max,ss}$, and $C_{12,ss}$ increased 58%, 48% and 113%, respectively. After 19 doses of BI 201335 (Day15), raltegravir $AUC_{0–12,ss}$, and $C_{12,ss}$ increased 19% and 56%, respectively, with no change in $C_{max,ss}$.

Summary of geometric mean ratios and 90% CIs for raltegravir and raltegravir glucuronide for raltegravir 400 mg coadministered with BI 201335 240 mg

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	N	gMean	N	gMean	Ratio[a] (%)	90% CI
Raltegravir	Day 7		Day 5			
$AUC_{0-12,ss}$ [µmol·h/L]	24	12.1	24	7.62	158	127, 197
$C_{max,ss}$ [nmol/L]	24	3123	24	2104	148	116, 190
$C_{12,ss}$ [nmol/L]	24	197	24	92.5	213	137, 332
	Day 15		Day 5			
$AUC_{0-12,ss}$ [µmol·h/L]	23	9.05	24	7.62	119	92.5, 152
$C_{max,ss}$ [nmol/L]	23	2105	24	2104	100	75.6, 132
$C_{12,ss}$ [nmol/L]	23	144	24	92.5	156	98.7, 245
Raltegravir glucuronide	Day 7		Day 5			
$AUC_{0-12,ss}$ [µmol·h/L]	24	8.09	24	5.58	145	118, 179
$C_{max,ss}$ [nmol/L]	24	1476	24	1249	118	95.7, 146
$C_{12,ss}$ [nmol/L]	24	296	24	95.8	309	202, 473
	Day 15		Day 5			
$AUC_{0-12,ss}$ [µmol·h/L]	23	7.89	24	5.58	141	115, 174
$C_{max,ss}$ [nmol/L]	23	1276	24	1249	102	83.4, 125
$C_{12,ss}$ [nmol/L]	23	227	24	95.8	237	148, 380

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Safety results:

During the treatment phase with raltegravir alone, 8 (33.8%) out of 24 subjects reported any AE, and a total of 21 (87.5%) subjects reported any AE during the treatment with raltegravir and BI 201335.

The system organ classes (SOC) most affected were the SOC nervous system disorders during the treatment phase of dosing with raltegravir alone, and the SOCs gastrointestinal disorders, eye disorders (including ocular icterus) and nervous system disorders during raltegravir + BI 201335 NA dosing.

The majority of AEs were nausea, reported by 16 (66.7%) subjects, ocular icterus reported by 11 (45.8%) subjects, headache reported by 10 (42.7%) subjects, fatigue reported by 8 (33.3%) subjects, dizziness, reported by 5 (20.8%) subjects, and ocular hyperaemia by 5 (20.8%) subjects.

Vital signs did not show any relevant changes during the observation period.

Consistent with previous observations, total bilirubin values increased in all subject during the combination treatment period. This increase was caused primarily by increases in the indirect bilirubin fraction as a result of inhibition of UGT1A1 by BI 201335, this is evident from that the ratio direct to total bilirubin was never above 0.4 for all subjects.

There were 2 subjects showing ALT values >3 ULN, one also with total bilirubin values >2x ULN based on increased indirect bilirubin, during the treatment phase. In addition, 2 subjects showed ALT values >2x ULN on Day 16. All subjects were followed up until the values for ALT and bilirubin values reached again the normal ranges. For further several subjects, liver enzymes were above normal during the period of combined treatment but not above >2x ULN.

For none of the subjects the criteria for Hy's law were met.

Overall tolerability was assessed as satisfactory for the majority of the subjects. For 2 subjects, the overall tolerability was assessed as not satisfactory because of ongoing mild/moderate headaches of long duration throughout the treatment period and due to moderate dizziness, nausea and fatigue during a long duration throughout the treatment period, respectively.

One subject discontinued the treatment period on Day13 after the evening dose due to ongoing moderate headache for several days.

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Conclusions:

Bioanalysis

The bioanalytical work at the Lab21 site in Cambridge, UK, including method validation and sample analysis, for the analytes raltegravir and raltegravir glucuronide were audited by personnel from DMPK, BIPI and QA, BI-GB-B (May 22-24, 2012). At the conclusion of the audit it was determined that the data were not reportable as GCP compliant due to a number of compliance and documentation issues found in the validation and sample reports.

Clinical pharmacology conclusion

BI 201335 appears to affect raltegravir pharmacokinetics in a time-dependent manner. With 3 doses of BI 201335 (480 mg loading dose, then two 240 mg doses at 12 h intervals), raltegravir $AUC_{0-12,ss}$, $C_{max,ss}$, and $C_{12,ss}$ were increased relative to raltegravir alone (geometric mean ratio (90% CI): $AUC_{0-12,ss}$:1.58 (1.27, 1.97), $C_{max,ss}$: 1.48 (1.16, 1.90), $C_{12,ss}$: 2.13 (1.37, 3.32)). However, with steady-state BI 201335, the changes in raltegravir $AUC_{0-12,ss}$, $C_{max,ss}$, and $C_{12,ss}$ were not as large (geometric mean ratio (90% CI): $AUC_{0-12,ss}$:1.19 (0.93, 1.52), $C_{max,ss}$: 1.00 (0.76, 1.32), $C_{12,ss}$: 1.56 (0.99, 2.45)).

The effect of BI 201335 NA on the activity of UGT1A1 using raltegravir as the probe drug substrate, and measuring the effect on raltegravir glucuronide pharmacokinetics, is inconclusive due to the high variability associated with raltegravir values. With both short-term and steady-state dosing of BI 201335, raltegravir glucuronide $AUC_{0-12,ss}$ increased about 40% with similar variability (geometric mean ratio (90% CI); 3 doses of BI 201335: 1.45 (1.18, 1.79); steady-state BI 201335: 1.41 (1.15, 1.74)).

Safety

Overall global tolerability was assessed as satisfactory.