2. Synopsis

Date of report:	14 Dec 2018
Study title:	Single center, open-label, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics after single administration of 200 mg [^{14}C]rogaratinib (oral solution) in healthy male subjects
Sponsor's study number:	BAY 1163877 / 18084
NCT number:	03484585
EudraCT number:	2017-002777-19
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany
Clinical phase:	1
Study objectives:	Primary objectives of the study were • to determine the mass balance and routes of excretion of total radioactivity after a single oral 200 mg dose of [^{14}C]rogaratinib given as a solution • to quantify rogaratinib concentrations in plasma • to quantify total radioactivity in whole blood and plasma Secondary objectives were not applicable in this study. Other objectives of this study were • to provide plasma and excreta samples for further metabolite profiling and chemical structure identification (to be reported separately) • to provide additional information on the safety and tolerability of a single oral dose of 200 mg rogaratinib
Test drug:	BAY 1163877
Name of active ingredient(s):	Rogaratinib (BAY 1163877)
Dose:	Approx. 177 mg rogaratinib containing approx. 3.7 MBq (100 µCi) of [^{14}C]BAY 1163877
Route of administration:	Oral solution
Duration of treatment:	Single dose
Reference drug:	Not applicable

Indication:	Not applicable in this study in healthy male subjects
Diagnosis and main criteria for inclusion:	Healthy male subjects aged 21 to 65 years with a body mass index (BMI) between18.5 and 32.0 kg/m^2 (both inclusive) and a total body weight of 55 to 100 kg (both inclusive) who agree to use adequate contraception during the study and in the 3 months following dosing
Study design:	Single center, open-label, single dose study
Methodology	Subjects received a single oral dose of [^{14}C]rogaratinib followed by: • feces and urine collection up to a planned maximum of 14 days post-dose in the clinical unit for mass balance evaluation and metabolite profiling • whole blood and plasma collection up to a planned maximum of 14 days post-dose for pharmacokinetic evaluation of radioactivity and rogaratinib Safety and tolerability evaluation: Occurrence of treatment-emergent adverse events, incidence of abnormal findings in vital signs, electrocardiogram, safety laboratory parameters and ophthalmologic examinations
Investigator:	Dr. Jan Jaap van Lier, MD PRA, Groningen, The Netherlands
Study center(s)/countries:	One study center in The Netherlands
Publication(s) based on the study (references):	None at the time of report finalization
Study period:	First subject, first visit: 06 Apr 2018 Last subject, last visit: 25 May 2018 Clean database: 09 Aug 2018
Early termination	No
Number of subjects:	Planned: 6 Actual (assigned to treatment): 6

Criteria for evaluation	
Pharmacokinetics:	Main parameters: • % of rogaratinib-associated radioactivity excreted into urine and feces: $A_{E,ur}$ (%), $A_{E,fec}$ (%) • C_{max}, AUC(0-t_{last}) and AUC of rogaratinib in plasma and of total radioactivity in blood and plasma Additional parameters: • t_{max}, $t_{1/2}$ of rogaratinib in plasma
Safety:	Adverse events, vital signs, ECG, safety laboratory parameters, ophthalmologic examination
Statistical methods:	In this exploratory study, all data were analyzed by descriptive statistics and graphical display, as appropriate. The main pharmacokinetic characteristics of rogaratinib in plasma and of total radioactivity in whole blood and plasma were summarized by geometric and arithmetic statistics. Arithmetic summary statistics were provided for the amount (%) of total radioactivity excreted into urine and feces. The amount (%) of total radioactivity excreted into urine and feces was graphically illustrated for each sampling interval, as well as for the whole sampling period (bar-charts for the individual data and for the arithmetic means including standard deviation).
Substantial protocol changes:	The study was conducted according to clinical study protocol version 1.0 dated 01 Mar 2018 and the following amendment: **Amendment no. 01** forming integrated protocol version 2.0, dated 26 Mar 2018 implemented the following changes: • Addition of exclusion criteria • More detailed definition of ophthalmologic examinations

Study subjects

Nineteen healthy male subjects were enrolled and screened at one center. Of them, 6 subjects successfully completed screening and were assigned to treatment. All of them received study medication and completed the study without any major validity findings.

All 6 subjects who received study medication were valid for safety and pharmacokinetic evaluation.

The 6 subjects included in the study were of an average age of 36.3 years (range: 22 to 60 years). All subjects were male and white. Their mean weight and height were 82.5 kg (range: 71.3 to 95.5 kg) and 184 cm (range: 177 to 189 cm), respectively. The mean BMI was 24.4 kg/m^2 (range: 22.5 to 26.7 kg/m^2).

Overall, subjects participating in this study were healthy according to their medical history records and physical examination.

Pharmacokinetic evaluation

The primary objective of this study was to measure the cumulative amount and time course of drug-related, radioactive-labeled material excreted in urine and feces. Other objectives were to quantify rogaratinib concentrations in plasma and total radioactivity in whole blood and plasma.

Radiochromatographic analysis including metabolite identification will be reported under separate cover.

Pharmacokinetic parameters of rogaratinib in plasma and of radioactivity in plasma and whole blood are summarized in Table 2–1.

Following administration of an oral dose of approximately 177 mg [^{14}C]rogaratinib given as solution, the compound was rapidly absorbed with geometric mean maximum plasma concentrations of 4960 µg/L observed between 0.50 and 1.00 h post dose. Subsequently, plasma concentrations declined in an essentially monophasic manner with a half-life of about 6 hours. In contrast, concentration profiles of radioactivity in plasma declined with a longer half-life of about 81 hours suggesting the presence of longer-lasting circulating metabolites. This is also supported by higher maximum plasma concentrations and overall exposure observed for radioactivity as compared to rogaratinib.

Based on geometric mean values, the blood to plasma ratio of total radioactivity is 0.450 for AUC and 0.463 for AUC(0-t_{last}) indicating that radioactivity is mainly distributed in plasma.

PK parameters of [^{14}C]rogaratinib associated radioactivity in urine and feces are shown in Table 2–2 and Table 2–3.

After a single oral dose of approximately 177 mg rogaratinib labelled with 3.7 MBq [^{14}C]rogaratinib, associated mean total radioactivity recovered in urine and feces within 7 days was 93%, with 83% of radioactivity excreted in feces, and 10% of radioactivity excreted in urine. Most of the fecal and urinary recovery was seen within the first two days after dosing, i.e. 60.0% and 9.28%, respectively.

Table 2–1: Pharmacokinetic parameters of rogaratinib in plasma and of radioactivity in plasma and blood following a single oral dose of approximately 177 mg [^{14}C]rogaratinib (PKS, N=6)

	Parameter	Unit	n	$Mean_{geo}$/%CV	Range
Rogaratinib in plasma	AUC	µg·h/L	6	16900 / 18.7	13500 - 20500
	AUC(0-t_{last})	µg·h/L	6	16900 / 18.7	13500 - 20500
	C_{max}	µg/L	6	4960 / 15.3	4400 - 6590
	t_{max}[a]	h	6	0.508	0.500 - 1.00
	$t_{1/2}$	h	6	5.98 / 38.1	3.61 - 10.8
Radioactivity in plasma	AUC	µg-Eq·h/L	6	39600 / 13.7	33800 - 48700
	AUC(0-t_{last})	µg-Eq·h/L	6	36600 / 13.2	32400 - 44800
	C_{max}	µg-Eq/L	6	6930 / 12.3	5830 - 8280
Radioactivity in blood	AUC	µg-Eq·h/L	6	17900 / 14.3	15000 - 21200
	AUC(0-t_{last})	µg-Eq·h/L	6	17000 / 14.8	14200 - 20300
	C_{max}	µg-Eq/L	6	3620 / 15.7	2910 - 4560
Blood:plasma ratio	AUC	µg-Eq·h/L	6	0.450 / 11.6	0.381 - 0.516
	AUC(0-t_{last})	µg-Eq·h/L	6	0.463 / 8.08	0.429 - 0.519

[a] Median

Table 2–2: Pharmacokinetic parameters of [^{14}C]rogaratinib associated radioactivity in urine (PKS, N=6)

Parameter	Unit	N	$Mean_{ar}$	%CV	Min	Max
$A_{E,ur}$(0-12)	%	6	8.14	14.9	6.58	10.0
$A_{E,ur}$(0-24)	%	6	8.92	15.0	7.47	11.2
$A_{E,ur}$(0-48)	%	6	9.28	15.0	7.83	11.7
$A_{E,ur}$(0-72)	%	6	9.39	14.9	7.87	11.8
$A_{E,ur}$(0-96)	%	6	9.44	14.7	7.89	11.8
$A_{E,ur}$(0-120)	%	6	9.46	14.7	7.89	11.9
$A_{E,ur}$(0-144)	%	6	9.48	14.7	7.89	11.9
$A_{E,ur}$(0-168)	%	6	9.49	14.7	7.89	11.9
$A_{E,ur}$(0-192)	%	2	N.C.	N.C.	7.89	8.37
$A_{E,ur}$(0-216)	%	1	N.C.	N.C.	8.37	8.37
$A_{E,ur}$(0-240)	%	1	N.C.	N.C.	8.37	8.37

N.C. not calculated

Table 2–3: Pharmacokinetic parameters of [^{14}C]rogaratinib associated radioactivity in feces (PKS, N=6)

Parameter	Unit	N	Mean$_{ar}$	%CV	Min	Max
$A_{E,fec}$(0-24)	%	6	14.7	172	0.00	63.6
$A_{E,fec}$(0-48)	%	6	60.0	51.4	0.0919	84.7
$A_{E,fec}$(0-72)	%	6	71.6	26.8	33.1	85.3
$A_{E,fec}$(0-96)	%	6	76.5	19.8	46.0	85.6
$A_{E,fec}$(0-120)	%	6	77.2	19.9	46.0	85.7
$A_{E,fec}$(0-144)	%	6	82.2	4.58	75.3	85.8
$A_{E,fec}$(0-168)	%	6	83.2	2.45	80.8	85.9
$A_{E,fec}$(0-192)	%	2	N.C.	N.C.	83.6	85.6
$A_{E,fec}$(0-216)	%	1	N.C.	N.C.	83.9	83.9
$A_{E,fec}$(0-240)	%	1	N.C.	N.C.	84.0	84.0

N.C. not calculated

Safety evaluation

No fatal TEAEs or SAEs were reported in this study and none of the subjects discontinued study participation prematurely due to an AE.

One subject (16.7%) experienced hemorrhoids bleeding and gingivitis, another subject (16.7%) headache and enlarged neck lymph node. All events were of mild intensity, assessed as not related to the study medication and had fully recovered by the end of the study without medical intervention.

Safety laboratory measurements revealed no relevant changes of medical concern after administration of the study drug.

The overall pattern of vital signs, ECG and ophthalmologic parameters did not indicate clinically relevant changes after administration of the study drug.

Overall, a single oral dose of approximately 177 mg [^{14}C]rogaratinib as applied in the present study was safe and well tolerated and no new safety risks were identified.

Overall conclusions

- After a single oral dose of approximately 177 mg of rogaratinib labelled with 3.7 MBq [^{14}C]rogaratinib, associated mean total radioactivity recovered in urine and feces was 93% of administered dose, with about 83% of radioactivity excreted in feces and about 10% of radioactivity excreted in urine.
- Based on geometric mean AUC and AUC(0-t_{last}), the blood to plasma ratio of total radioactivity was 0.450 and 0.463, respectively, indicating that [^{14}C]rogaratinib associated radioactivity is mainly distributed in plasma.
- A single oral dose of approximately 177 mg rogaratinib administered as oral solution was safe and well tolerated by healthy male subjects.