Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report	21-APR-2020
Study title	Open label, partially randomized, cross-over study to determine the absolute bioavailability and pharmacokinetics of BAY 1817080 using a simultaneous anticipated therapeutic oral dose along with an i.v. [$^{13}C_7{}^{15}N$]-labeled microtracer and to investigate the relative bioavailability of two formulations given under different diets at 2 dose levels in healthy volunteers
Sponsor	Bayer
Sponsor's study ID	19519
NCT number	NCT03773068
EudraCT number	2018-001814-13
Study Phase	1
Indication	Not applicable in this study with healthy subjects. Envisaged indications: endometriosis and refractory chronic cough
Study objectives	Primary objectives: • To determine the absolute bioavailability and pharmacokinetics (PK) of BAY1817080 using a simultaneous oral dose of 100 mg (Formulation B, fasted state) along with an i.v. [$^{13}C_7{}^{15}N$]-labeled microtracer • To determine the relative bioavailability of Formulation B administered in fasted state or with a high-fat, high-calorie (HF/HC) meal versus Formulation A administered with a moderate-fat, moderate-calorie (MF/MC) meal at two dose levels (100 and 400 mg) Secondary objectives: • To investigate the effect of a HF/HC meal on the PK of BAY1817080 after a single oral dose of Formulation B at two doses (100 and 400 mg) in comparison to the fasted state • To investigate the dose proportionality in BAY1817080 PK after a single oral dose of Formulation B at 25, 100 and 400 mg in fasted state • To investigate the safety and tolerability of BAY1817080
Test drug	BAY1817080
Active ingredient	BAY1817080
Dose	Formulation A: 100 mg (4 tablets of 25 mg) and 400 mg (2 tablets of 150 mg and 4 tablets of 25 mg) of BAY1817080 Formulation B: 25 mg (1 tablet), 100 mg (1 tablet) and 400 mg (4 tablets of 100 mg) of BAY1817080
Route of administration	Oral
Duration of treatment	Single dose
Test drug	[$^{13}C_7{}^{15}N$]-BAY1817080 stable isotope label (SIL)
Dose	0.1 mg

Route of administration Duration of treatment	Intravenous (i.v) infusion One single dose of [$^{13}C_7{}^{15}N$]-BAY1817080 was administered intravenously as 15-min infusion at the estimated t_{max} after administration of Formulation B tablet in the fasted state at the 100 mg dose level
Main inclusion criteria	Healthy male subjects between 18 and 55 years of age (inclusive), with a body weight of at least 45 kg and a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) without contraindications for the use of the study drug and in good general health
Study design	Single-center, open-label, partially randomized, three-fold cross-over study with 3 parallel arms
Methodology	Pharmacokinetics, safety and tolerability
Statistical methods	All data were listed and summary tables were provided where appropriate. <u>Assessment of absolute bioavailability</u> The absolute bioavailability (F) of Formulation B was estimated based on the PK data derived from the oral dose of 100 mg compared to the [$^{13}C_7{}^{15}N$] labeled microtracer of BAY1817080 under fasted conditions and was listed and summarized. As F was assumed to be log-normally distributed, the log-transformed absolute bioavailability of BAY1817080 was analyzed using an analysis of variance (ANOVA) including only the period effect. A point estimate for the overall mean (LS-Mean) and an exploratory 90% confidence interval (CI) was calculated by re-transformation of the logarithmic results given by the ANOVA using the intra-individual standard deviation. <u>Assessment of relative bioavailability of Formulation B (HF, HC or fasted) each compared to Formulation A (MF, MC)</u> Maximum observed drug concentration in plasma after single dose (C_{max}) and area under the concentration vs. time curve from zero to infinity after single dose (AUC[1]) of BAY1817080 were analyzed assuming log-normally distributed data. For each dose group the logarithm of these parameters was analyzed separately by using an ANOVA. For Dose Group 2 the ANOVA included the sequence, subject (sequence), period and formulation. For Dose Group 3 the ANOVA included only the formulation effect. Based on these analyses, point estimates (LS-Means) and exploratory 90% CIs for the ratios “Formulation B fasted / Formulation A MF/MC” and “Formulation B HF/HC / Formulation A MF/MC” were calculated by re-transformation of the logarithmic data using the intra-individual standard deviation of the ANOVA. All of the statistical analyses had exploratory character. A confirmatory statistical analysis was not intended.
Early termination	Not applicable
Substantial protocol changes	Not applicable

1 In case the AUC was not calculated reliably, AUC(0-t_{last}) could have been used.

Study period	Study Start Date: 13-DEC-2018 Study End Date: 12-AUG-2019
Study center(s)	One investigational site recruited subjects in the Netherlands
Number of subjects	Planned: 30 Analyzed: 30
Criteria for evaluation	
Efficacy	Not applicable
Safety	Incidence and severity of treatment-emergent adverse events (TEAEs), drug-related AEs, vital signs, lab data, electrocardiogram (ECG)
Clinical pharmacology	Pharmacokinetics: Primary variables: • Absolute oral bioavailability (F) of BAY1817080 • Relative bioavailability (frel) of Formulation A vs Formulation B given under different diets Secondary variables: • Effect of a HF/HC meal on the PK of BAY1817080 after a single oral dose of Formulation B at two doses (100 and 400 mg) in comparison to the fasted state • Dose proportionality in BAY1817080 PK after a single oral dose of Formulation B at 25, 100 and 400 mg in fasted state

Subject disposition and baseline

The study started on 13 DEC 2018 and the date of last visit was 19 JUL 2019.

Overall, 62 subjects were enrolled / screened at one center. Of these, 32 subjects were screening failures and 30 subjects were randomized to one of 3 Dose Groups 1-3 to have 6 subjects in Dose Group 1 (25 mg) and 12 subjects each in Dose Groups 2 and 3 (100 mg and 400 mg, respectively).

Two subjects that were randomized to Group 3 discontinued treatment prematurely after having taken 400 mg Formulation A MF/MC in period 2. In 1 subject study drug administration was interrupted between study Periods 1 and 2 because of an AE (dental inflammation). The TEAE resolved completely before study Period 2. For logistical reasons the subject did not participate in study Period 3. The other subject withdrew his consent. All other randomized subjects completed the study.

Therefore, all 30 subjects who were randomized and treated were included in the safety analysis set (SAF) for safety evaluation and in the pharmacokinetic analysis set (PKS1) for the PK evaluation, especially the evaluation of the relative bioavailability and of the food effect. As planned, only subjects of Dose Group 2 (treatment of BAY1817080 and [$^{13}C_7{}^{15}N$]-BAY1817080) were to be included in the PKS2. With these subjects the evaluation of the absolute bioavailability and the PK of [$^{13}C_7{}^{15}N$]-BAY1817080 after i.v. administration were performed. All 12 subjects, for whom the simultaneous intake of treatment of BAY1817080 and [$^{13}C_7{}^{15}N$]-BAY1817080 was planned, were included in the PKS2.

Demographic characteristics were well balanced, with no notable differences between dose groups. According to the inclusion criterion, only male subjects were included into the study; 22 (73.3%) were White, 4 (13.3%) were Black or African American, 1 (3.3%) was Asian and for 3 subjects (10.0%), multiple race entries were documented. A mean age (±standard deviation, SD) of 32.3±10.2 years (range: 18 to 52 years) was reported, and mean BMI (±SD) was 24.45±2.64 kg/m^2 (range: 19.6 to 29.6 kg/m^2).

Clinical Pharmacology

Pharmacokinetic evaluation

- The PK of BAY1817080 in plasma of healthy male subjects could be adequately described in all dose groups after administration of 25 mg, 100 mg or 400 mg administered as tablet Formulations A or B in fasted, MF/MC or HF/HC state.
- The C_{max} increased less than dose-proportionally, indicated by C_{max} divided by dose (C_{max}/D) values from 1.84 /mL (25 mg) to 0.507/mL (400 mg). AUC was dose-proportional at lower dosages of 25 to 100 mg and increased sub-proportionally between 100 mg and 400 mg BAY1817080.
- Up to 4-fold higher drug exposures (AUCs) were calculated after drug intake of tablet Formulation B compared to A after intake of 100 mg as well as after 400 mg BAY1817080 (for both states of B – fasted and fed). Similarly, maximal concentrations (C_{max}) were higher with B compared to A although less pronounced (especially if considering B fasted).
- Regarding the effect food of formulation B, the C_{max} increased under fed conditions (HF/HC) by about a factor of 2. The consumed HF/HC meal had, however, no pronounced effect on the overall extent of absorption (AUC).
- The oral bioavailability based on the AUC derived from the oral dose of 100 mg compared to the [$^{13}C_7{}^{15}N$]-labeled microtracer of BAY1817080 under fasted conditions was calculated to be 50.0%.

Safety

- No deaths, treatment-emergent serious AEs, severe TEAEs or other relevant TEAEs were reported. No subjects discontinued the study due to an TEAE.
- In total, 17 of the 30 subjects experienced TEAEs. There was no apparent difference in the frequency or intensity of the TEAEs between treatments with low or high doses of BAY1817080. Furthermore, no other differences were seen between the different treatment formulations (A vs B) nor with the dietary state in which BAY1817080 was administered (fasted, MF/MC or HF/HC) (Table 2-1).

Table 2-1: Overall summary of Treatment-emergent adverse events (SAF)

Number (%) of subjects with the specified TEAEs	25 mg Form B fasted N=6 (100%)	100 mg Form B + SIL fasted N=12 (100%)	100 mg Form B HF/HC N=12 (100%)	100 mg Form A MF/MC N=12 (100%)	400 mg Form B fasted N=12 (100%)	400 mg Form A MF/MC N=12 (100%)	400 mg Form B HF/HC N=10 (100%)	Total N=30 (100%)
Any AE	4 (66.7%)	2 (16.7%)	2 (16.7%)	5 (41.7%)	4 (33.3%)	5 (41.7%)	4 (40.0%)	17 (56.7%)
Maximum intensity for any AE								
MILD	4 (66.7%)	2 (16.7%)	2 (16.7%)	5 (41.7%)	3 (25.0%)	5 (41.7%)	4 (40.0%)	16 (53.3%)
MODERATE	0	0	0	0	1 (8.3%)	0	0	1 (3.3%)

Overall conclusions

- Following a single oral dose of the tablet Formulation B of BAY1817080 AUC increased dose proportionally from 25 mg to 100 mg and less than dose proportional from 100 mg to 400 mg.
- Up to 4-fold higher drug exposures (AUCs) were calculated after drug intake of tablet Formulation B compared to A after intake of 100 mg as well as after 400 mg BAY1817080 (for both states of B – fasted and fed). Similarly, maximal concentrations (C_{max}) were higher with B compared to A although less pronounced (1.2 to 1-7-fold).
- Regarding the effect of food of Formulation B, C_{max} increased under fed conditions (HF/HC) by about a factor of 2 compared to the fasted state. The consumed HF/HC meal had, however, no pronounced effect on the overall extent of absorption (AUC). Therefore, Formulation B might be administered with or without food.
- The oral bioavailability based on the AUC derived from the oral dose of 100 mg compared to the [$^{13}C_7{}^{15}N$]-labeled microtracer of BAY1817080 under fasted conditions was calculated to be 50.0%.
- BAY1817080 administered as single oral doses of 25 mg, 100 mg or 400 mg administered in under fasted conditions or after a MF/MC or HF/HC meal as tablet Formulation A or B was safe and well tolerated in healthy men.

Publication(s) based on the study

None at the time of report creation.