



Clinical trial report synopsis
HP7030-01

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DMS version 1.0

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Report date	02-May-2019	DMS version	1.0
Type of report	Full		
Trial code	HP7030-01		
Title of trial	An exploratory relative bioavailability trial to assess the effect of food on the pharmacokinetics of 2 immediate release formulations of oxycodone (a new abuse-deterrent formulation and a marketed tablet) administered in healthy adult subjects		
Trial design	Exploratory, randomized, single-site, open-label, active-comparator, 2-treatment, 4-period crossover trial in healthy male and female subjects treated with single oral doses of 2 oxycodone hydrochloride 10 mg formulations under fasted and fed conditions. The duration of each treatment period was 4 days, with a washout of at least 5 days between the administrations of investigational medicinal product in 2 successive treatment periods.		
Development phase	Phase I		
EudraCT number	2018-000771-33		
Investigational medicinal product(s)	Oxycodone immediate release (IR) abuse-deterrent formulation (ADF) (containing oxycodone hydrochloride 10 mg) Oxycodone IR marketed tablet (containing oxycodone hydrochloride 10 mg)		
Indication	Not applicable		
Principal investigator	Prof [REDACTED], MC Comac Medical Ltd.		
Trial site	Bulgaria (1 site)		
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany		
Sponsor's signatory	[REDACTED], MD, International Clinical Lead Contact number: +49 (0) 241-569-0		
Trial period	First subject in:	03 Sep 2018	
	Last subject out:	24 Oct 2018	

Objectives

The primary objective was to assess the effect of food on the pharmacokinetics of 2 different IR formulations of oxycodone hydrochloride 10 mg (a new ADF [test product] and a marketed tablet [comparator product]) following single-dose oral administration. The secondary objective was to assess the safety and tolerability of both treatments.

SDR-CTR-SYN-06**Investigational medicinal products (IMP)**

Oxycodone IR ADF tablets, containing oxycodone hydrochloride 10 mg, batch number: 180504, expiration date: 28 Feb 2019 (test product).

Oxycodone IR marketed tablet, Oxycodon HCl Aristo akut, containing oxycodone hydrochloride 10 mg, batch number: 180503, expiration date: 30 Apr 2022 (comparator product).

Trial treatments

Each subject received one 10 mg tablet of either the test product or the comparator product in each of the 4 treatment periods in a randomized order. IMP was administered orally either after a fasting interval of approximately 10 h or after a standard high-calorie, high-fat breakfast. Administrations of IMP in 2 successive treatment periods were separated by a washout period of at least 5 days.

Trial population

Healthy male and female subjects, aged 18 years to 55 years

Summary of the trial procedures and assessments

The trial consisted of an Enrollment Visit, 4 treatment periods (each separated by a washout period), and a Final Examination. Each subject was expected to be in the trial for up to 8 weeks.

In the Enrollment Visit, which took place between 28 days and 2 days before Treatment Period 1, the subject's suitability for the trial was assessed.

Each subject was allocated randomly to 1 of 4 treatment sequences and received the test product and the comparator product under both fasted and fed conditions. Each treatment period lasted 4 days and subjects were confined to the trial site. Blood and urine samples were taken for safety laboratory analysis. Blood samples were taken for pharmacokinetic evaluation. Vital signs, oxygen saturation, ECGs, adverse events, and concomitant medication were recorded.

The Final Examination took place 2 days to 7 days after discharge from the last treatment period.

Trial performance

There were no protocol amendments. There was no premature trial termination or suspension (clinical hold) of the trial.

Summary of the statistical methods***Sample size rationale***

As no information was available from previous trials concerning the variability of the pharmacokinetics of the new ADF, an intra-individual subject coefficient of variation of 30.0% was assumed for the main pharmacokinetic parameters. For 24 subjects completing the trial, the precision, expressed as the percentage of the true value, for the point estimate of the ratio of geometric means of the primary pharmacokinetic parameters, was expected to be 86.7% to 115.3% of the true geometric mean ratio with 90% confidence. Allowing for an early discontinuation rate of approximately 25% and taking into account the number of sequences, a total of 32 subjects were to be included in the trial. There were to be approximately equal numbers of male and female subjects.

Subject populations

Enrolled Set: all subjects who signed the informed consent form.

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Allocated Set: all subjects who were allocated to treatment.

Safety Set: all subjects with at least 1 IMP administration.

Pharmacokinetic Set: all subjects who had evaluable pharmacokinetic parameters (maximum plasma oxycodone concentration [C_{\max}] and area under the plasma oxycodone concentration curve from time 0 to t [AUC_{0-t}]) in all 4 treatment periods.

Extended Pharmacokinetic Set: all subjects who had evaluable pharmacokinetic parameters (C_{\max} and AUC_{0-t}) in at least 1 of the 4 treatment periods.

Statistical methods and analysis

Pharmacokinetics

Plasma concentration data were summarized by treatment and condition (fed or fasted) at each time point using descriptive statistics. Plasma concentration-time profiles for all treatment groups were displayed.

All descriptive pharmacokinetic analyses were performed using the Extended Pharmacokinetic Set. Pharmacokinetic parameters were summarized by treatment and condition (fed or fasted) using descriptive statistics.

All primary pharmacokinetic analyses were performed using the Pharmacokinetic Set. Pharmacokinetic parameters C_{\max} , AUC_{0-t} , and the area under the concentration curve from time 0 to infinity (AUC) of oxycodone were analyzed using the analysis of variance model on log-transformed values.

To analyze a food effect of test and comparator products, a linear mixed effect model was applied for each of the PK parameters by treatment (test and comparator), with condition (fed and fasted) as a fixed effect and subjects as a random effect.

To compare test versus comparator products administered under fed and fasted conditions, a linear mixed effect model was fitted to the data by the condition (fed and fasted) for each of the PK parameters, with treatment (test and comparator), period, and sequence as fixed effects and subjects nested within the treatment sequence as a random effect.

Statistical inference was based on log-transformed values of C_{\max} , AUC_{0-t} , and AUC.

The 2-sided 90% confidence intervals (CI) for the fed/fasted ratios of the geometric means of C_{\max} , AUC_{0-t} , and AUC were constructed for the test and comparator formulations, as well as for the respective test/comparator ratios in fasted state.

The median differences of time of maximum plasma oxycodone concentration (t_{\max}) for the different treatment groups were also provided.

If subjects vomited less than 12 h after IMP administration, the primary pharmacokinetic analysis was performed with and without these subjects.

Safety

All analyses were performed using the Safety Set. The incidence and distribution of treatment emergent adverse events (TEAEs) and the absolute and relative frequencies of subjects with any adverse events were summarized by treatment and condition (fed or fasted) and subject. The intensity, expectedness, causal relationship to the IMP, outcome, countermeasures taken, time to

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onset, and duration for adverse events were tabulated by treatment and condition (fed or fasted). For safety laboratory parameters, values at baseline and changes from baseline were presented by treatment and condition (fed or fasted) using descriptive statistics. For vital signs, body temperature, and oxygen saturation, values at baseline and changes from baseline at each assessment during the treatment period and at the Final Examination were presented by treatment and condition (fed or fasted) using descriptive statistics. Evaluations of 12-lead ECGs were listed by subject.

Interim analysis

No interim analysis was planned or performed.

Summary of results

Subject disposition

A total of 43 subjects were enrolled and 32 of these subjects were allocated to IMP and received IMP. Eleven subjects discontinued during the course of the trial: 5 subjects due to withdrawal by subject (with no reason given), 4 subjects due to an adverse event (a fifth subject also discontinued the trial due to an adverse event; however, the main discontinuation reason for this subject was “other, discontinuation criterion 2 met”), and 2 subjects due to other reasons (discontinuation criterion 2 met and discontinuation criterion 7 met).

A total of 21 subjects completed the trial as planned, although originally, the protocol had foreseen 24 completers. Replacement of subjects would have started if more than 8 subjects had discontinued from the trial for reasons other than adverse events. Subjects were not replaced as only 6 subjects discontinued for reasons other than adverse events. The higher discontinuation rate resulted in a minor difference in the precision of point estimates of the ratio of geometric means of primary pharmacokinetics parameters (expected with 24 subjects: 86.7% to 115.3%, expected with 21 subjects: 85.8% to 116.5%).

Demographics

Overall, 16 male and 16 female subjects were included in the Safety Set. All subjects were white. The mean age was 36.9 years, mean height was 1.65 m, mean weight was 69.2 kg, and mean body mass index was 25.39 kg/m².

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*Pharmacokinetics**Food effect*

Parameter	Oxycodone IR ADF 10 mg			Oxycodone IR marketed tablet 10 mg		
	CV [%]	Ratio of LS means: Fed / Fasted	90% CI of ratio	CV [%]	Ratio of LS means: Fed / Fasted	90% CI of ratio
AUC [h·ng/mL]	11.6	128.1	(120.5, 136.3)	13.5	124.1	(115.5, 133.3)
AUC _{0-t} [h·ng/mL]	11.7	128.0	(120.3, 136.2)	13.5	124.2	(115.6, 133.4)
C _{max} [ng/mL]	17.8	108.1	(98.4, 118.8)	24.7	107.2	(94.1, 122.0)

The ANOVA (Analysis of Variance) model includes the condition (fed or fasted) as fixed effects and subjects as random effect. One ANOVA model is fitted for each of the displayed parameters and for each of the two different treatments.

CI = confidence interval; CV = coefficient of intra-subject variation; LS means = least square means; PK = pharmacokinetic.

Source: Table 15.2.2.3.1

- The C_{max} values of oxycodone under fed conditions were 8% higher for the IR ADF (test) and 7% higher for the IR marketed tablet (comparator) formulation compared to fasted conditions. The AUC and AUC_{0-t} values of oxycodone were higher under fed conditions compared to fasted conditions for both formulations; by 28% for the IR ADF (test) and by 24% for the IR marketed tablet formulation (comparator).

Treatment effect

- The median t_{max} value for oxycodone was slightly later by 0.25 h for the IR ADF (test, 1.0 h) compared to the IR marketed tablet formulation (comparator, 0.75 h) under fasted conditions. No difference between median t_{max} was observed for the IR ADF (1.50 h) or the IR marketed tablet formulation (1.5 h) under fed conditions.
- Both IR ADF and IR marketed tablet formulation showed similar primary pharmacokinetic parameter values (C_{max}, AUC_{0-t}, and AUC) under each condition (fed or fasted).

Safety and tolerability results

- Most TEAEs were classified by the investigator as mild in intensity. One TEAE of severe intensity (presyncope, not IMP-related) was reported during IR marketed tablet formulation (comparator) treatment under fasted conditions.
- Most TEAEs were expected for IR ADF (test) and all TEAEs were expected for the IR marketed tablet formulation (comparator), not differing from the well-known safety profile of oxycodone, under both fed and fasted conditions. The unexpected TEAEs were all assessed as not related to IMP by the investigator.

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- There were no deaths or other serious TEAEs. TEAEs leading to discontinuation from IMP and from the trial were reported for 2 subjects (6.9%, 4 TEAEs) during IR ADF fasted (test) treatment and for 3 subjects (10.7%, 4 TEAEs) during IR marketed tablet formulation fasted (comparator) treatment. No subjects discontinued from IMP or the trial due to TEAEs under fed conditions.
- No clinically relevant overall trends were observed in the laboratory values, vital signs, body temperature, oxygen saturation, 12-lead ECG, or physical examination data.

Conclusions

- The data indicate that GRT7030 has similar *in-vivo* performance to the reference formulation under fed and fasted conditions. Both test and comparator showed a similar, clinically not relevant food effect: 28% and 24% (AUC), 8% and 7% (C_{\max}) higher exposure, respectively, under fed conditions.
- No relevant t_{\max} prolongation was observed for the new IR ADF formulation: under fasted conditions, median t_{\max} was 1.0 h (test) and 0.75 h (comparator) and, under fed conditions, median t_{\max} was 1.5 h, identical for both formulations.

The frequencies of TEAEs were overall lower during IR ADF (test) treatment than during IR marketed tablet formulation (comparator) treatment, under both fed and fasted conditions. The TEAEs in both IR ADF (test) and IR marketed tablet formulation (comparator) treatments were in line with the known safety profile of oxycodone.