Type of report	Abbreviated
Trial code	HP7030-02
Title of trial	An exploratory relative bioavailability trial of different amounts of 2 immediate release formulations of oxycodone (a new abuse-deterrent formulation and a marketed tablet) administered under fasted conditions in healthy adult subjects
Trial design	Exploratory, randomized, single-site, open-label, active-comparator trial comprising 2 consecutive 2-period, 2-treatment crossovers in healthy male and female subjects treated with single oral doses of 2 oxycodone hydrochloride 10 mg formulations under fasted conditions. Doses of 10 mg (1 tablet) and 50 mg (5 tablets) were evaluated. Each treatment period lasted from Day -1 to Day 4, with a washout of at least 5 days between successive administrations of investigational medicinal product (IMP).
Development phase	Phase I
EudraCT number	2018-000772-16
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	[redacted], MC Comac Medical Ltd.
Trial site	Bulgaria (1 site)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted], MD, Medically Qualified Person Contact number: +49 (0) 241-569-3223
Trial period	First subject in: 07 Jan 2019 Last subject out: 26 Feb 2019

Objectives

Primary objective:

- To assess the dose proportionality after dose normalization of 1 tablet and 5 tablets of a new IR ADF of oxycodone hydrochloride 10 mg (test product) following single-dose oral administration under fasted conditions.

Secondary objectives:

- To assess the relative bioavailability after dose normalization of 1 tablet and 5 tablets of a new IR ADF of oxycodone hydrochloride 10 mg (test product) and a marketed tablet (comparator product) following single-dose oral administration under fasted conditions.
- To assess the safety and tolerability of both treatments.

Investigational medicinal product(s) (IMP)

Test product: Oxycodone IR ADF tablets, containing oxycodone hydrochloride 10 mg, Bulk Batch Number: UCYA03, Collective Batch Number on label for kit containing 1 tablet: 180511, Collective Batch Number on label for kit containing 5 tablets: 180512, expiration date: Feb 2019, but after retest extended to Aug 2019.

Comparator product: oxycodone IR marketed tablet, Oxycodon HCl Aristo akut, containing oxycodone hydrochloride 10 mg, Bulk Batch Number: 7E140A, Collective Batch Number on label for kit containing 1 tablet: 180514, Collective Batch Number on label for kit containing 5 tablets: 180515, expiration date: 04/2022.

Trial treatments

In Part 1, each subject received 1 tablet of the test product (T1) and 1 tablet of the comparator product (C1) for oral administration in a randomized order. In Part 2, each subject was to receive 5 tablets of the test product (T2) and 5 tablets of the comparator product (C2) in a randomized order. The IMP was administered orally after a fasting interval of approximately 10 h. Administrations of IMP in successive treatment periods were separated by a washout period of at least 5 days.

Other medication (non-IMP, trial-specific medication)

Naltrexone hydrochloride tablets, 50 mg, oral, batch number: Bulk Batch Number: 6074814, Collective Batch Number on label for kit containing 28 tablets: 180517, expiration date: 01/2020.

In each treatment period, each subject received a single oral dose (1 tablet) of the opiate antagonist naltrexone hydrochloride 12 h and 3 h before and 24 h after IMP administration to decrease the potential for opioid-related adverse events.

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, 2 parts each comprising 2 treatment periods separated by washouts, and a Final Examination.

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

Each subject was allocated to 1 of 4 treatment sequences and was to receive single treatments of 2 different doses of the test product and the comparator product under fasted conditions. The inpatient treatment periods were each separated by a washout of at least 5 days. The opioid antagonist naltrexone hydrochloride was administered in each treatment period to decrease the potential for opioid-related adverse advents. In the first treatment period of Part 2, a dose leader approach was employed. At the start of the treatment period, 2 subjects (dose leaders) were administered IMP. One dose leader was administered test product and 1 dose leader was administered comparator product. In each treatment period, blood and urine samples were taken for analysis of safety laboratory parameters. Blood samples were taken for pharmacokinetic (PK) assessment. Vital signs, body temperature, 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 was 1 protocol amendment. The trial was terminated prematurely due to adverse events reported for both dose leaders in the first treatment period of Part 2.

Summary of the statistical methods

Sample size rationale

For this exploratory trial, the sample size calculation was driven by the level of precision of statistical estimators. An intra-individual subject coefficient of variation (CV) of 30.0% was assumed for the main PK parameters. For 24 subjects completing the trial, the precision range, expressed as the percentage of the true value, for the point estimate of the ratio of geometric means of the primary PK parameters was expected to be 86.7% to 115.3% of the true geometric mean ratio with 90% confidence. The sample size of 24 subjects provides a power of 90% to detect a geometric mean ratio of 0.75 with a 2-sided significance level of 0.05. 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.
Allocated Set	All subjects who were allocated to treatment.
Safety Set	All subjects with at least 1 IMP administration.
PK Set	All subjects who had evaluable PK 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 treatment periods.
Extended PK Set	All subjects who had evaluable PK parameters (C_{max} and AUC_{0-t}) in at least 1 of the treatment periods.

Statistical methods and analysis

Pharmacokinetics

All descriptive PK analyses were performed using the Extended PK Set. Pharmacokinetic parameters were summarized by treatment group (treatment and dose step) using descriptive statistics. Plasma concentration-time profiles for all treatment groups were displayed for the Extended PK Set. Plasma concentration data were summarized by treatment group at each time point using descriptive statistics.

All primary and secondary PK analyses were planned for the PK Set. Since the trial was terminated prematurely after the dose leaders of Part 2 (5 tablets), the PK Set contained 0 subjects. Therefore, the statistical analysis of AUC, AUC_{0-t}, and C_{max} of oxycodone was not performed.

Safety

All safety analyses were performed using the Safety Set. The incidence and distribution of treatment emergent adverse events (TEAEs) was summarized by treatment. For vital signs, body temperature, oxygen saturation, and safety laboratory parameters, values at baseline and changes from baseline at each assessment during the treatment period and at the Final Examination were presented by treatment 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 40 subjects were enrolled and 32 of these subjects were allocated to IMP and received IMP. All 32 subjects discontinued during the course of the trial: 27 subjects due to premature trial termination by the sponsor together with the principal investigator, 3 subjects due to withdrawal of informed consent, 1 subject due to personal reasons, and 1 subject due to an adverse event.
No subjects completed the trial as planned.

Pharmacokinetics (Part 1)

- PK parameters for the Extended PK Set were obtained for 31 subjects (96.9%).
- Both PK profiles for 10 mg (treatments T1 and C1) and all PK parameters for 10 mg are consistent.
- Individual PK profiles for 5 tablets (treatments T2 and C2) are only available for N=1 each, so no conclusions on dose proportionality (“clumping effect”) for test versus comparator can be drawn.
- PK profiles and parameters for 10 mg were also consistent with previous data.
- Naltrexone and 6β-naltrexol plasma concentrations in the 2 dose leaders were in line with literature data.

Safety and tolerability results

- The frequency of TEAEs was similar in Part 1 (10 mg oxycodone) for treatments T1 and C1: 14 subjects (46.7%) reported 23 TEAEs after treatment T1 and 14 subjects (45.2%) reported 25 TEAEs after treatment C1.
- The dose leader of Treatment Period 3 in Part 2 (treatment T2, 50 mg oxycodone) reported 9 TEAEs (dizziness [1 event], somnolence [1 event], oxygen saturation decreased [7 events]) and the dose leader of Treatment Period 3 in Part 2 (treatment C2, 50 mg oxycodone) reported 6 TEAEs (dizziness [1 event], somnolence [1 event], oxygen saturation decreased [3 events], bradycardia [1 event]).
- The benefit risk team (BRT) of the sponsor assessed the safety and tolerability data up to 48 h after IMP administration of the dose leaders (in Treatment Period 3 of Part 2 of the trial), as specified in the protocol, and decided not to dose any other subjects in the trial; the trial was stopped. This decision was based on the observed low oxygen saturation values down to 80% (4 h post-IMP treatment C2) and bradycardia down to 44 beats/min at 2.5 h post-IMP treatment C2 (despite naltrexone co-administration before IMP intake and 24 hours after IMP intake). Low oxygen saturation down to 87% was observed for the second dose leader 31 h post-IMP after treatment T2. These two dosed subjects were on the higher end of the body mass index (BMI) allowed for trial participation (20-30 kg/m^2), and hence there was a concern that other subjects with lower BMI would have worse symptoms with a single 50 mg oxycodone dose.
- The most frequently reported TEAEs in Part 1 were bradycardia (T1: 4 subjects [13.3%]; C1: 5 subjects [16.1%]) and sinus bradycardia (T1: 3 subjects [10.0%]; C1: 6 subjects [19.4%]). These TEAEs were in line with the known safety profile of oxycodone IR.
- Most TEAEs were assessed by the investigator as at least possibly related to the administration of IMP.
- All TEAEs were classified by the investigator as mild in intensity.
- Most TEAEs were expected for treatments T1 and C1, not differing from the well-known safety profile of oxycodone. One of the 3 unexpected TEAEs (ventricular extrasystoles) was assessed as possibly related to IMP by the investigator.
- There were no deaths or other serious TEAEs. One subject discontinued from the trial due to an adverse event (sinus bradycardia) during C1 treatment.
- 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

- This trial was **terminated early** due to safety reasons. Thus, the trial objective to gain pharmacokinetic information on the dose proportionality (if the exposure relationship is similar to the *in-vitro* release) could not be assessed.
- The PK results of 10 mg oxycodone IR for Test and Comparator were consistent and also consistent with previous data.

- The high frequency of reported (sinus-)bradycardia at the therapeutic dose of 10 mg oxycodone IR was not expected.
- Low oxygen saturation levels and bradycardia at 50 mg oxycodone IR under naltrexone co-administration were not expected. Naltrexone and 6ß-naltrexol plasma concentrations were in line with literature data.
- Other reported TEAEs were in line with the known safety profile of oxycodone IR.