



SDR-CTR-SYN-06

Trial code	HP7030-03
Title of trial	A single-site, randomized, double-blind, double-dummy, active-comparator, placebo-controlled, 3-way crossover trial in adult non-dependent recreational opioid users to compare the intranasal abuse potential of immediate release abuse-deterrent and standard formulations of oxycodone
Trial design	Single-site, randomized, double-blind, double-dummy, active-comparator, placebo-controlled, 3-way crossover trial in adult male and female non-dependent recreational opioid users.
Development phase	Phase I
Investigational medicinal products	Abuse-deterrent formulation (ADF) oxycodone immediate release (IR) (manipulated) Oxycodone active pharmaceutical ingredient (API) Placebo to match ADF oxycodone IR (manipulated) Placebo to match oxycodone API
Indication	Not applicable
Principal investigator	Dr [REDACTED], MD, Algorithme Pharma
Trial site	Canada (1 site)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[REDACTED], MD, International Clinical Lead Contact number: +49 (0) 241-569-3223
Trial period	First subject in: 24 Jul 2018 Last subject out: 20 Nov 2018

## Objectives

### Primary objective:

- To compare the intranasal abuse potential of manipulated ADF oxycodone IR and oxycodone API representing manipulated oxycodone IR standard formulation.

The primary endpoint was the peak effect ( $E_{max}$ ) for Drug Liking “at this moment” during the first 24 h after IMP administration, measured on a visual analog scale (VAS).

### Secondary objectives:

- To compare the pharmacokinetics of a manipulated ADF oxycodone IR and oxycodone API representing manipulated oxycodone IR standard formulation after single-dose intranasal administration.
- To compare further pharmacodynamic parameters of a manipulated ADF oxycodone IR and oxycodone API representing manipulated oxycodone IR standard formulation after single-dose intranasal administration.

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- To assess safety and tolerability of manipulated Investigational Medicinal product (IMP).

### Investigational medicinal products

- ADF oxycodone IR, tablets, manipulated. A single dose had a mass of 540 mg, containing oxycodone hydrochloride 30 mg, batch number: 180521, expiration date: Feb 2019.
- Oxycodone API, powder. A single dose had a mass of 30 mg, comprising oxycodone hydrochloride 30 mg, batch number: 180518, expiration date: Jan 2019.
- Placebo to match ADF oxycodone IR, pellets, manipulated, batch number: 180522, expiration date: Feb 2019.
- Placebo to match oxycodone API, powder, batch number: 180519, expiration date: Jan 2019.

### Trial treatments

Subjects insufflated IMP using their preferred naris or both nares.

#### *Qualification Phase*

Subjects were randomized to receive a single intranasal dose each of oxycodone API and matching placebo in a double-blind manner. The total mass of each single dose was 30 mg.

#### *Treatment Phase*

Subjects who successfully completed the Qualification Phase were eligible to be randomized to receive a single intranasal dose of each of the treatments (combined doses of IMP) in [Table 1](#) in a double-blind, double-dummy manner on Day 1, Day 4, and Day 7 of the Treatment Phase. A single dose of a treatment was defined as insufflation of single doses of the 2 applicable IMPs in quick succession. The 2 applicable IMPs had to be insufflated in the following pre-defined order. Oxycodone API or placebo to match oxycodone API had to always be insufflated first. ADF oxycodone IR or placebo to match ADF oxycodone IR had to always be insufflated second. The total mass of each single dose of combined insufflation of the 2 IMPs was 570 mg.

Table 1: Treatment codes and investigational medicinal product

Treatment code	Test	Comparator	Placebo
ADF oxycodone IR (manipulated)	x (second)		
Oxycodone API		x (first)	
Placebo to match ADF oxycodone IR (manipulated)		x (second)	x (second)
Placebo to match oxycodone API	x (first)		x (first)

ADF = abuse-deterrent formulation; API = active pharmaceutical ingredient; C = comparator; IR = immediate release; P = placebo; T = Test

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

Naloxone and a saline solution were used for the naloxone challenge test.

Naloxone hydrochloride ampoules for injection (0.4 mg/mL), 0.2 mg, intravenous, batch number: HK3338, expiration date: Sep 2020.

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Sodium chloride for injection, 0.9% (saline solution), intravenous, batch number: W8A11B0, expiration date: Apr 2019.

### **Trial population**

Subjects were healthy men and women, 18 years to 55 years of age, with a history of recreational opioid use defined as non-therapeutic use at least 10 times in the subject's lifetime and at least once in the 12 weeks prior to the Enrollment Visit and a history of intranasally insufflated drugs for recreational (non-therapeutic) purposes at least 3 times in the last 12 months before the Enrollment Visit.

The main exclusion criteria included unsuitable nasal condition, a current diagnosis of substance dependence as defined by Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM-IV-TR) criteria as well as earlier or planned treatment for substance disorders.

The Treatment Phase included subjects who successfully passed the Qualification Phase, i.e., subjects who were verified to be non-dependent on opioids, could discriminate between intranasally administered oxycodone and placebo, and were able to tolerate 30 mg oxycodone API administered intranasally.

### **Summary of the trial procedures and assessments**

The trial comprised an Enrollment Visit, a Qualification Phase, a Treatment Phase, a Final Examination, and a follow-up phone call. Each subject was expected to be in the trial for approximately 7 weeks.

In the Enrollment Visit, which took place between 28 days and 2 days before the Qualification Phase, the subject's eligibility for the trial was assessed. After obtaining informed consent, the procedures included the assessment of inclusion and exclusion criteria, collection of demographic data, medical history and the subjects' recreational drug use history, a physical examination and a 12-lead ECG, a nasal examination, a pregnancy test for female subjects, recording of prior/concomitant medication, vital signs, oxygen saturation, and body temperature, completion of the C-SSRS, and collection of urine and blood samples for safety laboratory tests. The tests were repeated as applicable during the trial.

#### *Qualification Phase*

The 4-day Qualification Phase consisted of a naloxone challenge test and a drug discrimination test. Procedures on Day -1 of the Qualification Phase included an alcohol and urine drugs of abuse test and a nasal examination. Subjects were trained on the subjective pharmacodynamic assessments using a visual analog scale (VAS) and training was repeated as necessary.

The naloxone challenge test was performed to confirm that subjects were not opioid-dependent and was done at least 12 hours before first IMP administration. Following naloxone administration by intravenous bolus, subjects were observed for signs or symptoms of withdrawal. Subjects with a Clinical Opiate Withdrawal Scale (COWS) score of less than 5 after naloxone challenge were considered not physically dependent and remained hospitalized to complete the drug discrimination test.

The drug discrimination test was performed to determine if subjects were able to distinguish intranasally administered oxycodone API powder from placebo. Subjects received oxycodone API and matching placebo in a randomized, double-blind, crossover design 24 hours apart. After IMP

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administration, subjective pharmacodynamic assessments were performed at specified time points using a VAS. Vital signs, oxygen saturation, 12-lead ECGs, adverse events, and concomitant medication were recorded and the C-SSRS was completed. The subjects' eligibility for the Treatment Phase that included the ability to discriminate active drug from placebo was assessed per discontinuation criterion.

#### *Treatment Phase*

Subjects who successfully completed the Qualification Phase were eligible to enter the Treatment Phase. The 10-day inpatient Treatment Phase included 3 treatment periods (separated by a 72-hour wash-out) in which subjects received a single treatment of Test, Comparator, and Placebo in a randomized, double-blind, double-dummy, 3-way crossover design. Procedures on Day -1 of the Treatment Phase included an alcohol and urine drugs of abuse test, a nasal examination, and training of the subjects on the subjective pharmacodynamic assessment. Following IMP administration, blood samples were taken for pharmacokinetic evaluation. Subjective pharmacodynamic VAS assessments, pupillometry, and the subject-rated intranasal irritation assessments were performed. The C-SSRS was completed and vital signs, oxygen saturation, 12-lead ECGs, adverse events, and concomitant medication were recorded.

The Final Examination was performed on the last day of the Treatment Phase, thereafter subjects were discharged from the trial site. Subjects who discontinued their participation in the trial early underwent an Early Termination Examination instead of a Final Examination.

The follow-up phone call took place between 2 days and 7 days after the Final Examination or Early Termination Examination; subjects were questioned about changes in their health or medications.

#### **Trial performance**

There were 2 protocol amendments. There was no premature trial termination or suspension (clinical hold) of the trial.

#### **Summary of the statistical methods**

##### *Sample size rationale*

For the primary endpoint, concerning the variability of  $E_{\max}$  for Drug Liking "at this moment" rated on a VAS during the first 24 h after IMP administration (score of 0 denotes "strong disliking", 50 denotes a neutral response, and a score of 100 denotes "strong liking"), an intra-subject standard deviation of 30% was assumed.

Using a one sample t-test for a normal mean difference with a two-sided significance level of 5% and assuming a standard deviation of 30, a sample size of 36 completers has enough power (>0.80) to detect a mean difference in score of 15.

It was to be ensured that 36 subjects completed the trial. This sample size is consistent with that used previously in similar trials (Setnik et al. 2017).

##### *Subject populations*

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

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- Qualification Allocated Set: all subjects who were allocated to treatment in the Qualification Phase.
- Treatment Allocated Set: all subjects who were allocated to treatment in the Treatment Phase.
- Qualification Safety Set: all subjects who received naloxone or IMP in the Qualification Phase.
- Treatment Safety Set: all subjects who received IMP at least once in the Treatment Phase.
- Pharmacodynamic Set: all subjects providing at least 1 VAS rating for Drug Liking “at this moment” between 0 h and 24 h after IMP administration in all 3 treatment periods.
- Extended Pharmacodynamic Set: all subjects providing at least 1 VAS rating for Drug Liking “at this moment” between 0 h and 24 h after IMP administration in at least 1 of the 3 treatment periods.
- 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 2 of 3 treatments.
- Extended Pharmacokinetic Set: all subjects who had evaluable pharmacokinetic parameters ( $C_{\max}$  and  $AUC_{0-t}$ ) in at least 1 of the 3 treatment periods.
- Completer Set: all subjects providing at least 1 VAS rating for Drug Liking “at this moment” within the first 4 h after IMP administration in all 3 treatment periods.

The inclusion of data from subjects who blew their nose or sneezed less than 1 h after IMP administration in a treatment period were decided on a case by case basis.

## Statistical methods and analysis

### *Pharmacodynamics*

Pharmacodynamic data were summarized by treatment (and at each time point, if applicable) using descriptive statistics. In the Qualification Phase, only descriptive statistics of pharmacodynamics parameters were provided. In the Treatment Phase, a linear mixed effects model was fitted to each pharmacodynamic parameter using treatment, period, sequence and sex as fixed effects, baseline measurement as a covariate and subject nested in the sequence as a random effect. For Drug Liking, Bad Effects, Overall Drug Liking Take Drug Again VAS, Ease of snorting and Pleasantness of snorting models were fitted without baseline as covariate. Least square (LS) means and 95% confidence intervals (CIs) for treatments and treatment differences were computed.

The primary endpoint was  $E_{\max}$  for Drug Liking “at this moment” during the first 24 h after IMP administration. All pairwise comparisons of IMPs were performed using the linear mixed effects model specified above. A difference between comparator and placebo was used to validate the appropriateness of the positive control (assay of sensitivity). Assay sensitivity was concluded if the 95% CI for the treatment difference (between comparator and placebo) did not include 15.

The 95% CI was also calculated for a treatment difference between test and comparator. A significant difference was demonstrated if this interval did not include zero. The estimated mean difference between test and placebo was used to evaluate an abuse potential of the test product

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against placebo. The comparison was done by investigating whether the 95% CI for the treatment difference included 11. These thresholds were chosen only for exploratory purposes in this trial.

To evaluate a possible impact of observed incomplete insufflation of IMP on pharmacodynamic parameters, the same linear mixed effects model used for the primary analysis was fit to each pharmacodynamic parameter, but with the actual amount of insufflated oxycodone and the level of insufflated IMP as additional covariates in two separate models. LS means and 95% CIs for treatments and treatment differences were calculated.

Subgroup analyses were performed on the Completer Set for all primary and secondary pharmacodynamic endpoints using different thresholds of incomplete insufflation with respect to the actual amount of IMP insufflated during Test treatment.

#### *Pharmacokinetics*

Plasma concentration data were summarized by treatment at each time point using descriptive statistics. Plasma concentration-time profiles for all treatments were displayed. Statistical inferences were based on log-transformed values of  $C_{max}$ ,  $AUC_{0-t}$ , and area under the plasma oxycodone concentration curve from time 0 to infinity (AUC). A linear mixed effect model was applied with treatments, period, and sequence as fixed effects and subject within sequence as random effect. A two-sequence two-period model was used in the analysis, excluding placebo.

In addition, all pharmacokinetic analyses were also provided dose-normalized (per mg of actual amount of insufflated oxycodone).

#### *Safety*

Safety analyses were performed separately for the Qualification Safety Set and the Treatment 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 subject.

The degrees of intensity, expectedness, causal relationship to the IMP, outcome, countermeasures taken, time to onset, and duration for adverse events were tabulated by treatment.

For safety laboratory parameters, values at baseline and changes from baseline were presented by treatment 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 using descriptive statistics.

Evaluations of 12-lead ECGs were listed by subject.

Nasal examination findings and intranasal irritation assessment findings were presented by treatment sequence. C-SSRS outcomes were listed.

#### *Interim analysis*

No interim analysis was planned or performed.

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## Summary of results

### *Subject disposition*

A total of 123 subjects were enrolled; 52 subjects underwent the naloxone challenge test, 47 were allocated and completed the Qualification Phase, 42 of the 47 subjects qualified for the Treatment Phase, i.e. fulfilled the criteria to successfully pass the Qualification Phase, and 38 of these subjects were allocated to IMP in the Treatment Phase. One subject discontinued during the Treatment Phase due to an adverse event. A total of 37 subjects completed the trial.

### *Demographics*

Overall, 31 male and 7 female subjects were included in the Treatment Safety Set. Twenty-eight subjects were White, 4 were of 'Other' race, 3 were Asian, and 3 were Black or African American. The mean (SD) age was 35.7 (9.5) years, the mean height was 1.76 (0.09) cm, the mean weight was 75.95 (12.58) kg, and the mean body mass index was 24.52 (2.91) kg/m<sup>2</sup>.

### *Level of IMP insufflation*

Insufflation of oxycodone API or matching placebo was almost complete in most cases, mean levels exceeding 95%. Insufflation of ADF oxycodone IR or matching placebo was incomplete in many cases, with a high intra- and inter-subject variability. Mean (SD) level of insufflated ADF oxycodone IR was 60.19 (32.51) %, ranging from 6.9% to 100.2%. Similar values were observed for placebo to match ADF oxycodone IR.

### *Pharmacodynamics*

#### Primary endpoint

For the primary endpoint,  $E_{\max}$  of Drug Liking "at this moment" VAS, Test showed statistically significantly lower  $E_{\max}$  than Comparator.

The treatment difference was -20.4 (95% CI: -25.3, -15.6).

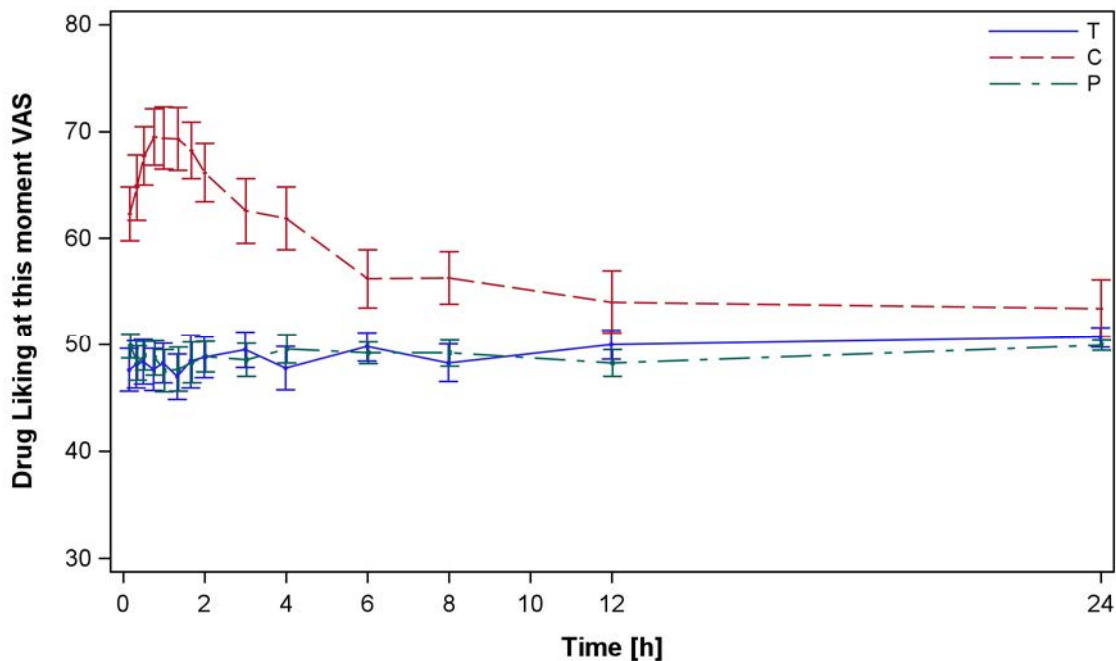
Comparator showed statistically significantly higher  $E_{\max}$  than Placebo, with a treatment difference of 22.6 (95% CI: 17.8, 27.5), thereby confirming assay sensitivity and the validity of the trial.

Test and Placebo showed no statistically significant difference in  $E_{\max}$ .

Drug Liking VAS ratings for Test were close to the neutral point during the first hour after insufflation and throughout the 24-hour assessment period, in contrast to Comparator showing rapidly increasing Drug Liking scores within the first hour after insufflation.

Mean VAS Drug Liking "at this moment" over time in the Treatment Phase is depicted below for the Completer Set.

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Arithmetic mean is displayed. Error bars represent the standard error of the mean.

0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking;

T = abuse-deterrent formulation oxycodone IR (manipulated) and placebo to match oxycodone API (Test);

C = oxycodone API and placebo to match abuse-deterrent formulation oxycodone IR (manipulated) (Comparator);

P = placebo to match abuse-deterrent formulation oxycodone IR (manipulated) and placebo to match oxycodone API; API = active pharmaceutical ingredient; IR = immediate release; VAS = visual analog scale.

Source: [REDACTED]

## Secondary pharmacodynamic measures

### Secondary subjective measures

- Positive Effects (High VAS):**  
Consistent with the Drug Liking results, the mean VAS High scores increased rapidly following Comparator, whereas Test showed substantially lower High scores over time. Mean  $E_{max}$  for High VAS was significantly lower for Test relative to Comparator. Comparator showed significantly higher mean  $E_{max}$  relative to Placebo and there was no significant difference in the mean  $E_{max}$  between Test and Placebo.
- Overall Effects:**  
Test showed significantly lower mean Overall Drug Liking and mean Take Drug Again than Comparator at both 12 hours and 24 hours. For mean Overall Drug Liking, the treatment difference at 24 hours was -17.9 (95% CI: -23.2, -12.6). For mean Take Drug Again, the treatment difference at 24 hours was -20.4 (95% CI: -27.4, -13.5). Mean scores for both measures for Test were close to the neutral point and were similar to Placebo.
- Negative Effects:**  
The VAS ratings for Bad Effects were generally low, indicating modest bad effects. The



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mean  $E_{\max}$  for Bad Effects was slightly higher (indicating greater bad effects) for Comparator relative to Test and Placebo.

- Snorting effects measures:

The assessment using the Ease of Snorting VAS and Pleasantness of Snorting VAS considered the combined insufflation of the 2 respective IMPs (i.e., 30 mg of verum or placebo powder, followed by 540 mg of verum or placebo manipulated ADF).

The mean Ease of Snorting VAS and Pleasantness of Snorting VAS ratings indicated that snorting was moderately difficult and unpleasant for all 3 treatments (Test, Comparator, and Placebo). There were no marked differences between the treatments.

Secondary objective measure: Pupillometry

- Pupillometry showed a marked pharmacodynamic response following Comparator. Test showed significantly less maximum pupil constriction relative to Comparator. The mean apparent minimum post dose pupil diameter ( $PC_{\min}$ ) value was smallest following Comparator, and only slightly lower for Test relative to Placebo. Mean partial area over the curve (PAOC) values were significantly lower for Comparator relative to Test. Consistent with the subjective pharmacodynamic measures, the pupillometry data show that Test was overall associated with significantly smaller pupillary effects relative to the Comparator.

Overall, secondary pharmacodynamic outcomes consistently supported the primary outcome,  $E_{\max}$  for Drug Liking “at this moment”.

Sensitivity and subgroup analysis

- Considering that the amount of IMP insufflation was not complete in many cases, additional analyses were conducted to assess the impact of incomplete insufflation on the pharmacodynamic assessments (i.e., sensitivity analyses, subgroup analyses). The analyses showed that incomplete insufflation had no relevant impact on the primary and secondary outcomes.

*Pharmacokinetics*

- Oxycodone absorption was reduced following insufflation of Test compared to Comparator. Dose-normalized pharmacokinetic analyses, taking the actual amount of oxycodone insufflated into account, showed that the mean dose-normalized  $C_{\max}$  values following Test insufflation were approximately 40% of those following Comparator insufflation and the mean dose-normalized AUC values were approximately 60%.
- The median  $t_{\max}$  occurred later for Test (3.03 h) than for Comparator (1.75 h).
- Oxycodone plasma concentrations declined with a similar geometric mean  $t_{1/2,z}$  for both treatments Test (5.1 h) and Comparator (4.7 h).

*Safety and tolerability results*

Qualification Phase

- The frequency of TEAEs after oxycodone API was higher than after placebo. 38 subjects (80.9%) reported 117 TEAEs after oxycodone API and 3 subjects (6.4%) reported 8 TEAEs after placebo. The most frequently reported TEAEs were euphoric mood and pruritus.

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### Treatment Phase

- The frequency of TEAEs after Test was lower than after Comparator and similar to Placebo. 16 subjects (42.1 %) reported 23 TEAEs after Test, 33 subjects (89.2%) reported 86 TEAEs after Comparator, and 14 subjects (37.8%) reported 21 TEAEs after Placebo.
- The most frequently reported TEAEs were nasal congestion, euphoric mood and pruritus. Euphoric mood, recognized as an abuse liability-related TEAE, and pruritus were reported most frequently after Comparator, whereas nasal congestion occurred with similar frequency after all 3 treatments. Nasal congestion was the most commonly reported unexpected TEAE.
- The majority of TEAEs were judged by the investigator to be at least possibly related to IMP for all 3 treatments.
- Most TEAEs were mild in intensity. One severe TEAE of dizziness was reported after Comparator, but was judged by the investigator not to be related to IMP.
- No deaths or other serious adverse events were observed. One TEAE led to trial discontinuation after Test. The TEAE was migraine, moderate in intensity, and judged by the investigator to be possibly related to IMP.
- No clinically relevant overall trends were observed in the laboratory values, vital signs, body temperature, oxygen saturation, 12-lead ECG, or physical examination data.
- No abnormal nasal examination findings were observed by the investigator. Subject-rated intranasal irritation assessments were overall similar after the 3 treatments, highest scores being reported for need to blow nose and nasal congestion.

### **Conclusions**

- The outcome of the primary measure demonstrates a statistically significantly lower maximal Drug Liking “at this moment” (mean  $E_{max}$ ) for insufflated, manipulated ADF oxycodone IR compared with insufflated oxycodone API in the Completer Set.
- Statistically significant differences were observed for Drug Liking “at this moment” VAS  $E_{max}$  between Comparator and Placebo, confirming assay sensitivity and trial validity.
- Primary and secondary pharmacodynamic measures consistently indicate that ADF oxycodone IR separates from oxycodone API, showing significantly lower Positive Effects and Overall Effects in a similar range to Placebo.
- The pharmacodynamic results are consistent with pharmacokinetic data indicating a delayed and reduced absorption of ADF oxycodone IR relative to oxycodone API.
- All treatments were safe. The frequency of TEAEs after Test was lower relative to Comparator, including a lower incidence of euphoric mood.
- ADF oxycodone IR can be expected to have a lower potential of intranasal abuse compared to oxycodone API.