SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical, K.K.
Name of Investigational Product	JNJ-268229 (remifentanil hydrochloride)

Status: Approved

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Prepared by: Janssen Pharmaceutical, K.K.

Protocol No.: ULTIVAANS3001

Title of Study: An Open-Label Study to Evaluate the Efficacy and Safety of JNJ-268229 in Pediatric Subjects General Anesthetised.

NCT No.: NCT01998165

Clinical Registry No.: CR102524

Coordinating Investigator: No coordinating investigator (multicenter)

Study Centers: 10 sites in Japan

Publication (Reference): Not applicable

Study Period: 27 November 2013 – 13 November 2014

Phase of Development: Phase 3

Objectives:

Primary objective

The primary objective of this study was to evaluate efficacy and safety of JNJ-268229 in pediatric subjects between 1 and 15 years of age during maintenance of general anesthesia.

Exploratory objective

The exploratory objective of this study was to determine concentrations of remifentanil in pediatric subjects who were possible to take drawing of blood sample for pharmacokinetics, and investigate the relationships among concentrations, infusion rates, and age wherever possible.

Methodology:

This was a multicenter, open-label, one-arm study of JNJ-268229 in pediatric subjects receiving general anesthesia. The subjects were children aged 1-15 years old, planned to undergo head and neck, thoracic, intraperitoneal, ophthalmological, otorhinolaryngological, urological, orthopedic or plastic surgery. The targeted total number of subjects was approximately 80. These subjects were divided into two groups by age (1-6 and 7-15 years old). Pharmacokinetic (PK) samples were to be collected from at least 3 subjects between the ages of 1 and 6 years and at least 3 subjects between the ages of 7 and 15 years.

The study was composed of 4 phases (screening phase, treatment phase, recovery phase and follow-up phase).

After intubation, continuous intravenous infusion of JNJ-268229 (0.25 µg/kg/min as remifentanil) was started, while anesthesia was maintained with inhaled or intravenous anesthetics. In cases where sedation by general anesthetics and analgesia by lidocaine did not seem to provide a sufficient means of analgesia at the time of intubation, JNJ-268229 could be used, beginning before intubation. After the evaluation for

response to skin incision, the infusion rate could be changed as needed. The rate of infusion could be adjusted while monitoring the subject's general condition in 25% to 100% increments or in 25% to 50% decrements every 2 to 5 minutes, but could not exceed 1.3 µg/kg/min.

Efficacy, safety, and PK were assessed in this study. Efficacy measurements included response to skin incision, hemodynamics and respiratory stability, global assessment on analgesic effect of JNJ-268229 during operation, time until arrival of Steward Postanesthetic Recovery Score at 6, and time interval between completion of anesthesia and extubation. Safety assessments included adverse events (AEs), vital signs, laboratory parameters, electrocardiograms (ECGs), and respiratory parameters. The concentrations of remifentanil in whole blood were also measured for PK assessment.

Number of Subjects (planned and analyzed):

Planned sample size was 80 subjects (at least 25 were to be enrolled in each age group [1-6 years, 7-15 years]). A total of 84 subjects (42 in each age group) provided the informed consent. Of these, 80 subjects (40 in each age group) were treated with JNJ-268229, and all subjects who received JNJ-268229 were included in the safety analysis set and the full analysis set (FAS). The PK analysis set included 36 subjects (18 in each age group).

Diagnosis and Main Criteria for Inclusion:

Children aged 1-15 years old who planned to undergo head and neck, thoracic, intraperitoneal, ophthalmological, otorhinolaryngological, urological, orthopedic or plastic surgery were included in the study. Children classified as American Society of Anesthesiologists (ASA) Physical Status I or II at the time of operation planning were to be eligible.

Test Product, Dose and Mode of Administration, Batch No.:

JNJ-268229 (remifentanil hydrochloride) is a potent, selective, 4 anilidopiperdine µ-opioid agonist with pharmacologic action typical of this class of compound. It supplied for this study was a white to pale yellow powder, to be reconstituted before use.

After intubation, continuous intravenous infusion of JNJ-268229 (0.25 µg/kg/min as remifentanil) was started, while anesthesia was maintained with inhaled or intravenous anesthetics. This state needed to be maintained for at least 15 minutes until the start of skin incision. In cases where sedation by general anesthetics and analgesia by lidocaine did not seem to provide a sufficient means of analgesia at the time of intubation, JNJ-268229 could be used, beginning before intubation. In such cases, JNJ-268229 was serially infused at a rate of 0.25 µg/kg/min as remifentanil and its infusion needed to be continued after completion of intubation. The length of time from completion of intubation to the start of skin incision was to be at least 15 minutes also in cases where this drug began to be used before intubation. During the evaluation for response to skin incision, the dose immediately before skin incision was to be maintained. If the responses to stimuli were observed or the 5-minute assessment period was completed, the infusion rate could be changed. In emergency, the infusion rate could be changed.

If clinically significant decrease of blood pressure (BP) or heart rate (HR) were observed during the administration of JNJ-268229 over 15 minutes from completion of intubation to skin incision and judged that the infusion rate had to be reduced, the investigator or subinvestigator could decrease the infusion rate of 0.25 µg/kg/min. After reduction, if possible, the infusion rate was to be increased to 0.25 µg/kg/min again before few minutes of skin incision.

After skin incision, the infusion rate could be increased by 25-100% or decreased by 25-50% at intervals of 2-5 minutes, provided the infusion rate did not exceed 1.3 µg/kg/min.

For inadequate anesthesia, it was acceptable to administer a single supplemental bolus injection of JNJ-268229 (1.0 µg/kg as remifentanil) over 30 seconds or longer at an interval of 2-5 minutes. Also,

after confirming the stable general condition, a single bolus injection was possible to discontinue on the way.

JNJ-268229 was to be completed upon completion of general anesthetics treatment.

The batch number of study drug was 3501-1 in this study.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Duration of Treatment:

JNJ-268229 was administered after the intubation until completion of general anesthetics treatment. In cases where sedation by general anesthetics and analgesia by lidocaine did not seem to provide a sufficient means of analgesia at the time of intubation, JNJ-268229 could be used, beginning before intubation.

Criteria for Evaluation:

Efficacy

- Primary endpoint
  - Proportion of subjects who responded to skin incision (proportion of inadequate anesthesia)

Responses to surgical stimuli (stress reactions) were rated by the investigator or subinvestigator during the 5-minute assessment period after skin incision in accordance with the criteria given below. Presence of at least one of the responses listed within evaluation period was deemed as "positive". In addition, during the 5-minute assessment period, HR was measured at 1, 2, 3, 4, and 5 minutes, and systolic blood pressure (SBP) was measured at least at 1, 3, and 5 minutes, but when increase of more than 20% was observed at either point, SBP was measured at 1 minute later and confirm presence of the continuation for 1 minute. The acceptable range of the time for each point was ±0.5 minutes from the planned point of time. Once a positive response to stimuli was observed, evaluation for a second positive response in remaining period was not to be needed.

Hemodynamic response	HR increased ≥20% above baseline [a] for ≥1 minute SBP increased ≥20% above baseline [a] for ≥1 minute
Somatic response	Gross movement, swallowing, eye opening [b] or grimacing
Autonomic response	Sweating, lachrymation or mydriasis [b]

[a] Measured under stable hemodynamics after intubation, and 1-5 minutes before the planned start of skin incision

[b] If there were patches on the eyes, this assessment could not be evaluated

- Secondary endpoints
  - Hemodynamics and respiratory stability
  - Global assessment on analgesic effect of JNJ-268229 during operation.
  - Drugs used to deal with insufficient anesthesia (inadequate anesthesia) or excessive anesthesia
  - Total dose level of JNJ-268229
  - Concomitant anesthetic dose level (maintenance dose)
  - Time from completion of anesthesia to resumption of spontaneous respiration
  - Time until arrival of Steward Postanesthetic Recovery Score at 6

  - Time from completion of anesthesia to discharge from the recovery room

- Exploratory endpoints
  - Time from intubation to skin incision
  - Time from start of JNJ-268229 treatment to skin incision
  - Time from completion of anesthesia to extubation

Pharmacokinetics

After obtaining consent of a legally acceptable representative for collecting blood samples, arterial blood samples were collected for the assay of remifentanil from subjects who were possible to take drawing of arterial blood by catheter placed in arterial (A line) or arterial puncture during the period from 15 minutes after the start of infusion to the end of infusion of JNJ-268229 (except for during the 5-minute assessment period of response to skin incision), wherever possible. Samples were to be collected at the time-point when infusion rate was constantly maintained for more than 10 minutes after infusion rate was changed.

Safety

The safety and tolerability of JNJ-268229 were evaluated by physical examinations, clinical laboratory tests, vital signs, ECG, respiratory parameters, and AEs. The causal relationship between an AE and JNJ-268229 was defined as "not related", "doubtful", "possible", "probable", or "very likely", and an AE was considered associated with the use of JNJ-268229 if the attribution was "possible", "probable", or "very likely". The severity grade of an AE was assessed using category of "mild", "moderate" or "severe".

Statistical Methods:

Efficacy

The primary endpoint is the proportion of subjects who responded to skin incision (proportion of inadequate anesthesia). The primary efficacy was analyzed using data from FAS. In this primary analysis, the proportion of subjects who responded to skin incision was summarized using frequencies and percentages with two sided 95% confidence interval (CI). For secondary endpoints, the continuous variables were summarized using descriptive statistics, which included the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. The categorical variables were summarized using frequencies and percentages. For exploratory endpoints, the same analyses above were performed.

Pharmacokinetics

Analysis was performed using remifentanil concentration which was obtained at a constant infusion rate maintained for a certain period time. Data were summarized using descriptive statistics and presented graphically. If deemed necessary, exploratory analysis, such as examination of the relation of remifentanil concentration to the time length maintained at a constant administration rate, could be conducted.

Safety

Safety was evaluated by examining the incidence, severity, relationship to JNJ-268229, and type of AEs; changes in clinical laboratory results; vital signs; ECG; and respiratory parameters. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Data were summarized using descriptive statistics. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs [TEAEs] including AEs that had worsened since baseline) were to be included in the analysis.

RESULTS:

STUDY POPULATION:

Of the 84 subjects (42 in each age group) who provided the informed consent, 80 (40 in each age group) were treated with JNJ-268229 (ie, safety analysis set), and 4 (2 in each age group) discontinued the study before treatment. All 80 subjects who received JNJ-268229 completed the study. The safety analysis set and the FAS included all 80 treated subjects (40 in each age group). The PK analysis set included 36 subjects (18 in each age group).

Among 80 treated subjects, the mean age was 7.1 years. There were 38 female subjects (47.5%) and 42 male subjects (52.5%). The mean weight at screening was 26.032 kg. Of the 80 subjects, 63 (78.8%) were classified as ASA physical status I. The most common operative location was head or neck (30.0%) followed by abdominal region, and extremities or joints (18.8% each). The median duration of surgery was 73.5 minutes.

Forty subjects were included in each age group. The numbers of male subjects were 25 subjects (62.5%) in the 1-6 years group and 17 subjects (42.5%) in the 7-15 years group. The most common operative location in the 1-6 years group was head or neck (37.5%) followed by abdominal region (27.5%) and urology (20.0%). The most common operative location in the 7-15 years group was extremities or joints (25.0%) followed by head or neck, and back (22.5% each).

Major protocol deviations were reported in 5 subjects (6.3%; 4 in the 1-6 years group, 1 in the 7-15 years group). Of these subjects, 3 in the 1-6 years group received wrong treatment or incorrect dose, and 1 in each age group received a disallowed concomitant treatment. Of the 3 subjects who received wrong treatment or incorrect dose, the infusion rate of JNJ-268229 was increased before skin incision and the increased rate was maintained during the evaluation in 2 subjects, and JNJ-268229 was administered at inappropriate initial infusion rate (0.1 μg/kg/min) in 1 subject.

The mean initial infusion rate was 0.248 μg/kg/min (range: 0.10-0.26 μg/kg/min). The mean duration of exposure was 168.0 minutes (range: 34-579 minutes). The mean total exposure including bolus injection was 57.730 μg/kg (range: 8.76-312.26 μg/kg). A total of 2 subjects (2.5%) received bolus injection, and the total exposure of bolus injection was 2.00 μg/kg and 10.00 μg/kg, respectively.

PHARMACOKINETIC RESULTS:

Of the 36 subjects in the PK analysis set (18 in each age group), most (33) of subjects (15 in the 1-6 years group, 18 in the 7-15 years group) received JNJ-268229 at the infusion rate of 0.24-0.26 μg/kg/min as remifentanil when blood samples were collected. In the 1-6 years group, 2 subjects received JNJ-268229 at the infusion rate of >0.26 μg/kg/min as remifentanil, and 1 received JNJ-268229 at the infusion rate of <0.24 μg/kg/min as remifentanil. The median values of remifentanil concentration in subjects with infusion rate of 0.24-0.26 μg/kg/min were 4.330 ng/mL in the 1-6 years group, and 5.405 ng/mL in the 7-15 years group. The median value of remifentanil concentration was slightly lower in the 1-6 years group than in the 7-15 years group.

The median values of remifentanil clearance (CL) were 57.506 mL/min/kg in the 1-6 years group, and 46.110 mL/min/kg in the 7-15 years group. The median value of remifentanil CL was slightly higher in the 1-6 years group than in the 7-15 years group. However, across range of age 1-15 years, no consistent pattern in remifentanil CL depending on age was observed.

EFFICACY RESULTS:

- The primary endpoint was the proportion of subjects who responded to skin incision (proportion of inadequate anesthesia). Nine subjects (11.3% [95% CI: 5.3%, 20.3%]) responded to skin incision. Hemodynamic responses were reported for these subjects (SBP increased in 8 subjects [10.0%], HR increased in 2 subjects [2.5%]). No apparent difference was shown between the age groups

(1-6 years, 7-15 years). Of 40 subjects in each age group, 5 (12.5%) and 4 (10.0%) responded to skin incision in the 1-6 years group and in the 7-15 years group, respectively.

- No apparent change was observed in the mean±SD of HR from before skin incision (92.6±24.52 bpm) to immediately before extubation (103.9±27.33 bpm) (maximum value within 5 minutes after skin incision: 96.7±26.97 bpm). No apparent changes were observed for each age group.
- No apparent change was observed in the mean±SD of SBP from before skin incision (93.0±13.50 mm Hg) to immediately before extubation (110.2±20.00 mm Hg) (maximum value within 5 minutes after skin incision: 100.7±17.43 mm Hg). No apparent changes were observed for each age group.
- The mean±SD of respiratory rate (RR) were 22.6±6.03 breaths/min before intubation and 16.4±6.18 breaths/min immediately before extubation. The mean RR slightly increased after extubation (5 minutes after extubation: 20.8±8.78 breaths/min), and returned to the similar level before intubation at follow-up (120 minutes after recovery room discharge: 23.4±5.61 breaths/min). No apparent changes were observed for each age group.
- The mean oxygen saturation of peripheral artery (SpO_2) exceeded 98% throughout the study period.
- No apparent change was observed in the mean±SD of end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) from 5 minutes after intubation (39.5±6.11 mm Hg) to immediately before extubation (44.4±9.47 mm Hg) (maximum value within 5 minutes after skin incision: 35.3±4.22 mm Hg). No apparent changes were observed for each age group.
- JNJ-268229 was assessed effective in all 80 subjects by global assessment on analgesic effect.
- A total of 47 subjects (58.8%) received drugs for insufficient anesthesia or excessive anesthesia. The most commonly used drug was sevoflurane (46.3%), followed by propofol (13.8%), ephedrine hydrochloride (8.8%) and phenylephrine hydrochloride (2.5%). The proportion of propofol use was lower in the 1-6 years group (2.5%) than in the 7-15 years group (25.0%). All subjects who received ephedrine hydrochloride or phenylephrine hydrochloride were in the 7-15 years group.
- Although the mean±SD of total dose level of JNJ-268229 was 57.730±67.0937 μg/kg as remifentanil, the median was 29.015 μg/kg (range: 8.76-312.26 μg/kg). The mean total dose level of JNJ-268229 as remifentanil was higher in the 7-15 years group (73.235 μg/kg) than in the 1-6 years group (42.225 μg/kg). However, no apparent difference was represented in median between the age groups (26.568 μg/kg for 1-6 years, 30.978 μg/kg for 7-15 years).
- The mean±SD of dose levels of concomitant propofol and sevoflurane were 7.865±1.1131 mg/kg/hr and 2.166±0.6069%, respectively. No apparent difference was noted in the concomitant anesthetic dose levels between the age groups.
- The mean±SD of time from completion of anesthesia to resumption of spontaneous respiration was 15.7±7.44 minutes. The mean±SD of time until arrival of steward postanesthetic recovery score at 6 was 25.6±8.71 minutes. The mean±SD of time from completion of anesthesia to discharge from the recovery room was 33.8±14.56 minutes. No apparent difference was shown between the age groups.
- The mean±SD of time from intubation to skin incision was 32.7±18.47 minutes. The mean±SD of time from start of JNJ-268229 treatment to skin incision was 38.8±19.86 minutes. The mean±SD of time from completion of anesthesia to extubation was 17.6±7.63 minutes. No apparent difference was noted between the age groups.

SAFETY RESULTS:

- All reported AEs with onset during the treatment phase including AEs that had worsened since baseline (ie, TEAEs) were included in the analysis.

- Of the 80 subjects in the safety analysis set, 65 (81.3%) had at least 1 TEAE, and 24 (30.0%) had at least 1 drug-related TEAE. Treatment-emergent AEs with special interest were reported in 9 subjects (11.3%). No TEAEs leading to death or study drug discontinuation, or no serious TEAEs were reported.
- The most common TEAEs (an incidence of ≥10%) were wound complication (51.3%), heart rate decreased (40.0%), heart rate increased (35.0%), pyrexia (21.3%), blood pressure systolic increased (18.8%), vomiting (16.3%), nausea (15.0%), blood pressure increased (11.3%) and eyelid edema (10.0%).
- Forty subjects were included in each age group. Treatment-emergent AEs were reported in 30 subjects (75.0%) in the 1-6 years group, and the most common TEAEs (an incidence of ≥20%) were heart rate decreased (32.5%), wound complication (32.5%), heart rate increased (27.5%) and pyrexia (22.5%). In the 7-15 years group, TEAEs were reported in 35 subjects (87.5%), and the most common TEAEs (an incidence of ≥20%) were wound complication (70.0%), heart rate decreased (47.5%), heart rate increased (42.5%), blood pressure systolic increased (25.0%), pyrexia (20.0%) and nausea (20.0%). The incidence of wound complication was lower in the 1-6 years group (32.5%) than in the 7-15 years group (70.0%). The incidences of eyelid edema, swelling face and oliguria were higher in the 1-6 years group (17.5%, 15.0%, 12.5%) than in the 7-15 years group (2.5%, 2.5%, 0%).
- Of all 80 subjects, 65 (81.3%) had at least 1 TEAE, and 37 (46.3%) and 28 (35.0%) experienced mild and moderate TEAEs as the worst severity, respectively. No severe TEAEs were reported.
- Of all 80 subjects, drug-related TEAEs were reported in 24 subjects (30.0%). The most common drug-related TEAE was heart rate decreased (26.3%).
- Of all 80 subjects, 65 (81.3%) had at least 1 TEAE, and most subjects experienced a first TEAE during the periods from 5 minutes after intubation until the end of JNJ-268229 administration (49 subjects [61.3%]), or after the end of JNJ-268229 administration (15 subjects [18.8%]). One subject (1.3%) reported a first TEAE during the period until 5 minutes after intubation.
- Of all 80 subjects, the TEAEs with special interest were reported in 9 subjects (11.3%). "Blood pressure decreased" and "convulsion" as "risk name" occurred in 8 subjects (10.0%) and 1 subject (1.3%), respectively. All TEAEs with special interest were mild in severity. No events classified as other "risk name" were reported.
- No apparent change was observed in the mean values of HR, SBP and diastolic blood pressure (DBP) from before skin incision to immediately before extubation. No apparent difference was shown between the age groups. The HR increased from baseline by 20% or more in 23 subjects (28.8%), and the HR was less than 80 bpm (for 1-7 years) or less than 60 bpm (for 8-15 years) in 22 subjects (27.5%). Systolic blood pressure increased from baseline by 20% or more in 23 subjects (28.8%), and decreased from baseline by 20% or more in 8 subjects (10.0%).
- The mean±SD of RR were 22.6±6.03 breaths/min before intubation (baseline) and 16.4±6.18 breaths/min immediately before extubation. The mean RR increased after extubation and recovered to the baseline level during the follow-up phase (120 minutes after recovery room discharge: 23.4±5.61 breaths/min). The mean SpO_2 exceeded 98% throughout the study period. No apparent change was observed in the mean±SD of $P_{ET}CO_2$ from 5 minutes after intubation (baseline value: 39.5±6.11 mm Hg) to immediately before extubation (44.4±9.47 mm Hg).

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

JNJ-268229 was shown to be effective and safe for analgesia in maintenance of general anesthesia for pediatric patients aged 1-15 years.

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