CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212295Orig1s000

<u>OTHER REVIEW(S)</u>

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 30, 2020

To: Rigoberto Roca, M.D., Acting Director
Division of Anesthesia, Addiction Medicine, and Pain Medicine (DAAP)

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Controlled Substance Staff (CSS)

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Subject: NDA 212295 (IND 102486)
Remimazolam as lyophilized powder (20 mg) for reconstitution and injection
Proposed trade name, conditionally accepted: Byfavo
Indication: Induction and maintenance of procedural sedation
Dosage: 5.0 mg (i.v.) plus 2.5 mg (i.v.) supplemental doses
Sponsor: Cosmo Technologies, Ltd.

Materials reviewed: NDA 212295 (submitted April 5, 2019, and subsequent amendments)
Statistical review of human abuse potential study
(Ran Bi, Ph.D., Office of Biostatistics, October 2, 2019)

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I. SUMMARY

1. Background

The Division of Anesthesia, Addiction Medicine, and Pain Medicine (DAAP) requested that CSS conduct an abuse potential assessment of the preclinical and clinical studies conducted with remimazolam under NDA 212295, submitted by Cosmo Technologies, Ltd.

Remimazolam is a novel benzodiazepine that is being developed as an (b) (4) intravenous (IV) agent for use in the induction and maintenance of procedural sedation (e.g., for colonoscopies, bronchoscopies, etc). It has a rapid onset, an extremely short half-life (half-life of 9 minutes), and its primary metabolite is inactive. It will only be used in a clinical setting.

On January 23, 2020, remimazolam was approved in Japan. It is unclear from Sponsor press releases and pharmaceutical news whether the Japanese product was given controlled substance status in Japan.

Each single-patient-use vial contains 27.2 mg remimazolam besylate as a lyophilized powder for reconstitution, equivalent to 20 mg remimazolam for injection. The recommended bolus dosing regimen for procedural sedation is an initial dose of remimazolam administered intravenously (IV) as a 5 mg (2 mL) push injection over a 1-minute time period. As needed, supplemental doses of 2.5 mg (1 mL) of remimazolam may be administered intravenously over a 15-second time period. At least 2 minutes must have elapsed prior to the administration of any supplemental dose.

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CSS was consulted 11 times between 2014 and 2018 regarding protocol designs for animal self-administration, drug discrimination, and physical dependence studies, as well as design of an intravenous human abuse potential (HAP) study and intranasal/oral bioavailability studies (with and without alcohol).

In the NDA, the Sponsor concludes that remimazolam has abuse potential similar to that of other currently marketed benzodiazepines, all controlled in Schedule IV of the Controlled Substances Act (CSA). Thus, the Sponsor proposes that remimazolam be placed into Schedule IV of the CSA.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 212295 for remimazolam and concludes that the drug has abuse potential similar to that of Schedule IV benzodiazepines under the CSA. This conclusion is based on the data described below:

- Remimazolam has a chemical structure that is similar to the Schedule IV benzodiazepine, midazolam.

- In receptor binding and functional studies, remimazolam has highly selective activity at GABA-A receptors as an agonist. This is the same mechanism of action as Schedule IV benzodiazepines.

- In a general behavior test in rats, remimazolam produced dose-dependent increases in sedation, as would be expected from a benzodiazepine.

- In a drug discrimination study in rats, remimazolam generalized to the cue produced by the Schedule IV benzodiazepine, midazolam. This would be expected, since the pharmacological mechanisms of action of the two drugs are similar.

- In a self-administration study in monkeys, remimazolam produced self-administration that was similar to, or greater than that produced by the Schedule IV barbiturate, pentobarbital. CSS agrees with the Sponsor that this study had a poor design but still produced abuse-related signals indicative that remimazolam produces rewarding effects.

- In a monkey physical dependence study, chronic administration of remimazolam produced signs of withdrawal during drug discontinuation. This suggests that remimazolam produces physical dependence, consistent with physical dependence produced by other benzodiazepines.

- In a human abuse potential (HAP) study, intravenous administration of remimazolam (5 and 10 mg) and intravenous administration of midazolam (2.5 and 5 mg) produced responses on positive subjective measures such as Drug Liking, Overall Drug Liking, and Good Drug Effects that were statistically significantly greater than placebo. The remimazolam doses are within the proposed therapeutic range but larger doses were not feasible because they would

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induce sedation in subjects. These data suggest that remimazolam produces rewarding effects.

- Euphoria as an adverse event (AE) was reported at an incidence of 4.5% in Phase 1 studies with healthy individuals following administration of remimazolam, but was not reported at an incidence of 2% or greater in Phase 2/3 studies with patients undergoing procedural sedation. In Phase 1 studies, the only other abuse-related AE was somnolence (6.3%). In Phase 2/3 studies, CNS AEs included sleep disorder (7.7%), agitation (7.5%), delirium (2.5%), and insomnia (2.3%), but these are not considered signals of abuse potential in the absence of a euphoria signal.

3. Recommendations

Based on the CSS determinations that remimazolam has abuse potential, will have a currently accepted medical use upon NDA approval, and produces physical dependence, CSS concludes that:

a) Remimazolam should be recommended for placement in Schedule IV of the CSA.

b) If approved, remimazolam product labeling should have a Section 9 Drug Abuse and Dependence, which should appear as:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[This section cannot be completed until the Drug Enforcement Administration completes a scheduling action under the Controlled Substances Act.]

9.2 Abuse

TRADENAME contains the benzodiazepine, remimazolam. Benzodiazepines are a class of sedative drugs with a known potential for abuse. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In a human abuse potential study conducted in recreational sedative abusers (n=39), remimazolam (5 and 10 mg, i.v.) produced responses on positive subjective measures such as “Drug Liking,” “Overall Drug Liking,” “Take Drug Again,” and “Good Drug Effects” that were statistically similar to those produced by the sedative midazolam (2.5 and 5 mg), and statistically greater than the responses on these measures that were produced by placebo.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Benzodiazepines are known to produce physical dependence if used daily or frequently over a period of weeks or longer. In a monkey physical

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dependence study, continuous intravenous infusion of remimazolam for 28 days produced withdrawal signs such as tremors, muscle rigidity, restlessness, impaired motor activity, and a reduction in food consumption upon drug discontinuation. One of six monkeys in this study exhibited systemic convulsions and dissociation from the environment. These behaviors are consistent with benzodiazepine withdrawal, which suggests that remimazolam produces physical dependence.

II. DISCUSSION

1. Chemistry

1. Drug Substance

Remimazolam (USAN name) is a new molecular entity identified by CAS registry number: 308242-62-8. It is chemically known as 4H-imidazol[1,2a][1,4]benzodiazepine-4-propanoic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-, methyl ester, benzene-sulfonate (1:1). It has a molecular formula of $C_{21}H_{19}BrN_4O_2$ and a molecular weight of 439.3 g/mol. It is (b) (4) soluble in water.

1.2 Drug Product

The drug product is a sterile, preservative-free, white to off-white lyophilized powder requiring reconstitution with 0.9% w/v sterile saline solution prior to intravenous administration. The drug product is provided in a 12-ml vial containing (b) (4) mg of remimazolam besylate (20 mg remimazolam free base). Following reconstitution with 8.2 ml of sterile saline, the concentration is 2.5 mg/ml of remimazolam (as free base).

2. Preclinical Abuse-Related Studies with Remimazolam

2.1 Receptor Binding Studies *(Study # 146078, 146079, AL-5589-G, FR095-0004149; Kilpatrick et al., 2007)*

In a receptor binding study, remimazolam was found to have high affinity for GABA-A receptors in rats (Ki = 32 nM), Yucatan micropigs (Ki = 28 nM), and humans (Ki = 30 nM). In contrast, CNS-7054, the metabolite of remimazolam, produced an affinity for GABA-A receptors that was > 8000 nM for rats, micropigs, and humans. These data show consistency in binding affinity across species for these two compounds.

When remimazolam and CNS-7054 were tested at 44 other binding sites at a concentration of 10 μM, neither compound displaced radioligand binding by >50%. These sites included abuse-related sites such as dopamine (D1-D5), serotonin (1A, 2A, 2C, 3, 5A, 6, and 7), opioid (mu, kappa, and delta), cannabinoid (CB-1 and CB-2), nicotine, GABA (A and B), glutamate (AMPA, phencyclidine, glycine, kainate), sigma, orexin (1 and 2), and transporters (dopamine, serotonin, norepinephrine, and GABA).

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Thus, remimazolam is a highly-selective GABA-A ligand that is inactive at other abuse-related sites.

2.2 Animal Behavioral Studies

a. General Behavioral Observations

i. Rat Irwin Test (Study #DRMN1046)

In an Irwin study conducted in rats during a toxicity study, remimazolam was administered intravenously at doses of 10, 20, and 30 mg/kg. Each dose of the drug produced sedative effects within 5 minutes after drug administration, including decreases in locomotion, alertness, startle/touch response, fearfulness, body tone, and grip strength. At the 30 mg/kg dose, there were additional decreases in righting reflex and increases in abnormal gait. As is typical of intravenous pharmacodynamics, the behavioral effects subsided rapidly and most animals showed full recovery after 45 minutes.

Thus, remimazolam produces the sedative responses in rats that would be expected from a benzodiazepine.

b. Abuse-Related Behavioral Studies

i. Drug Discrimination Study with Remimazolam (Study #NO11381)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq$80% on the bar associated with the training drug.

Method

Male rats (n = 20) were trained to discriminate midazolam (3.0 mg/kg, i.p.) from vehicle. Midazolam is a benzodiazepine that has a similar chemical structure and mechanism of action to that of remimazolam. During training, the schedule of reinforcement was gradually raised from fixed ratio (FR) 1 to FR10. Full generalization was defined as 80% accuracy on the drug-associated lever.

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When intraperitoneal midazolam discrimination was stable, animals were challenged with midazolam (0.3, 1.0, and 3.0 mg/kg, i.p., 15-minute pretreatment time), and then with remimazolam (2.5, 5, 10, and 20 mg/kg, i.p., no pretreatment time, based on observations of immediate sedation).

In a previous study to determine remimazolam doses for the drug discrimination study (Study #NO11276), the lowest observed effect level of remimazolam was 10 mg/kg, but the behavioral changes from this dose disappeared within 15 minutes. This dose was selected as the initial dose in the drug discrimination study, with higher and lower doses selected around this dose.

Results

Midazolam dose-dependently increased the degree of generalization to the midazolam drug cue, with full generalization (95%) occurring only at the 20 mg/kg dose.

Remimazolam dose-dependently increased the degree of generalization to the midazolam drug cue, with full generalization (80%) occurring only at the 20 mg/kg dose.

Conclusions

This study shows that remimazolam produces full generalization to the cue for midazolam. This would be expected since these two drugs have similar mechanisms of action.

ii. Self-Administration Study in Rats with Remimazolam (Study # NO11366)

A self-administration study was conducted in Rhesus monkeys (n = 6 males and 2 females; n = 4/group) to evaluate whether remimazolam produces sufficient reward to be reinforcing.

Methods

A dose-finding study was conducted first, using the following reasoning (presented **verbatim** from the protocol):

> "Based on the data provided by the sponsor, 0.5 and 1 mg/kg, doses at which some clinical signs were expected to be observed but no severe changes such as anesthesia, extreme excitement, convulsions and vomiting would be induced when remimazolam is administered once intravenously to rhesus monkeys, were selected as the dose levels for the first trial. When remimazolam was administered once intravenously to 2 animals each at 0.5 and 1 mg/kg (0.5 and 1 mL/kg) in the first trial, ataxia, slowed motion, hyporeactivity to the observer and decreased aggression to the observer and decreased grimacing at the observer were observed in 2 animals at 0.5 mg/kg from immediately to 30 minutes post-dosing and eye-closing in 1 animal immediately after dosing. At 1 mg/kg, ataxia, slowed motion, hyporeactivity to the observer, eye-closing and lying down on the side were observed in 2 animals and decreased aggression to the observer or decreased grimacing at the observer was also observed in 1 animal each from

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immediately to 30 minutes post-dosing. Based on these results, the dose levels for the second trial were selected at 0.125 and 0.25 mg/kg. When remimazolam was administered once intravenously to 2 animals each at 0.125 and 0.25 mg/kg in the second trial, ataxia and slowed motion in 2 animals and decreased aggression to the observer in 1 animal were observed at 0.125 mg/kg immediately after dosing. At 0.25 mg/kg, ataxia and decreased grimacing at the observer were observed in 2 animals and slowed motion and decreased aggression to the observer or hyporeactivity to the observer was observed in 1 animal each from immediately to 15 minutes post-dosing. Based on these results, the dose levels for the third trial were selected at 0.03 and 0.06 mg/kg."

Doses for the Main Study were then determined using the following reasoning (presented **verbatim** from the protocol):

"In Experiment 1, no gross behavioral signs were observed at 0.03 or 0.06 mg/kg. At 0.125 mg/kg and above, ataxia, slowed motion, and decreased aggression to the observer were observed. In addition, gross behavioral signs were observed as follows: decreased grimacing at the observer and hyporeactivity to the observer at 0.25 mg/kg and above, eye-closing at 0.5 mg/kg and above and lying down on the side at 1 mg/kg. Based on these results, 0.125 mg/kg was considered to be the minimum effective dose level. Since no death occurred in any monkey receiving 20 mg/kg for 4 weeks by intravenous administration in a 4-week intravenous (bolus) repeated dose toxicity study in the cynomolgus monkey with a 2-week recovery period (Study No. RXA5004), no lethal toxicity was expected at 0.125 mg/kg even if self-administration was conducted at least 10 times/day on consecutive days. Therefore, 0.125 mg/kg/infusion, a dose which was below the minimum effective dose level and at which no severe toxicity would be expected even after frequent self-administration, was selected as the high dose level. Then, the lower dose levels of 0.06, 0.03, 0.015 and 0.008 mg/kg/infusion were selected using a common ratio of approximately 2.

"During the 2-hour self-administration in Experiment 2, frequent self-administration of at least 11 times/day was noted in 1 of the 4 animals at all dose levels and in another animal at all dose levels other than 0.125 mg/kg/infusion. The mean number of self-administrations was the largest at 0.03 mg/kg/infusion in both animals. On the other hand, frequent self-administration of at least 11 times/day was not noted in the other 2 animals. Based on these results, 0.03 mg/kg/infusion was selected as the mid dose level for the 24-hour self-administration and 0.06 and 0.015 mg/kg/infusion were selected as the high and low dose levels, respectively."

Two-hour sessions

Animals were trained to press a lever to receive pentobarbital (1.0 mg/kg/infusion, i.v.) using an FR5 schedule of reinforcement during two-hour sessions. Priming through forced administration was conducted twice on the first day of each session with pentobarbital at the dose level to be tested immediately prior to animal placement in the test cage. After pentobarbital self-administration was stable for three sessions ((≥11 infusions/session with infusions limited to 20

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infusions/day), animals were provided with vehicle to induce extinction for three, two-hour sessions. Challenge sessions with remimazolam were then started.

Remimazolam was tested at (0.125, 0.06, 0.03, 0.015 and 0.008 mg/kg/infusion) using a FR5 schedule of reinforcement for 4 days/dose in descending order of the dose levels without limitation on the number of self-administrations during two-hour sessions. Priming through forced administration was conducted twice on the first day of each session with remimazolam at the dose level to be tested immediately prior to animal placement in the test cage.

Twenty-four-hour sessions

The 24-hour sessions with pentobarbital and vehicle were run using the same procedures as those for the two-hour sessions. Priming through forced administration was conducted twice on the first day of each session with pentobarbital at the dose level to be tested immediately prior to animal placement in the test cage. Forced administration was repeated if the number of self-administrations of pentobarbital at each dose level was not greater than once/day for at least 3 consecutive days during the 24-hour procedure.

For the 24-hour sessions with remimazolam, there were no limitations on self-administration of the high dose (0.06 mg/kg/infusion; 9-16 days), but there were limits of 100 infusions/day for the middle and low doses (0.03 and 0.015 mg/kg/infusion; 5 days). Priming through forced administration was conducted twice on the first day of each session with pentobarbital at the dose level to be tested immediately prior to animal placement in the test cage. Forced administration was repeated if the number of self-administrations of remimazolam at each dose level was not greater than once/day for at least 3 consecutive days during the 24-hour procedure.

The Sponsor states that remimazolam would be considered rewarding if animals self-administered remimazolam ≥11 times/day for at least 5 consecutive days. Any animal that achieved this criterion was then stopped from receiving further access to the drug and was observed the following day for withdrawal signs.

Results

Two-hour sessions

The results show that all 4 monkeys self-administered pentobarbital (1 mg/kg/infusion) 13-16 infusions (limit of 20 infusions/session) for each of 3 consecutive days in the two-hour sessions. In contrast, there was a low degree of self-administration of vehicle (n = 0.3-6.3 infusions) for each of the 3 consecutive days.

When animals were allowed to self-administer remimazolam, 1 of the 4 monkeys never self-administered the drug at 4 of the 5 doses (0.125, 0.03, 0.015 or 0.008 mg/kg/infusion) and only self-administered an average of 0.7 times over the 3 sessions, despite having self-administered pentobarbital an average of 13 times over 3 sessions.

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Similarly, 1 of the 4 monkeys self-administered each of the 5 doses an average of 3-4 times over the 3 sessions, which is less than it self-administered vehicle (an average of 6 times over 3 sessions).

The other two monkeys self-administered remimazolam at a rate similar to pentobarbital (an average of 10-16 times over 3 sessions for the 0.6, 0.03, and 0.015 mg/kg/infusion doses) or at a rate much higher than that for pentobarbital (an average of 22-38 times over 3 sessions for the 0.125, 0.6, 0.03, and 0.015 mg/kg/infusion doses).

Based on the results showing that the 0.03 mg/kg/infusion dose produced the greatest number of daily self-administrations during the 2-hour self-administration procedure, this dose was selected by the Sponsor as the mid dose level and 0.06 and 0.015 mg/kg/infusion were selected as the high and low dose levels, respectively, for the 24-hour self-administration procedure.

Twenty-four-hour sessions

The results show that all 4 monkeys self-administered pentobarbital (1 mg/kg/infusion) 15-20 infusions (limit of 20 infusions/session) for each of 3 consecutive days in the 24-hour sessions. In contrast, there was a low degree of self-administration of vehicle (n = 0.3-2.7 infusions) for each of the 3 consecutive days.

When animals were allowed to self-administer remimazolam in the 24-hour sessions, all 4 monkeys self-administered remimazolam, which contrasts with the data from the 2-hour sessions in which only 2 of 4 monkeys self-administered the drug. The 0.06 mg/kg/infusion dose of remimazolam produced self-administration ranging an average of 36-360 times/session over 9-16 days. At the 0.03 and 0.015 mg/kg/infusion doses, monkeys self-administered remimazolam an average of 70-100 times/session over 5 days.

Conclusions

Remimazolam produces rewarding properties that sustain reinforcement, as evidenced by self-administration of the drug to a degree that was similar to or greater than that produced by pentobarbital.

2.3 Physical Dependence Studies in Animals

a. Rat Physical Dependence Study with Remimazolam (Study #17.0186)

A physical dependence study was conducted in rats to determine if chronic administration of remimazolam produces a withdrawal syndrome upon drug discontinuation, compared to midazolam and vehicle.

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Methods

Rats (n = 10/condition) were implanted with an indwelling i.v. femoral catheter. They subsequently received intravenous doses of remimazolam, midazolam, or vehicle over the 28-day dosing period. Table 1 (below) shows the dose escalation schedule for the two drugs.

Table 1: Dose Escalation for Remimazolam and Midazolam (28-Day Dosing Period)

Dosing period	Group	N of rats	Treatment	Daily Total	Daily Initial bolus (2 minutes)		Daily Infusion (2 hours)	
				Dose *(mg/kg)*	Dose *(mg/kg)*	Concentration (mg/ml)	Dose *(mg/kg)*	Concentration (mg/ml)
Days 1 - 4	1	10	Vehicle	0	0	na	0	na
	2	10	Remimazolam	30	15	3	15	1.5
	3	10	Midazolam	10	5	1	5	0.5
Days 5 - 14	1	10	Vehicle	0	0	na	0	na
	2	10	Remimazolam	40	20	4	20	2
	3	10	Midazolam	20	10	2	10	1
Days 15 - 21	1	10	Vehicle	0	0	na	0	na
	2	10	Remimazolam	50	25	5	25	2.5
	3	10	Midazolam	25	10	2	15	1.5
Days 22 - 28	1	9	Vehicle	0	0	na	0	na
	2	10	Remimazolam	60	30	6	30	3
	3	10	Midazolam	25	10	2	15	1.5

Remimazolam was administered on a daily basis for 28 consecutive days in two phases each day: initially as an i.v. bolus injection over 2 minutes, followed by a continuous i.v. infusion over the next 2 hours, using the following dose escalation schedule:

- Day 1 - Day 4: 15 mg/kg i.v. bolus + 15 mg/kg i.v. infusion (30 mg/kg/day)
- Day 5 - Day 14: 20 mg/kg i.v. bolus + 20 mg/kg i.v. infusion (40 mg/kg/day)
- Day 15 - Day 21: 25 mg/kg i.v. bolus + 25 mg/kg i.v. infusion (50 mg/kg/day)
- Day 22 - Day 28: 30 mg/kg i.v. bolus + 30 mg/kg i.v. infusion (60 mg/kg/day)

Midazolam was administered on a daily basis for 28 consecutive days in two phases each day: initially as an i.v. bolus injection over 2 minutes, followed by a continuous i.v. infusion over the next 2 hours, using the following dose escalation schedule:

- Day 1 - Day 4: 5 mg/kg i.v. bolus + 5 mg/kg i.v. infusion (10 mg/kg/day)
- Day 5 - Day 14: 10 mg/kg i.v. bolus + 10 mg/kg i.v. infusion (20 mg/kg/day)
- Day 15 - Day 21: 10 mg/kg i.v. bolus + 15 mg/kg i.v. infusion (25 mg/kg/day)
- Day 22 - Day 28: 10 mg/kg i.v. bolus + 15 mg/kg i.v. infusion (25 mg/kg/day)

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Vehicle (D-lactose monohydrate solution) was administered on a daily basis for 28 consecutive days in two phases each day: initially as an i.v. bolus injection over 2 minutes, followed by a continuous i.v. infusion over the next 2 hours.

During the drug administration period, rats were evaluated daily during weekdays for food and water consumption, body weight, righting reflex, startle/touch response, corneal reflex, pinch response, general activity, and muscle tone.

At the end of the dosing period, rats were discontinued from drug administration and were observed for an additional 7 days for withdrawal signs, including Straub tail, hunched posture, chewing movements, piloerection, general activity, and tremor.

Results

Effects of vehicle

Vehicle administration produced few behavioral changes. During the drug discontinuation period, there were no changes in the experimental measures.

Effects of midazolam

Midazolam administration produced no changes compared to vehicle in food and water consumption, and body weight gain.

None of the rats treated with midazolam showed loss of righting reflex (LRR). However, in each of the four dosing periods in which midazolam was increased from 10 to 25 mg/kg/day, 100% of the animals showed sedation signs that could include a decrease of fear/startle response, a decrease of reactivity to touch, a loss of corneal reflex, a decrease of activity and a decrease of abdominal muscle tone.

Following midazolam discontinuation there were no statistically significant differences in body weight gain, mean daily food consumption or mean water consumption compared to vehicle. There were also no behavioral signs of withdrawal, except for one incident of Straub tail in one rat.

Effects of remimazolam

Remimazolam administration produced no changes compared to vehicle in food and water consumption, and body weight gain.

During Days 1-4 (30 mg/kg/day), 60-70% of rats showed loss of righting reflex (LRR), and 70-100% of rats showed sedation signs including a decrease of fear/startle response, decreased reactivity to touch, a loss of corneal reflex, a decrease of activity and a decrease of abdominal muscle tone. Typically, these behaviors started 10 minutes after the start of drug administration and lasted less than 30 minutes.

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During Days 5-14 (40 mg/kg/day), 50-70% of rats showed LRR and 78-100% of rats showed sedation signs that started 10 minutes after the start of drug administration and lasted less than 20 minutes.

During Days 15-21 (50 mg/kg/day), 50-60% of rats showed LRR and 80% to 100% of rats showed sedation signs that started 10 minutes after the start of drug administration and lasted less than 55 minutes.

During Days 22-28 (60 mg/kg/day), 60-78% of rats showed LRR and 70% to 100% of rats showed sedation signs that started 10 minutes after the start of drug administration and lasted less than 10 minutes.

Following remimazolam discontinuation there were no statistically significant differences in body weight gain, mean daily food consumption or mean water consumption compared to vehicle. There were also no behavioral signs of withdrawal, except for hunched posture observed in three rats on Day 29 and one rat on Day 32.

Conclusions

In this study, the positive control drug, midazolam, did not produce a withdrawal syndrome during drug discontinuation after chronic administration.

Thus, this study is not valid as a means of determining whether remimazolam produces physical dependence, since it is not clear whether this laboratory is capable of producing or accurately observing the presence of a withdrawal syndrome following long-term administration of a CNS depressant.

Therefore, the conclusion that the lack of withdrawal signs during remimazolam discontinuation demonstrates that the drug does not produce physical dependence is unsupported.

b. Cynomolgus Monkey Physical Dependence Study (Study #NO11401)

A crossover physical dependence study was conducted in cynomolgus monkeys to determine if prolonged administration of remimazolam produces a withdrawal syndrome upon drug discontinuation.

Methods

Remimazolam or placebo were administered to monkeys (n = 6) via continuous intravenous infusion for 28 days. The dose levels for each monkey are shown below in Table 2. On Day 29, remimazolam was discontinued and the animals continued to be observed for another 7 days.

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Table 2: Monkey Remimazolam Dose Levels

Animal No	Dose level for Week 1 of dosing (mg/kg/h)	Dose level for Week 2 of dosing (mg/kg/h)	Dose level for Week 3 of dosing (mg/kg/h)	Dose level for Week 4 of dosing (mg/kg/h)
BK07	0.75	0.75	1.0	1.0
BK02	0.75	0.75	0.75	1.0
BK03	0.75	0.75	0.75	1.0
BK04	0.5	0.75	0.75	1.0
BK05	0.75	0.75	0.75	1.0
BK06	0.75	0.75	1.0	1.0

The dosing groups were as follows;

Group 1 (n = 3)
- 0.75 mg/kg/h from Days 1 to 22
- 1.0 mg/kg/h from Days 22 to 29

Group 2 (n = 2)
- 0.75 mg/kg/h from Days 1 to 15
- 1.0 mg/kg/h from Days 15 to 29

Group 3 (n = 1)
- 0.5 mg/kg/h from Days 1 to 8
- 0.75 mg/kg/h from Days 8 to 22
- 1.0 mg/kg/h from Days 22 to 29

During the drug dosing period, twice-daily observations included salivation, retching (dry heaves), vomiting, continual movement, hypoactivity, crouching posture, lying down on the side, aggression, eye-closing, hyporeactivity, grimacing, pupil size, slowed motion and ataxia. Findings were recorded as present (+) or absent (−) or were graded in 3 levels (−, +, 2+) or 4 levels (−, +, 2+, 3+). Body weight and food consumption were recorded daily.

During the drug discontinuation period, once-daily observations included body temperature, facial apprehension, hyperirritability, restlessness, piloerection, tremors, muscle rigidity, impaired motor activity, retching or vomiting, systemic convulsions, hallucinatory behavior, nystagmus and dissociation from environment. Findings were recorded as present (+) or absent (−) or were graded in 3 levels (−, +, 2+) or 4 levels (−, +, 2+, 3+). Body weight and food consumption were recorded daily.

Results

During the drug dosing period with remimazolam, all monkeys showed sedative signs such as ataxia, slowed motion, and hyporeactivity. During drug administration, tolerance developed to these effects, even as the dose was increased over the study duration.

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During the drug discontinuation period, all monkeys showed withdrawal signs including facial apprehension, hyperirritability, piloerection, muscle rigidity, retching and vomiting, tremors, restlessness and impaired motor activity. Monkeys also exhibited decreases in food consumption and body weights. One of the monkeys demonstrated severe withdrawal signs that included dissociation from environment, systemic convulsions and continuously prone position 25 hours into the drug discontinuation period. This animal then received humane administration of remimazolam to lessen the withdrawal syndrome.

Conclusions

Remimazolam produces physical dependence, as evidenced by the production of a withdrawal syndrome following drug discontinuation after chronic administration.

3. Animal and Human Pharmacokinetics of Remimazolam

Given that remimazolam is proposed for therapeutic treatment via intravenous administration, the Sponsor did not conduct pharmacokinetic studies in rats using intraperitoneal (i.p.) administration. Thus, it is not possible to show a comparative pharmacokinetic profile between rat i.p. administration (as used in the drug discrimination study) and i.v. administration in humans.

Similarly, although the Sponsor conducted pharmacokinetic studies in monkeys using i.v. administration of remimazolam, the lowest dose tested was 1.5 mg/kg, which is ~10- to ~185-fold greater than intravenous doses tested in the monkey self-administration study (0.008 to 0.125 mg/kg) and 0.5- to 3-fold greater than the intravenous doses tested in the monkey physical dependence study (0.5 to 1.0 mg/kg).

However, since each of these abuse-related studies were positive (e.g., showed full generalization to a benzodiazepine, was self-administered, and produced withdrawal signs following chronic drug discontinuation), there are no concerns that the doses used in the animal studies were insufficient.

4. Clinical Abuse-Related Studies with Remimazolam

During drug development, CSS had considered the need for the Sponsor to conduct a human abuse potential study using both intravenous and intranasal administration of remimazolam. However, CSS determined that the intravenous human abuse potential study, in conjunction with the intranasal and oral bioavailability studies in humans, was sufficient to provide necessary data regarding the abuse potential of remimazolam in humans.

4.1 Human Abuse Potential Study: A Double-blind, Randomized, Crossover Study to Assess the Subjective Abuse Potential of Intravenous Remimazolam Compared to Midazolam and Placebo in Recreational CNS-depressant Users (Study CNS7056-014)

This was a randomized, double-blind, placebo-controlled, 5-way crossover study that evaluated the abuse potential, safety, and tolerability of intravenous remimazolam compared to placebo and

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midazolam in healthy nondependent recreational CNS-depressant drug users. The study consisted of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

Subjects

Subjects

Subjects were healthy male and female adults, between 18 and 55 years of age, inclusive, who were non-dependent, non-treatment seeking recreational CNS-depressant drug users. Of the 83 subjects who participated in the Qualification Phase, 40 entered the Treatment Phase, with a total of 39 study completers.

Inclusion Criteria for participation are standard but included the following criteria that are relevant for a human abuse potential study:

- ≥ 10 lifetime non-therapeutic experiences (i.e., for psychoactive effects) with CNS depressants (e.g., benzodiazepines, barbiturates, opioids, zolpidem, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate)
- ≥ 1 non-therapeutic use of a CNS depressant within the 8 weeks prior to Screening
- ≥ 1 non-therapeutic use of benzodiazepines within the 12 months prior to Screening

The Sponsor included the following statement regarding their rationale for including subjects who were experienced with opioids:

> PAION acknowledges the comments from CSS that opioid users should not be enrolled in this study. However, based on the data above, enrolling benzodiazepine abusers alone would not have been feasible. In addition, PAION sought the opinion of Drs (b) (4) , experts in the field of substance abuse, who confirmed that the chances of recruiting a population of benzodiazepine abusers who are not also chronic opioid abusers is remote. And more importantly, opioid exposure doesn't alter the sensitivity to a benzodiazepine, whereas chronic excessive alcohol use might. The ability to determine benzodiazepine drug-liking would not be influenced by whether an individual is a recreational opioid abuser. The Discrimination Phase will determine whether or not a subject can differentiate sufficiently between placebo and test drug. For this, it is essential for subjects to have used and like using benzodiazepines as recreational drugs.

Exclusion Criteria are standard but included the following criteria that are relevant for a human abuse potential study:

- Alcohol or substance dependence within the 12 months prior to Screening (except nicotine) including cannabis, as defined by the DSM-IV-TR, or any self-reported dependence or “addiction” within the subject’s lifetime (with the exception of nicotine).

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- Subjects who had ever been in treatment for substance use disorder(s) (except smoking cessation) or who are currently seeking treatment for substance use disorder(s).

- Subjects who failed to abstain from alcohol and other drugs 48 hours prior to and throughout the study period.

Main Study:

The Main Study consisted of a Qualification Phase and a Treatment Phase. In both phases, subjective drug effects were measured using visual analogue scales (VAS) of 0 to 100 mm, such as for the following examples:

- "At the Moment" Bipolar Drug Liking VAS with anchors at 0 = "Strong Disliking", 50 = "Neither Like or Dislike", and 100 = "Strong Liking." Subjects were asked "*At this moment, my liking for this drug is*."
- Global Bipolar Overall Drug Liking VAS with anchors at 0 = "Strong Disliking", 50 = "Neither Like or Dislike", and 100 = "Strong Liking." Subjects were required to respond to the statement "*Overall, my liking for this drug is*."
- Global Bipolar Take Drug Again VAS with anchors at 0 = "Definitely Not", 50 = "Neutral", and 100= "Definitely So." Subjects were required to respond to the statement "*I would take this drug again*."
- "At the Moment" Unipolar Good Drug Effects VAS with anchors at 0 = "Not at All" and 100 = "Extremely." Subjects were required to respond to the statement "*At this moment, I have good drug effects*."
- "At the Moment" Unipolar Bad Drug Effects VAS with anchors at 0 = "Not at All" and 100 = "Extremely." Subjects were required to respond to the statement "*At this moment, I have bad drug effects*."

Subjects passed the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- Emax in response to intravenous midazolam 2.5 mg greater than that of placebo on drug-liking bipolar VAS (difference of at least 15 points) and Emax score of at least 65 points for midazolam in the first 60 minutes postdose, and acceptable overall responses to midazolam and placebo on the subjective measures, as judged by the investigator or designee.

- Acceptable placebo response based on drug-liking VAS (score between 40 and 60 points, inclusive).

- Subject was able to tolerate intravenous midazolam 2.5 mg, as judged by the investigator, including ability to complete all PD assessments administered within 60 minutes postdose.

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- General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

Subjects also were required to pass a Tolerability Assessment in order to be eligible for participation in the Treatment Phase:

- Subject was able to tolerate IV midazolam 5 mg, defined as ability to complete the subjective PD assessments administered within 60 minutes postdose (i.e., subject remained conscious or could be roused), oxygen saturation that did not fall below 90% for any period longer than 60 seconds in duration, and as otherwise judged by the investigator based on other safety parameters (e.g., telemetry, AEs, vital signs).

Subjects were required to fast (abstain from food) from at least 8 hours prior to and until at least 2 hours after study drug administration in the Qualification and Treatment Phases.

Subjects were not permitted to consume caffeine or xanthine-containing food or beverages while housed at the study site.

Subjects were required to abstain from smoking or use of nicotine replacement therapy for at least 2 hours prior to each study drug administration. Smoking or use of nicotine replacement therapy were permitted at short breaks (approximately 10 minutes in duration) after the 8-hour post-dose procedures.

Drug Doses

Main Study

Qualification Phase (single blinded)

The following treatments were administered intravenously:

- 2.5 mg midazolam
- placebo

The 2.5 mg midazolam is 1/4X to 1/2X the two doses administered in the Treatment Phase (5 and 10 mg).

There was a washout period of at least 48 hours in between treatments.

Treatment Phase (double-blind)

Subjects received each of the following 5 treatments (on days 5, 7, 9, 11, and 13), administered intravenously over 1 minute, in a randomized, double-blind, crossover manner following an overnight fast:

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- Remimazolam 5 mg
- Remimazolam 10 mg
- Midazolam 2.5 mg
- Midazolam 5 mg
- Placebo (saline injection)

Each drug administration was separated by approximately 48 hours. Serial PD evaluations were conducted up to 8 hours postdose.

The remimazolam doses (5 and 10 mg) reflect 1X and 2X the proposed therapeutic dose. Given that remimazolam is a benzodiazepine with sedating properties, subjects would not have been likely to complete the study measures if the dose was increased further.

The doses of midazolam (2.5 and 5 mg) have been used in published human abuse potential studies.

There was a washout period of 48 hours between treatments.

Pharmacodynamic Variables

All subjective endpoints were assessed at baseline, 2, 10, 15, 20, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after drug administration, with two exceptions: 1) VAS Drug Liking was also assessed at 5 minutes after drug administration, while VAS for Overall Drug Liking, and Take Drug Again were assessed at 4 and 6 hours after drug administration.

<u>Primary Measure:</u>

Drug Liking VAS (bipolar)

<u>Secondary Measures:</u>

Balance of effects:

- Overall Drug Liking VAS (bipolar)
- Take Drug Again VAS (unipolar)

Positive and negative effects:

- Good Effects VAS (unipolar)
- Bad Effects VAS (unipolar)

Memory test:

The Paired Associates Learning assesses visual memory and new learning, and is a sensitive tool for accurate assessment of episodic memory.

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Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG
- Physical examination findings
- Columbia Suicide Severity Rating Scale (C-SSRS) examination
- Concomitant medication usage.

Pharmacokinetic Evaluation

During the Treatment Phase, blood samples were collected immediately before each study drug administration and 5, 15, 30, 60, 120, 240, and 480 minutes after the start of each study drug administration to monitor the pharmacokinetics of each study treatment.

Results

The following analysis of the HAP study subjective measures presented below in quotations is the **verbatim** statement from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ran Bi ("the reviewer"), FDA Office of Biostatistics (October 2, 2019):

"To evaluate the abuse potential of Remimazolam, the reviewer performed statistical analysis for the primary endpoint, Drug Liking Emax, for the following questions, with the tested hypotheses and contrasts defined as follows:

"1. Does the positive control (C-Midazolam) produce mean Drug Liking Emax that shows greater abuse potential compared to Placebo (P)?

H_0: $\mu_C - \mu_P \leq 15$ vs. H_a: $\mu_C - \mu_P > 15$

"This hypothesis is for the study validation. Test value of 15 was chosen to be consistent with the value used in the Qualification Phase. Hypothesis 1 was applied to the following contrasts:

- Mi2.5 [midazolam 2.5 mg] versus P
- Mi5 [midazolam 5 mg] versus P

"2. Does the test drug (T-Remimazolam) produce mean Drug Liking Emax that shows less abuse potential compared to positive control (C-Midazolam)?

H_0:$\mu_C - \mu_T \leq 0$ vs. H_a:$\mu_C - \mu_T > 0$

"This hypothesis is for investigation of the abuse potential of the test drug Remimazolam, compared to the positive control Midazolam. Test value of 0 was chosen same as the sponsor did. Hypothesis 2 was applied to the following contrasts:

- Mi2.5 [midazolam 2.5 mg] versus Re5
- Mi2.5 [midazolam 2.5 mg] versus Re10
- Mi5 [midazolam 5 mg] versus Re5
- Mi5 [midazolam 5 mg] versus Re10

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"3. Does the test drug (T-Remimazolam) produce mean Drug Liking Emax that shows similar abuse potential compared to placebo (P)?

H_0: $\mu_T - \mu_P \geq 11$ vs. H_a: $\mu_T - \mu_P < 11$

"This hypothesis is to investigate whether the test drug Remimazolam had similar abuse potential compared to Placebo. Test value of 11 was chosen based on Chen and Bonson (2013). Hypothesis 3 was applied to the following contrasts:

- Re5 [remimazolam 5 mg] versus P
- Re10 [remimazolam 10 mg] versus P

"If the comparison of a dose of Remimazolam did not have a statistically significantly lower mean than any dose of Midazolam, the comparison between the dose of Remimazolam and Placebo would not be performed.
"The reviewer's primary analysis showed that for Drug Liking Emax:

- The mean differences between both doses of Midazolam and Placebo were statistically significantly greater than 15 points, confirming the study validity;
- Remimazolam 5 mg had statistically significantly smaller mean compared to Midazolam 5 mg, but there was no statistically significant difference in means between Remimazolam 5 mg and Midazolam 2.5 mg;
- There were no statistically significant differences in medians between Remimazolam 10 mg and both doses of Midazolam;

"Several subjects who responded similar maximum drug liking across all 5 treatments. Sensitivity analysis excluding those subjects was performed as well, but was omitted here since the results remained the same as using the Completer Population.

"The results from the reviewer's secondary analysis showed that for Overall Drug Liking Emax, Take Drug Again Emax, Good Drug Effects Emax, Bad Drug Effects Emax:

- The mean/median of each dose of Midazolam was statistically significantly greater than that of Placebo
- Remimazolam 5 mg had statistically significantly smaller mean/median compared to Midazolam 5 mg; there was no statistically significant difference in means/medians between Remimazolam 5 mg and Midazolam 2.5 mg except Take Drug Again Emax
- There were no statistically significant differences in means/medians between Remimazolam 10 mg and both doses of Midazolam, except the comparison between Remimazolam 10 mg and Midazolam 5 mg for Take Drug Again Emax (p-value = 0.0369);
- The mean of Take Drug Again Emax for Remimazolam 5 mg was statistically significantly greater than that of Placebo."

Study Data

Table 3 (below) depicts the effects of study treatments on subjective measures used in this study.

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The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an acceptable placebo range of 40-60. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20.

The mean and standard deviation numbers provided below were drawn from the statistical review performed by Dr. Ran Bi.

Table 3: Effects of Oral Placebo, Midazolam (2.5 and 5 mg), and Remimazolam (5 and 10 mg) on Subjective Measures (VAS) – E_{max} Scores (scale 0-100, mean and standard deviation) (n = 39)

	Placebo	**MIDAZ 2.5 mg**	**MIDAZ 5 mg**		**REMIM 5 mg**	**REMIM 10 mg**
Drug Liking (bipolar)	53 ± 8	79 ± 14 *	82 ± 12 *		77 ± 14 * ~	80 ± 15 *
Overall Drug Liking (bipolar)	53 ± 14	67 ± 17 *	69 ± 16 *		62 ± 17 * ∧	67 ± 19 * ∧
Good Drug Effects (unipolar)	7 ± 19	66 ± 25 *	73 ± 21 *		65 ± 24 * ∧	71 ± 23 * ∧
Take Drug Again (unipolar)	17 ± 28	56 ± 33 *	59 ± 32 *		37 ± 36 * ∧	49 ± 34 * ∧
Bad Drug Effects (unipolar)	0 ± 1	13 ± 22	28 ± 33		15 ± 21 *	31 ± 34 *

MIDAZ = midazolam, REMIM = remimazolam
* = $p < 0.01$ compared to placebo, ^ = $p < 0.01$ compared to midazolam 2.5 mg,
~ = $p < 0.01$ compared to midazolam 5 mg

Study Validation

As shown in Table 3 (above), the positive control drug, midazolam (2.5 and 5 mg), produced expected increases in positive subjective responses on the primary measure of Drug Liking (77 and 80 out of 100, respectively), that were outside the acceptable placebo range (40-60 out of 100 on a bipolar scale) and were statistically significantly greater than those produced by placebo. This validates the study.

Drug Liking and Overall Drug Liking

- On the Drug Liking primary measure, remimazolam at 5 and 10 mg produced an increase in response that was statistically significantly greater than placebo (77-80 vs. 53 out of 100, respectively) on a bipolar scale (acceptable placebo range = 40-60 out of 100). This was similar to the response produced by midazolam at 2.5 and 5 mg (79 and 82 out of 100, respectively).

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- On the Overall Drug Liking measure, remimazolam at 5 and 10 mg produced statistically significant increases on this measure compared to placebo (62-67 vs. 53 out of 100, respectively), but these responses were barely outside of the acceptable placebo range (40-60 out of 100 for a bipolar scale). This was similar to the response produced by midazolam at 2.5 and 5 mg (67 and 69 out of 100, respectively).

Good Drug Effects, Take Drug Again, and Bad Drug Effects

- For Good Drug Effects, remimazolam at 5 and 10 mg produced a response that was statistically significantly greater than placebo (65 and 71 vs. 7 out of 100), on a unipolar scale (acceptable placebo range = 0-20 out of 100). This was similar to the response produced by midazolam at 2.5 and 5 mg (66 and 73 out of 100, respectively).

- For Take Drug Again, remimazolam at 5 and 10 mg produced a response that was statistically significantly greater than placebo (37 and 49 vs. 17 out of 100). This suggests that subjects would take remimazolam again. Midazolam at 2.5 and 5 mg produced a statistically significantly greater response (56 and 59 out of 100) that was greater than both remimazolam and placebo.

- For Bad Drug Effects, remimazolam at 5 mg produced an increase in response (15 out of 100) that was within the acceptable placebo range (0-20 for unipolar scales) or for the 10 mg dose was slightly outside the acceptable placebo range (31 out of 100) compared to actual placebo response (0 out of 100). A similar response was seen for the low (2.5 mg) and high (5 mg) dose of midazolam (13 and 28 out of 100).

Adverse Events

The AEs profile was evaluated from the subjects who participated in the Treatment Phase (n = 39-40). Remimazolam produced a low degree of euphoria, but a high degree of somnolence and amnesia, which would be expected from a benzodiazepine.

Euphoria

The positive control drug, midazolam (2.5 and 5 mg), produced a relatively low incidence of euphoria (n = 3 (8%), and n = 1 (3%), respectively). Placebo produced no euphoria (0%). Remimazolam produced a euphoria response in 1 of 40 subjects (3%) at the 5 mg dose, while the 10 mg dose produced no reports of euphoria.

Somnolence

The positive control drug, midazolam (2.5 and 5 mg), produced a relatively high incidence of somnolence (n = 4 (10%), and n = 9 (23%), respectively). Placebo produced somnolence in 1 subject (3%). Remimazolam (5 and 10 mg) produced a relatively high incidence of somnolence (n = 6 (15%), and n = 10 (26%), respectively).

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Amnesia

The positive control drug, midazolam (2.5 and 5 mg), and placebo produced no reports of amnesia. In contrast, remimazolam produced a low incidence of amnesia (n = 1 (3%), and n = 3 (8%), respectively).

Pharmacokinetics

Concentrations of remimazolam decreased very rapidly until no longer quantifiable, which was generally about 0.5 hours (5 mg iv) to 1 hour (10 mg iv). The rapidity of the drug disappearance led to difficulty in calculating half-life, but when it was measurable, the half-life was less than 0.5 hour.

Overall Conclusions

Midazolam at both doses (2.5 and 5 mg) produced the expected positive subjective response on the primary measure of Drug Liking that was statistically significantly greater than placebo. This validates the study. Additionally, midazolam at both doses also produced expected positive subjective responses on the secondary measures of Overall Drug Liking, Good Effects, and Take Drug Again.

Remimazolam (at the therapeutic dose of 5 mg and 2X therapeutic dose at 10 mg) produced increases on the positive subjective scales that were statistically similar to responses produced by midazolam. Although neither drug produced a meaningful adverse event signal of “euphoria”, both produced a high degree of “somnolence”, as would be expected from a CNS depressant.

These data support the conclusion that remimazolam has abuse potential.

4.2 Abuse-Related Adverse Events in Clinical Studies

a. Phase 1 Studies (CNS7056-001, CNS7056-002, CNS7056-005, CNS7056-016, CNS7056-017, CNS7056-019, ONO-2745-01, and ONO-2745-02, CNS7056-012, ONO-2745IVU007)

To identify potential safety signals following administration of remimazolam in healthy individuals, abuse-related adverse events from 10 Phase 1 studies (n = 223) were evaluated:

Eight studies in healthy volunteers:

- CNS7056-001 (intravenous: 0.01, 0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.25, and 0.3 mg/kg)
- CNS7056-002 (intravenous: 0.25 mg/kg over 1 min and followed by flumazenil and intravenous: 0.04, 0.075, or 0.1 mg/kg, with additional doses of 0.04 mg/kg up to 6 doses)
- CNS7056-005 (intravenous: 10 and 20 mg)

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- CNS7056-016 (intravenous: 0.025 mg/kg; oral solution: 0.14 mg/kg)
- CNS7056-017 (intravenous: 5 mg/min for 5 min, followed by 3 mg/min for 15 min, followed by 1 mg/min for 15 min)
- CNS7056-019 (intravenous: 4 mg; intranasal powder: 10, 20, and 40 mg; oral solution: 10, 20, and 40 mg)
- ONO-2745-01 (intravenous: 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg; then testing at 0.1 mg/kg and 0.3 mg/kg)
- ONO-2745-02 (intravenous: 1 mg/kg/hour)

One study in subjects with end stage renal disease or subjects with normal renal function

- CNS7056-012 (intravenous: 0.15 mg/kg)

One study in subjects with hepatic impairment and healthy volunteers

- ONO-2745IVU007 (intravenous: 0.1 mg/kg/hour)

One other Phase 1 study was also conducted (CNS7056-014) during drug development, but this is the HAP study described above and is not included in the AE analyses below. This is justified because supratherapeutic doses of remimazolam were used in this study with the intention of inducing abuse-related AEs. Those AEs are reported in the summary of the HAP study above.

During the 10 Phase 1 studies listed above, there were only two abuse-related AEs reported following remimazolam administration at an incidence of at least 2%: euphoric mood (n = 10 of 223, 4.5%) and somnolence (n = 14, 6.3%). In contrast, there were no reports following placebo administration of euphoric mood (n = 0 of 98, 0%) or somnolence (n = 0 of 98, 0%).

These data show that in healthy individuals, remimazolam produce rewarding and sedative effects that were much greater than that produced by placebo, as would be expected from a benzodiazepine.

b. Phase 2/3 Studies (Study #ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011)

To identify potential safety signals following administration of remimazolam in a patient population, abuse-related adverse events were evaluated from 4 Phase 2/3 studies (n = 442) in which remimazolam was administered to subjects for procedural sedation (ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011). During these studies, remimazolam sedation was induced at either 6 mg/kg/hour or 12 mg/kg/hour.

As shown below in Table 4, there were few CNS-related AEs that were reported at an incidence of 2% or greater. The CNS AEs that were reported included sleep disorder (7.7%), agitation (7.5%), delirium (2.5%), and insomnia (2.3%).

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Unexpectedly, each of these AEs were reported more frequently at the 6 mg/kg/hour dose compared to the 12 mg/kg/hour dose, with the exception of insomnia. Euphoric mood was not reported at an incidence of 2% or greater in the patient population.

Table 4: Treatment-emergent Adverse Events Reported for ≥ 2% of Subjects in the Total Remimazolam Group by Preferred Term in Phase 2/3 Studies (ONO-2745-05, ONO-2745-06, CNS7056-010 and CNS7056-011)

	Propofol	**Remimazolam 6 mg/kg/h (N=233)**	**Remimazolam 12 mg/kg/h (N=209)**	**Remimazolam TOTAL (n = 442)**
Sleep disorder	13 (12.0%)	22 (9.4%)	12 (5.7%)	34 (7.7%)
Agitation	7 (6.5%)	20 (8.6%)	12 (6.2%)	33 (7.5%)
Delirium	3 (2.8%)	7 (3.0%)	4 (1.9%)	11 (2.5%)
Insomnia	1 (0.9%)	5 (2.1%)	5 (2.4%)	10 (2.3%)

These data show that in patients who participated in Phase 2/3 studies, remimazolam does not produce euphoric mood, suggesting that the risk of abuse potential is low in a patient population.

4.3 Assessment of Human Physical Dependence

The Sponsor did not conduct a clinical study to evaluate the ability of remimazolam to produce physical dependence in humans.

However, in assessing the ability of remimazolam to produce physical dependence, it is important to consider the pharmacokinetics of the drug. Remimazolam is administered as an intravenous bolus for procedural sedation, with the option of additional intravenous bolus doses to maintain sedation. As with any intravenous administration, plasma levels of the drug rise rapidly and diminish rapidly following the last drug administration. Since patients only receive exposure to remimazolam on a single day for a limited period of time, it is unlikely that such drug exposure would allow for the neuroadaptation necessary to induce a state of physical dependence. However, diversion of the remimazolam drug product by medical professionals for abuse purposes could lead to physical dependence if individuals used the drug chronically.

5. Regulatory Issues and Assessment

After reviewing the abuse potential-related data in the NDA for remimazolam (see Sections II.1 through II.4, above), CSS has concluded that the drug has an abuse potential consistent with other benzodiazepines that are in Schedule IV of the CSA.

Thus, CSS prepared an Eight Factor Analysis (8FA) recommending that remimazolam be placed into Schedule IV of the CSA. The 8FA is a document that is responsive to the requirements of the CSA that is prepared in conjunction with the National Institute on Drug Abuse (NIDA) on

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behalf of the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS).

The 2015 Improving Regulatory Transparency for New Medical Therapies Act ("the Act") streamlined the scheduling process by establishing time lines for DEA scheduling actions in relation to NDA approval actions. Under the Act, FDA approval of an NDA for a drug with abuse potential may not take effect until DEA issues an interim final rule under 21 U.S.C. 811(j) establishing a temporary scheduling placement for the drug, in accordance with 21 U.S.C. 355(x).

DEA has 90 days to publish the interim final rule in the Federal Register, once both of the following events have occurred (in any order): 1) FDA has approved the NDA and formally notified DEA of the approval, and 2) the 8FA for the drug has been transmitted from the ASH to the DEA. Once the interim rule has been issued, the new drug applicant may update their product labeling to reflect the scheduling action (through supplement submission to their NDA) and then market their drug. Subsequently, DEA will issue a final rule that permanently places the drug under the CSA.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 22, 2020

To: Renee Petit-Scott, M.D.
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Taiye Adedeji, Regulatory Project Manager
Division of Regulatory Operations for Neuroscience

Lisa Basham, Associate Director for Labeling, (DAAP)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for Remimazolam for Injection for Intravenous Use

NDA: 212295

In response to DAAP's consult request dated June 17, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Remimazolam for injection for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAP on February 19 and April 15, 2020 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 27, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@fda.hhs.gov.

44 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4596477

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/s/

KOUNG U LEE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Review

Date: 1/21/2020 **Date consulted:** 5/9/2019

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Division of Pediatric and Maternal Health (DPMH)

To: Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)

Drug: Remimazolam

NDA: NDA 212295

Applicant: Cosmo Technologies, Ltd.

Subject: Pregnancy and Lactation Labeling

Indication: The induction and maintenance of procedural sedation in adults

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 212295
- DPMH consult request dated May 9, 2019, DARRTS Reference ID 4431895
- FDA Drug Safety Communication regarding General Anesthetics and Sedation Drugs in Pregnant Women

Reference ID: 4549287

- DPMH Review of XANAX and XANAX XR (alprazolam) NDA 18276 and 21434, Catherine Roca, M.D., Medical Officer, November 16, 2018. DARRTS Reference ID 4351248.[1]
- DPMH Review of FORANE (isoflurane) NDA 17624, Catherine Roca, M.D., Medical Officer, May 1, 2017. DAARTS Reference ID 4091500[2]

Consult Question: "Please review the initial proposed labeling and confirm compliance with PLLR."

INTRODUCTION AND BACKGROUND

On April 5, 2019, Cosmo Technologies, Ltd, submitted an original NME NDA for Remimazolam for the indication of "induction and maintenance of procedural sedation in adults." DAAP consulted DPMH on May 9, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

Remimazolam Drug Characteristics[3]

Drug Class	Remimazolam is a benzodiazepine
Mechanism of action	Remimazolam binds to brain benzodiazepine sites (gamma amino butyric acid type A GABA A receptors) (b) (4)
Molecular weight	439.3 Daltons
Protein Binding	(b) (4)
Half-life	The mean terminal half-life is 37 to 53 minutes.
Absorption/Bioavailability	Administered intravenously, C_{max} was achieved 20-30 minutes post dose

[1] The XANAX review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.
[2] The FORANE review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.
[3] Remimazolam proposed package insert

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Serious Adverse Reactions	• Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory (b) (4) coma and death. • (b) (4) • •

REVIEW

PREGNANCY

General Anesthesia and Pregnancy

General anesthesia may be required during pregnancy either to facilitate needed surgery or in some cases, during delivery. Surgery during pregnancy can be for a variety of maternal and fetal conditions. It is estimated that up to 2% of pregnant women require non-obstetric surgery.[6] The American College of Obstetricians and Gynecologists (ACOG) recommends that a pregnant woman should never be denied indicated surgery, regardless of trimester, that elective surgery be postponed until after delivery, and if possible, non-urgent surgery be performed in the second trimester when preterm contractions and spontaneous abortion are least likely.[7]

General anesthesia may also be required, in some cases, for cesarean delivery. In the United States, the cesarean birth rate in 2014 was 32.2% of all births.[8] Most women who deliver by cesarean delivery receive some form of neuraxial (spinal, epidural, or combination) anesthesia.[9] The American Society of Anesthesiologists Task Force on Obstetric Anesthesia

[4] ASA III: A patient with a severe systemic disease that is not life-threatening.
[5] ASA IV: A patient with a severe systemic disease that is a constant threat to life.
[6] Anaesthetic agents in pregnant women undergoing non-obstetric surgical or endoscopic procedures: A review of the safety and guidelines. Canadian Agency for Drugs and Technologies in Health. 2015. June.
[7] Committee on Obstetric Practice. Nonobstetric surgery during pregnancy. No. 474, February 2011. (Reaffirmed 2015) http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Nonobstetric-Surgery-During-Pregnancy
[8] National Vital Statistics Reports. Births: Final Data for 2014. Vol 64, No 12, December 23, 2015. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf
[9] Butwick AJ, et al. Racial and ethnic disparities in mode of anesthesia for cesarean delivery. Anesth Analg. 2016. 122(2):472-9.

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states in its guidelines[10] that neuraxial techniques are preferred to general anesthesia for most deliveries. However, general anesthesia may be the most appropriate choice in some circumstances (e.g., profound fetal bradycardia, ruptured uterus, severe hemorrhage).[10]

On December 14, 2016, the Agency issued a Drug Safety Communication (DSC) warning patients and prescribers that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains" and that warnings would be added to the labels of general anesthetic and sedation drugs about this potential risk.[11]

Nonclinical Experience

At a daily dose 30-times the anticipated maximum human dose for procedural sedation, administered for four weeks (males) or two weeks (females) prior to mating there was no influence of remimazolam on pregnancy in rats and rabbits, and no abortions or dead or malformed fetuses were observed even at the highest dose levels, which displayed maternal toxicity and marginal embryotoxic properties such as reduced fetal and placental weights (consistent with reduced food intake and body weight gain of the dams).
No treatment-related post-natal changes in behavior were noted in the litters from remimazolam-treated dams.

The reader is referred to the full Pharmacology/Toxicology review by Katie Sokolowski Ph.D., and Newton Woo, Ph.D.

Reviewer Comment:
Pharmacology-toxicology revisions were not finalized at the time this review was completed.

Review of Pharmacovigilance Database

The applicant searched the clinical studies database and found one case of exposure to remimazolam during pregnancy.

- A 21-year-old woman with a previous history of an elective abortion (no information regarding congenital malformations) was exposed to remimazolam on (b) (6). On (b) (6) she had a positive pregnancy test (last menstrual period [LMP], (b) (6). She delivered a healthy term male infant. At 3 ½ months follow-up, the infant was reported to be developing normally.

Review of Literature

Applicant's Review of Literature

The applicant performed a search of the published literature using the PubMed and Embase databases and the following search terms, "remimazolam" and "pregnant," "pregnancy," "fetal," "neonate," "gestation," "birth," and "infant."

[10] American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology. 2007. 106(4):843-863.
[11] http://www fda.gov/Drugs/DrugSafety/ucm532356.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

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No reports related to remimazolam and pregnancy were found in the search.

DPMH Review of Literature
DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex[12] using the search terms, "remimazolam" or "benzodiazepines" and "pregnancy," "pregnancy outcomes," "congenital anomalies," "stillbirth," and "spontaneous abortion."

Remimazolam is not referenced in Reprotox,[13] Briggs,[14] or Micromedex.[15]

A search of the published literature did not yield any papers regarding remimazolam and pregnancy.

There is extensive literature on the use of benzodiazepines (as anti-anxiety or hypnotic agents) as a class during pregnancy. See Appendix A, Tables 1 and 2, for a brief overview of this literature. In summary, studies indicate that infants exposed to benzodiazepines during the late third trimester of pregnancy or during labor have been reported to exhibit sedation and neonatal withdrawal symptoms. Observational studies do not report a clear association with benzodiazepines and major birth defects. Based on animal data, use of sedation drugs during pregnancy may affect brain development, therefore, the FDA released a Drug Safety Communication related to the use of anesthetic and sedation drugs in pregnancy.

FDA Drug Safety Communication regarding General Anesthetics and Sedation Drugs in Pregnant Women[16]
The key messages of the DSC issued by the Agency in December 2016 include the following:

- Repeated or lengthy (greater than 3 hours) use of general anesthetic and sedation drugs in pregnant women and young children during surgery or other procedures may affect the child's developing brain.
- Parents, pregnant women, care providers, obstetricians, surgeons, and anesthesiologists should be aware of the potential risks that anesthetics and sedation drugs pose to the developing brain and carefully decide on the appropriate timing for potentially elective surgery, particularly for pregnant women in their third trimester and children under three years of age.

Reviewer comment:
Data from nonclinical studies do not indicate an increased risk of fetal malformations with remimazolam use in pregnant animals. Clinical data are too limited to be informative regarding reproductive risk. Data from epidemiologic studies on benzodiazepines in general do not indicate a clear increased risk for major birth defects. Many of the studies (particularly several done decades ago that did indicate an increased risk for major birth defects) lack control for

[12] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 11/4/2019
[13] 2018 Reproductive Toxicology Center Accessed 11/4/2019
[14] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 11/4/2019
[15] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 11/4/2019
[16] https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-use-general-anesthetic-and-sedation-drugs

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confounding by severity, diagnosis, or lack of randomized design. Infants exposed during the late third trimester or during labor have been reported to exhibit sedation and/or neonatal withdrawal symptoms. In addition, repeated or lengthy (greater than 3 hours) use of sedation drugs may affect the developing brain. DPMH recommends a Warning and Precaution for Sedation and Neonatal Withdrawal Syndrome, and for Pediatric Neurotoxicity, similar to other benzodiazepine and anesthetic labelings.

LACTATION

Nonclinical Experience

Remimazolam and metabolite CNS7054 were both quantifiable in milk samples obtained from rabbits after the end of a 20 mg/kg infusion on Day 10 or 11 of lactation.

The reader is referred to the full Pharmacology/Toxicology review by Katie Sokolowski Ph.D., and Newton Woo, Ph.D.

Reviewer Comment:
Pharmacology-toxicology revisions were not finalized at the time this review was completed.

Review of Pharmacovigilance Database

The applicant searched the clinical studies database. No cases related to lactation were found in the search.

Review of Literature

Applicant's Review of Literature

The applicant performed a search of the published literature using the PubMed and Embase databases and the following search terms, "remimazolam" and "lactation," "breast milk," "milk," and "nursing."

No reports of cases related to lactation were found in the search.

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk,*[17] the Drugs and Lactation Database (LactMed),[18] Micromedex,[19] and of the published literature using the search terms, "remimazolam," and "lactation," or "breastfeeding."

[17] Hale TW, Hale's medications and mothers' milk. 2019. Springer Publishing Co. NY, New York.
[18] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[19] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 11/5/2019

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Remimazolam is not referenced in Hale,[20] LactMed,[21] or Micromedex.[22] No papers relating to remimazolam and lactation were located in the search.

Data from studies of lactating women receiving benzodiazepines have reported sedation in breastfeeding infants,[23,24] and, in cases of chronic exposure, signs of irritability, restlessness and disturbed sleep when the medication was stopped.[25]

Reviewer comment:
The applicant provided an adequate literature and safety database review. The applicant concluded that remimazolam should not be contraindicated during breastfeeding, but that interruption of breastfeeding for (b) (4) hours should be considered to minimize exposure to the breastfed infant. This reviewer agrees that breastfeeding may be interrupted for a period of time after administration of remimazolam, however; it is unclear whether a (b) (4) hour period of interruption is necessary. Withholding breastfeeding for five half-lives (5 hours) may be sufficient to limit infant exposure and less disruptive to lactation. Since this drug will likely be used in women of reproductive age, and therefore, potentially, lactating women, a milk-only lactation study is recommended to quantify the amount of medication that passes into breast milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The administration of remimazolam to male rats, rabbits and minipigs over four weeks at daily doses corresponding to 30-fold or more of maximum anticipated dose for procedural sedation gave no indication of an influence on fertility parameters.

The administration of remimazolam to female rats and rabbits over two weeks prior to mating, at daily doses corresponding to 30-fold of maximum anticipated dose for procedural sedation i.e. up to 30 mg/kg, gave no indication of an influence on fertility parameters.

The reader is referred to the full Pharmacology/Toxicology review by Katie Sokolowski Ph.D., and Newton Woo, Ph.D.

Reviewer Comment:
Pharmacology-toxicology revisions were not finalized at the time this review was completed.

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[20] Hale TW, Hale's medications and mothers' milk. 2019. Springer Publishing Co. NY, New York.
[21] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[22] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 11/5/2019
[23] Ito S, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol. 1993;168(5):1393-1399.
[24] Kelly LE, et al. Neonatal benzodiazepine exposure during breastfeeding. J Pediatr. 2012;161:448-51.
[25] Anderson PO and McGuire GG. Neonatal alprazolam withdrawal-possible effects of breast-feeding. Annals Pharmacotherapy. 1989;23:614.

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Review of Pharmacovigilance Database

The applicant searched the clinical studies database. No cases related to fertility were found in the search.

Review of Literature

Applicant's Review of the Literature

The applicant performed a search of the published literature using the PubMed and Embase databases and the following search terms, "remimazolam" and "fertility," "infertility," "sterility," "abortion," "placenta," "placental," and "sperm."

No reports of cases related to fertility or hormonal contraceptives were found in the search.

DPMH Review of Literature

DPMH conducted a search of the published literature using PubMed, Embase, Reprotox, and Micromedex[26] using the search terms, "remimazolam" and "infertility," "hormonal contraception," or "fertility."

No cases related to infertility or hormonal contraception were located in the search. A search of the published literature related to "benzodiazepines," and "fertility," "infertility," and "hormonal contraception," did not produce any cases indicating an increased risk of infertility or interference with the efficacy of hormonal contraceptives.

Reviewer comment:

(b) (4)

However, since nonclinical data do not indicate an adverse effect on fertility, and human data do not indicate a risk of infertility with other benzodiazepines, (b) (4)

DISCUSSION AND CONCLUSIONS

Pregnancy

Nonclinical data do not indicate remimazolam has adverse effects in pregnant animals or their offspring. Clinical data are limited to one case that occurred during the clinical trials and are too limited to determine an adverse effect of remimazolam during pregnancy. Data from studies in other benzodiazepines do not indicate a clear increased risk for major birth defects, however; infants exposed to benzodiazepines late in the third trimester or during labor have experienced sedation. Labeling will include a Warning for Sedation and Neonatal Withdrawal Syndrome and for Pediatric Neurotoxicity, based on the FDA Drug Safety Communication, Subsection 8.1 will include the Risk Summary, Clinical Consideration and Data subheadings.

Lactation

Nonclinical data indicate that remimazolam is present in animal milk. While there are no data on remimazolam in human milk, effects on the breastfed infant, or lactation, other benzodiazepines

[26] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 11/5/2019

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are known to pass into breastmilk.[27] With acute benzodiazepine use, sedation has been reported in breastfeeding infants. Remimazolam has a short half-life (37-53 minutes) and the proposed indication is for the induction and maintenance of procedural sedation in adults, which would be acute exposure. Because remimazolam will likely be used in females of reproductive potential, and therefore, potentially lactating women, a milk-only lactation study is recommended to quantify the amount of remimazolam passing into breast milk. Labeling will include the Risk Summary and Clinical Considerations along with the following statement, "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Remimazolam and any potential adverse effect on the breastfed infant from Remimazolam or from the underlying maternal condition."

Females and Males of Reproductive Potential

Nonclinical data do not indicate an adverse effect of remimazolam on fertility. There are no clinical data on the effects of remimazolam on fertility or hormonal contraception. Data do not indicate remimazolam is a major teratogen, so pregnancy testing or contraception subheadings are not required. DPMH recommends the animal data remain in subsection 13.1; (b) (4)

LABELING RECOMMENDATIONS

DPMH revised Highlights, Warnings and Precautions, subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Benzodiazepine use during pregnancy can result in neonatal sedation and withdrawal syndrome. (5.x, 8.1)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* A lactating woman may pump and discard breast milk for 5 hours after treatment with remimazolam.

FULL PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

5.X Sedation and Neonatal Withdrawal Syndrome

Use of benzodiazepines during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate. Observe newborns for signs of sedation and neonatal withdrawal syndrome and manage accordingly *[see Use in Specific Populations (8.1)]*.

[27] Furugen A, et al. Quantification of eight benzodiazepines in human breastmilk and plasma by liquid-liquid extraction and liquid-chromatography tandem mass spectrometry: application to evaluation of alprazolam transfer into breastmilk. J Pharmaceutical Biomed Analysis. 2019;168:83-93.

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5.X Pediatric Neurotoxicity

Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans *(See Precautions)*. Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anesthetic agents early in life and may result in adverse cognitive or behavioral effects. These studies have substantial limitations, and it is not clear if the observed effects are due to the anesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Anesthetic and sedation drugs are a necessary part of the care of children and pregnant women needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Infants born to mothers using benzodiazepines during the later stages of pregnancy have been reported to experience symptoms of sedation and neonatal withdrawal *[see Warnings and Precautions (5.X), Clinical Considerations)]*. Although there are no data on the effects of remimazolam use in pregnant women, available data from published observational studies of pregnant women exposed to other benzodiazepines have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).*

Studies in juvenile animals suggest that administration of sedative drugs during a time period that corresponds to the third trimester of pregnancy is associated with prolonged cognitive deficits in learning and memory *[see Warnings and Precautions (5.x)]*. The clinical significance of these nonclinical findings is not known, and the benefits of appropriate anesthesia in pregnant women who require procedures should be balanced with the potential risks suggested by the nonclinical data.

Reviewer Comment:
Pharmacology-toxicology revisions were not finalized at the time this review was completed.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

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Clinical Considerations

Fetal/Neonatal adverse reactions

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation, respiratory depression, withdrawal, and feeding problems and manage accordingly *[see Warnings and Precautions (5.x)]*.

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of more recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco and other medications, have not confirmed these findings. There are no data on the specific effects of remimazolam on pregnancy. Infants exposed to benzodiazepines during the late third trimester of pregnancy or during labor have been reported to exhibit sedation and neonatal withdrawal symptoms.

Animal Data

(b) (4)

Reviewer Comment:

Pharmacology-toxicology revisions were not finalized at the time this review was completed.

8.2 Lactation

Risk Summary

There are no data on the effects of remimazolam in human milk, the effects on the breastfed infant or the effects on milk production. Remimazolam is present in animal milk. When a drug is present in animal milk, it is likely that it will be present in human milk. There are reports of sedation in infants exposed to benzodiazepines through breast milk *(see Clinical Considerations).* The developmental and health benefits of breastfeeding should be (b) (4) the mother´s clinical need for Remimazolam and any potential adverse effect on the breastfed child, (b) (4) the underlying maternal condition.

(b) (4) for sedation, respiratory depression, and feeding problems. A lactating woman may consider interrupting

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breastfeeding and pumping and discarding breast milk during treatment and for 5 hours (approximately 5 elimination half-lives) after remimazolam administration in order to minimize drug exposure to a breastfed infant.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Advise mothers using benzodiazepines to monitor neonates for signs of sedation, respiratory depression, withdrawal, and feeding problems. Instruct patients to inform their healthcare provider if they are pregnant (b) (4) during treatment with remimazolam *[see Warnings and Precautions (5.x), Use in Specific Populations (8.1)]*.

Lactation

Advise (b) (4) Women (b) (4) consider reducing infant exposure (b) (4) pumping and discarding breastmilk (b) (4) for 5 hours after (b) (4) remimazolam *[see Use in Specific Populations (8.2)]*.

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APPENDIX A –

Table 1.Benzodiazepines and pregnancy (reviewer's table)

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
Yonkers KA, et al.[28] 2017 USA	Prospective, cohort study	2654 pregnant women from community-based obstetrics practices (panic disorder (PD) n=98; general anxiety disorder (GAD) n=252) exposure to (benzodiazepines) BZD and selective serotonin reuptake inhibitors (SSRI) use compared to non-use	Any trimester, any BZD or SSRI	GAD and PD not independently associated with adverse pregnancy outcomes. Maternal BZD use associated with Cesarean delivery (OR 2.45, 95% CI 1.36-4.40), low birth weight (OR 3.41, 95% CI 1.61-7.26), use of ventilatory support for the newborn (OR 2.85, 95%Ci 1.81, 95%CI 1.39-2.37)	Limited power, small sample size for PD. Adjusted for age, race/ethnicity, educational level, smoking, alcohol and illicit drug use during pregnancy
Gidai J, et al.[29] 2008 Hungary	Case series	10 children born after mothers' attempted suicide with alprazolam	Dose range 7.5-100mg alprazolam; six infants were exposed during gestational	Two infants with congenital anomalies 1) gastroschisis (mother took 30 mg alprazolam at gestational week 14) and 2) mild pectus excavatum, exposure determined to have happened after the critical period for producing this defect; no neurodevelopmental abnormalities seen at follow-up between 8-12 months	Formal evaluation of neurobehavioral outcomes was performed using the Hungarian Development Test

[28] Yonkers KA, et al. Association of panic disorder, generalized anxiety disorder, and benzodiazepine treatment during pregnancy with risk of adverse birth outcomes. JAMA Psychiatry. 2017;74(11):1145-1152.

[29] Gidai J, et al. An evaluation of data for 10 children born to mothers who attempted suicide by taking large doses of alprazolam during pregnancy. Toxicology and Industrial Health. 2008;24:53-60.

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Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
			ages 6-12 weeks		
Brandlistuen RE, et al.[30] Norway 2017	Prospective, sibling-controlled, cohort study	71,996 children (19,296 siblings) at 1.5 years and 55081 children (13,779 siblings) assessed using a modified Child Behavior Checklist	Any BZD or z-hypnotic use during pregnancy assessed by questionnaire at 17- and 30-weeks' gestation and 6 months postpartum Short term use: during only one pregnancy period (0-13 weeks, 14-29 weeks, 30weeks-birth); Long term use- 2 or more pregnancy periods	Long-term prenatal exposure to BZD anxiolytics increased internalizing behavior at age 1.5 years (β 0.25, 0.01-0.49) and 3 years (β 0.26, 0.002-0.52) after adjusted for propensity score sibling-matched fixed effects models. The authors report this suggests a modest association between BZD-anxiolytic exposure and child internalizing behaviors that in not likely due to stable familial confounding factors.	Adjusted for indication, education, pre-pregnancy BMI, sleep problems, chronic disease and folic acid supplementation, other medication, length of BZD use, paracetamol use

[30] Brandlisteun RE, et al. Association of prenatal exposure to benzodiazepines and child internalizing problems: a sibling-controlled cohort study. PLoS One. 2017;12(7):e0181042.

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Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
Ogawa Y, et al.[31]	Retrospective Case-control using a claims database	Women who had given birth to preterm (n=737) or low birthweight (n=1615) infants vs controls (n=39,706)	Months 5-8 gestation	Use of BZD was associated with preterm birth (adj OR 2.03, 95% CI 1.11-3.69, p<0.05) but not with low birth weight	Exposure defined by prescriptions filled; actual use not verified; no control for confounding by severity or diagnosis
Zhao J-P, et al.[32] 2018 Canada	Nested case-control study using the claims database	Pregnancies that ended in spontaneous abortion (n=17180) compared to controls (n=85,562)	BZD exposure the year prior to pregnancy and from the first day of gestation to the date of the spontaneous abortion	Early pregnancy BZD use associated with increased risk of spontaneous abortion (adj OR 1.55, 95% CI 1.36-1.76), but not prior year BZD exposure. Maternal exposure to alprazolam was not associated with increased risk of spontaneous abortion.	Based on prescriptions, not verified use. Adjusted for potential confounders that are not described in detail
Freeman MP, et al.[33] 2018 USA	Prospective pregnancy registry study	Pregnant women exposed to BZD (n=144) and controls (n=650)	Any trimester	Increased risk of NICU admission in BZD exposed infants (OR 2.02, 95% CI 1.11-3.66) and small head circumference (OR 3.89, 95% CI 1.25-12.03) compared to unexposed infants. Respiratory problems were not significantly different between groups.	Controlled for maternal age, diagnosis, psychiatric illness severity, concomitant medication and substance abuse. Not randomized design

[31] Ogawa Y, et al. Maternal exposure to benzodiazepine and risk of preterm birth and low birth weight: a case-control study using a claims database in Japan. Asia-Pacific Psychiatry. 2018;10(3):e12309.
[32] Zhao J-P, et al. Individual benzodiazepine exposure during early pregnancy and the risk of spontaneous abortion. Pharmacoepidemiology and Drug Safety. 2018. 27Suppl2:(237-238).
[33] Freeman MP, et al. Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: results from a prospective registry of women with psychiatric disorders. Gen Hosp Psychiatry. 2018;53:73-79.

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Table 2: Summary of publications and key findings on the use of hypnotics during pregnancy (from Okum ML, et al.[34])

Study	Design/Population	Drug Used	Outcome/Results	Key Findings	Strengths(S)/ Limitations(L)
#1-Ban *et al* 2014 United Kingdom	Retrospective cohort design/Neonates of women who used either benzodiazepine (BZDP) or non-benzodiazepine (n-BZDP) hypnotic without concomitant antidepressant (AD) in the first trimester (TM): 1159 infants-exposure to diazepam (DZ); 379 infants-exposure to temazepam (TZ); 19,193 infants with maternal diagnosis of depression/anxiety with no drug exposure	DZ TZ	Rate of major congenital abnormalities (MCA): 2.7% among women with no depression/ anxiety; 2.7% among women with diagnosis of depression/anxiety but no medication 2.7% among women who used DZ 2.9% among women who used TZ	No significant ↑risk for congenital malformations (CM)	**S**- Adjusted for year for childbirth, maternal age (MA), smoking, body mass index (BMI), socio-economic status (SES), Excluded women with epilepsy, psychosis or bipolar and concomitant AD meds, Prospective recording of drug exposure data as routine care **L**- Drugs prescribed but no proof that they were taken, Confounding by indication possible
#2- Czeizel *et al* 2003 Hungary	Used the dataset of the nationwide Hungarian Case-Control Surveillance of Congenital Abnormalities from 1980-1996 Matched case-population control pair analysis/Neonates of women who, while pregnant, self-reported or medically verified use of DZ for a short period (≈ 3 weeks): 38,151 population-control neonates without congenital abnormalities (CA); 22,865 neonates with CA; 812 neonates with Down syndrome (served as patient controls to estimate the effect of recall bias)	DZ	2746 cases (with CA) who received DZ (12%), 4130 (10%) population controls (received diazepam and no CAs) and 97 (11.9%) Down syndrome control infants born to mothers treated with DZ Higher rate of limb deficiencies, rectal-anal atresia/stenosis, cardiovascular (CV) malformations and multiple CAs after DZ use during the 2nd and 3rd months of gestation in main comparison group (self-reported and medically recorded); however, the evaluation of only medically recorded DZ use did not indicate a higher use of DZ in CA groups except for intestinal atresia/stenosis	No significant ↑risk for CAs among the 3 groups in the medically recorded information	**L-** Likely recall bias in combined group with self-reported DZ use, some of the statistically significant findings may be due to chance error caused by multiple comparisons, Not adjusted for alcohol or smoking

[34] Okun ML *et al.* A review of sleep-promoting medications used in pregnancy. AJOG. 2015; 212(4)428-41. Modified by the reviewer to include additional studies and to add strengths and limitations.

Reference ID: 4549287

#3-Eros *et al* 2002 Hungary	Retrospective matched case-control study /Women who were pregnant while using BZDPs [nitrazepam (NZ), medazepam (MZ), tofisopam (TZ), alprazolam (AZ), clonazepam(CZ)] who delivered infants with CA (n =57, 0.20%) and pregnant women controls who used BZDPs who gave birth to infants without defects (n = 75, 0.25%) whose cases were found in the dataset of the nationwide Hungarian Case-Control Surveillance of Congenital Abnormalities from 1980-1996	NZ MZ TZ AZ CZ	Rates of CAs were not significantly different from national average	No significant ↑risk for CM	**S-**Controlled for MA, birth order, acute and chronic maternal disorders and other drug use **L-** Some of the statistically significant findings may be due to chance error caused by multiple comparisons, All but three (2.3%) also received concomitant medications
#4-Lin et al 2004 USA	Retrospective cohort study/52 of 28,565 total infants were exposed to CZ (43 monotherapy, 33 during the 1st TM) as found in surveying medical records over a 32-month period as part of a hospital-based malformation surveillance program	CZ	1/33 infants exposed to clonazepam monotherapy during the first trimester had major malformations	No significant ↑risk for major malformations	L- Small sample size
#5-Reis and Kallen 2013 Sweden	Used Swedish Medical Birth Registry Retrospective population-based cohort study/ All infants born to mothers who used benzodiazepines alone (n= 1000), infants born to mothers using selective serotonin reuptake inhibitor (SSRI)+BZDP (n=406)	BZ DP	37 infants with relative severe malformation in BZDP alone group, OR=1.10 ; 95% CI 0.79-1.54, 13 with cardiovascular defect, OR=1.3; 95% CI 0.75-2.24 SSRI + BZDP: 16with severe	No significant ↑risk for malformations	S- Prospective collection of exposure data, Adjusted for MA, year for childbirth, smoking, BMI, parity, diabetes, hypertension and thyroid disease L- Did not adjust for maternal diagnosis of psychiatric disease, alcohol or illicit drug use, study data only on live-born infants, Small sample size
#6-St Clair and Schirmer 1992 USA	Used Swedish Medical Birth Registry, Prospective cohort study/Pregnant women who reported 1st TM use of alprazolam and who were followed through delivery (n = 411)	AZ	Among 411 pregnancies, 47 spontaneous abortions (SABs), and 88 elective abortions (TAB); of 276 live births: 263 infants without CA, 13 infants with CA	No ↑risk in CM observed, No ↑risk SABs	S-Prospective collection of exposure data, Adjusted for MA, year for childbirth, smoking, BMI, parity, diabetes, hypertension and thyroid disease L- S Did not adjust for maternal diagnosis of psychiatric disease, alcohol or illicit drug use, Small sample size

Reference ID: 4549287

#7-Wikner et al 2007 Sweden	Used Swedish Medical Birth Registry Population-based retrospective cohort study/ Pregnant women (n = 1944) who gave birth to 1979 infants who were exposed to BZDPs and/or hypnotic benzodiazepine receptor agonists (HBRA) during early pregnancy /Pregnant women (n = 390) who gave birth to 401 infants who were exposed to BZDPs and/or hypnotic benzodiazepine receptor agonists (HBRA) during late pregnancy	BZ DP HB RA	↑preterm birth, (early exposure) OR=1.48; 95% CI 1.26-1.75, (late exposure) OR=2.57; 95% CI 1.92-3.43,↑low birth weight (early exposure) OR=1.30; 95% CI 1.06-1.59, (late exposure) OR=1.89; 95% CI 1.29-2.76 Slight ↑ in major CMs in infants exposed early in pregnancy to only BZDP (OR=1.37, 95% CI 1.07-1.76) ↑risk for alimentary atresia, RR=2.63, 95% CI 1.01-	Slight ↑risk of major CMs, ↑risk preterm birth, low birth weight	S- Prospective collection of exposure data, Adjusted for MA, year for childbirth, smoking, BMI, parity, diabetes, hypertension and thyroid disease L- 31% of woman also received antidepressants (ADs) and some (% unknown) received anticonvulsants, no data on amount of drug used, information only on live-born infants, Not controlled for EtOH exposure or maternal indication
#8-Enato et al 2011, Dolovich et al 1998 Multiple Countries	An updated (Enato) meta- analysis of case-control and cohort studies-original meta-analysis from 1988 included 23 studies (Dolovich)- 3 cohort studies added by Enato	BZ DP	Original-Pooled cohort data-no association between BZDP and major CM (OR=0.90, 95% CI 0.61-1.35) or cleft lip (OR=1.19, 95%CI .34-4.15) Pooled case-control data +association between BZDP and	Original- Slight ↑risk of major CMs in case-control data only Updated- No ↑risk in CMs	L- Not a systematic review, no formal assessment of the quality of the included studies, marked heterogeneity between studies, 14 studies (8 case-control) did not control for exposure to concomitant teratogenic medications, Updated results mainly driven by 2 studies; Wikner (2007)
#9-Addis et al 2000 Multiple Countries	Summary of the original data from the Dolovich et al (1998) meta-analysis	ZD P	See above under Enato et al 2011, Dolovich et al 1998	Original- Slight ↑risk of major CMs in case-control data only	See above under Enato et al 2011, Dolovich et al 1998
#10-Oberlander et al 2008 British Columbia	Population level retrospective cohort study-records from 119,547 live births Incidence of CA following prenatal exposure to serotonin reuptake inhibitor antidepressants (SSRI) used alone or in combination with BZDP compared to no exposure	BZ DP SS RI	↑risk of congenital heart disease (CHD) with combined use of SSRI and BZDP compared with no exposure No ↑risk of CA or CHD with BZDP exposure alone	No ↑risk of CA with BZDP use alone	S- Controlled for length of exposure and maternal illness severity, MA, Diabetes L-no verification of the clinical significance of the congenital heart anomalies, did not control for, parity, tobacco, EtOH, illicit drug use, weight gain

Reference ID: 4549287

#11-Sheehy 2015 Canada	Nested case-control study using the Quebec Pregnancy Cohort 17,367 cases of spontaneous abortion (SAB) randomly matched to 5 controls for use of BZDPs between the 1st day of gestation until index date compared with non-use during the same window	BZ DP	703 (4.1%) with one filled script for BZDP vs 1553 (1.8%) with non-use, OR=2.24, 95% CI 2.05-2.45, after adjustment for confounders OR= 1.72, 95% CI 1.54-1.92,	↑risk of SAB with BZDP use	L- Drugs prescribed but no proof that they were taken, no information provided in publication regarding what confounders were controlled or adjusted for
#12- Calderon- Margalit et al 2009 USA and Israel	Prospective cohort study in Seattle, Washington of 2793 Pregnant women	BZ DP	Maternal use associated with an adjusted OR of 6.79 for preterm delivery (95% CI=4.01–11.5; p<0.001). ↑risk of low birth weight (adjusted OR=7.43, 95% CI: 4.15–13.3; p<0.001), but not with SGA, Low	↑risk of preterm birth, low birth weight, low APGARS, NICU admit, RDS	S- Adjusted for MA, race, marital status, education, smoking, parity, pre- eclampsia, detailed info on type and timing of treatment, 95% follow-up rate L-no info on maternal indications, Drugs prescribed but no proof that they were taken, did not adjust for possible confounding by illicit drug use, small
#13-Iqbal et al 2002 Multiple Countries	Literature review of 118 articles regarding use of BZDPs in pregnancy and lactation-specifically-DZ,), CZ, LZ, AZ, Chlordiazepoxide (CHL)	DZ CH L CZ LZ AZ	Currently available information is insufficient to determine whether the potential benefits of BZDPs to the mother outweigh the risks to the fetus. The available literature suggests that it is safe to take DZ during pregnancy but not during		
#14- Bellantuono et al 2013 Multiple Countries	Review of 12 Studies published after the year 2000 looking at specific BZDPs-AZ (1), CZ (2), CHL (2), DZ (4), MZ (1), NZ (1), bromazepam (BZ) (1) with regard to risk of CM	AZ CZ CH L DZ MZ NZ	BDZ exposure during the first trimester of pregnancy seems not to be associated with an increasing risk of CMs	No ↑risk in CM observed	L- timing of exposure not specified in 8/12 studies, dose not specified in 11/12, recall bias for retrospective studies, multiple confounding medications in 9/12 studies, maternal indication not known
#15-Saxen I 1975	Used Finnish Register of Congenital Malformations (CM) Case-control study-599 oral cleft cases, consumption of "antineurotic drugs" (meprobamate, diazepam and related drugs) during the 1st TM	DZ	3X↑risk of facial clefts with 1st TM DZ use	3X↑risk of facial clefts	S-prospective collection of exposure data for most prescription medications L-may be due to chance error caused by multiple comparisons, not controlled for concomitant drugs, EtOH, tobacco, other illicit drugs, BZDP lumped with other "anti-neurotics"

Reference ID: 4549287

#16-Safra MJ + Oakley GP Jr 1975	709 women with infants with all birth defects interviewed, 278 mothers of infants with Cleft lip (CL) and/or CL with cleft palate (CL/CP)	DZ	4X↑risk in mothers of infants with facial clefts with 1st TM DZ use as compared to mothers of infants with all other defects	4X↑risk of facial clefts	S- excluded chromosomal disorders L- may be due to chance error caused by multiple comparisons, not controlled for concomitant drugs, EtOH, tobacco, other illicit drugs
#17 Pastuszak et al. 1996	Case-control study with 137 cases (exposed to low dose BZDP, 127/137 in first trimester and 137 controls: AZ, BZ, CHL, CZ, DZ, flurazepam (FZ), lectopam (LM), lorazepam (LZ), NZ, oxazepam (OZ), TZ, triazolam (Tri)	Az Bz Chl DZ FZ LM LZ OZ NZ TZ Tri	No statistical difference in the rates of major birth defects, reported miscarriages, or elective abortions	No ↑ risk in CM observed	S-prospective assessment

Reference ID: 4549287

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/s/

CATHERINE A ROCA
01/21/2020 02:51:52 PM

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01/21/2020 02:57:50 PM

LYNNE P YAO
01/23/2020 06:11:42 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 17, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Taiye Adedeji, RPM
DAAAP

Subject: QT Consult to NDA 212295 (SDN 031)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 12/20/2019 regarding the sponsor's response to FDA comment regarding labeling for QT prolongation. We reviewed the following materials:

- Previous QT review for NDA 212295 dated 08/02/2019 in DARRTS; and
- Sponsor's response to FDA comment (Page 55-58) (Submission 0030).

1 IRT Responses

Sponsor's Question: The Applicant would therefore like to ask FDA to reconsider their view on the inclusion of a label description solely based on the results of Trial CNS7056-005.

IRT's Response: (b) (4) The TQT study showed small increases in QTcF at the supratherapeutic dose level (b) (4)

2 Internal Comments to the Division

(b) (4)

[redacted]

3 BACKGROUND

Previously the IRT reviewed a thorough QT study (CNS7056-005) under NDA 212295 and concluded a small dose- and concentration-dependent effect of remimazolam (10 mg and 20 mg IV bolus injection), despite of an observed heart rate increase. The findings from this study is also supported by a separate study (CNS7056-017) where heart rate is kept constant. The IRT proposes to report the QT findings from the TQT study.

The following comment from the previous IRT review has been sent to the sponsor:

(b) (4)

[redacted]. *We intend to include a description of the drug effect on HR and QTcF from the TQT study, CNS7056-005, in labeling, if the drug is approved. The final labeling language is still being discussed and has not been finalized.*

The following comment from the previous IRT review was not delivered to the sponsor:

(b) (4)

[redacted]

Reference ID: 4547917

(b) (4)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Reference ID: 4547917

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/s/

NAN ZHENG
01/17/2020 08:42:12 AM

CHRISTINE E GARNETT
01/17/2020 08:44:24 AM

Clinical Inspection Summary

Date	January 17, 2019
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Taiye Adedeji, Pharm.D., Regulatory Project Manager Renee Petit Scott, M.D., Medical Officer Martha Van Clief, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application	NDA 212295
Applicant	Cosmo Technologies, Ltd.
Drug	Remimazolam (Byfavo®)
NME / Original NDA	Yes
Review Status	Standard
Proposed Indication	Induction and maintenance of procedural sedation in adults
Consultation Date	June 18, 2019
CIS Goal Date	January 22, 2019
Action Goal Date	April 3, 2019
PDUFA Due Date	April 5, 2019

I. OVERALL ASSESSMENT OF FINDINGS

Four clinical investigator (**CI**) sites were inspected for three pivotal studies supporting this NDA. For all CI sites, no significant good clinical practice (**GCP**) deficiencies were observed. A Form FDA 483 was issued at one site (Feldman) for minor deficiency observations unlikely to be significant to the study outcome.

Based on the inspections of these four CI sites, study conduct appeared GCP-compliant, including sponsor oversight. All audited data were verifiable against source records and case report forms (**CRFs**). The data from the inspected CI sites appear reliable as reported in the NDA.

II. BACKGROUND

This NDA 212295 supports the approval of remimazolam (Byfavo®) for the induction and maintenance of procedural sedation in adults. The three major studies presented in the NDA share similar study designs (and claimed study outcomes):

- ***CNS 7056-015:*** *A Study Evaluating the Safety and Efficacy of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in ASA III and IV Patients Undergoing Colonoscopy*

  This partially blinded randomized controlled trial (**PBRCT**) was conducted over 13 months (2015-2016) in 79 subjects undergoing colonoscopy. The primary study objective was to assess the safety of remimazolam relative to placebo and midazolam following standard fentanyl analgesia. The primary efficacy endpoint was the successful completion of colonoscopy.

- ***CNS 7056-006:*** *A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Colonoscopy*

  This PBRCT was conducted over 13 months (2015-2016) in 461 subjects undergoing flexible colonoscopy (study population similar as in CNS 7056-015). The primary study objective was to show that remimazolam is more effective than placebo or midazolam in inducing and maintaining adequate sedation in combination with standard fentanyl analgesia. The primary efficacy endpoint was the successful completion of colonoscopy, without using rescue medication.

- ***CNS 7056-008:*** *A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy*

  This PBRCT was conducted over 21 months (2015-2017) in 446 subjects undergoing flexible bronchoscopy. The primary study objective and the primary efficacy endpoint were identical to those for CNS 7056-006, to show that remimazolam is more effective than placebo or midazolam in inducing/maintaining adequate sedation in combination with standard fentanyl analgesia. The primary efficacy endpoint was the successful completion of bronchoscopy without rescue or excessive study medication use.

In each study, the initial and additional doses of the study medication were administered to achieve a level of sedation deemed adequate to begin the respective endoscopic procedure, as assessed using Modified Observer's Assessment of Alertness and

Sedation (**MOAA/S**) score, including scores for Visual Analog Scale (**VAS**) for injection site pain and drowsiness. Additional doses were given as needed to maintain adequate sedation to complete the procedure. The inability to achieve/maintain adequate sedation despite per-protocol maximal dosing was considered treatment failure. Per CI discretion, midazolam could be used as the (only permissible) rescue medication.

III. INSPECTION OUTCOMES

1. Bal Bhandari, M.D.
608 Grammont Street
Monroe, LA 71201

Inspection dates: August 26-29, 2019

Study CNS7056-006, Site 002: 116 subjects were screened, 110 were enrolled, and 108 completed the study. Two subjects withdrew consent, one due to spousal concerns and another following an adverse event (**AE**).

Study CNS7056-015, Site 001: 70 subjects were screened, 66 were enrolled, and 62 completed the study. Two subjects withdrew consent. One subject withdrew following a serious AE (**SAE**) of severe dehydration. One subject was discontinued due to the lack of a nurse anesthetist.

For each study, case records were reviewed in detail for all enrolled subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuations.

No significant deficiencies were observed. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Taddese Desta, M.D.
292 Euclid Avenue, Suite 115
San Diego, CA 92114

Inspection dates: November 18 – 22, 2019

Study CNS7056-006, Site 005: 121 subjects were screened, 107 were enrolled, and 107 completed the study.

Case records were reviewed for all enrolled subjects, including detailed review for 18 subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuations.

A Form FDA 483 was issued for minor GCP deficiency observations, primarily for three discrepancies (three different subjects) between the source record and the CRF, apparently minor isolated recordkeeping errors unlikely to be significant, as follows:

- MOAA/S scores of 1 (source) and 4 (CRF), initial time point
- VAS drowsiness scores of 15 (source) and 20 (CRF)
- VAS injection site pain scores of 13 (source) and 3 (CRF)

Study conduct appeared GCP-compliant, including sponsor oversight. GCP deficiencies associated with short colonoscopy times were not observed. All audited NDA data were otherwise adequately verifiable against source records and CRFs.

Note: The Establishment Inspection Report (**EIR**) for this inspection has not been received from the field office (as of 1/17/2020) and the results reported in this Clinical Inspection Summary (**CIS**) is based on preliminary communication with the field investigator. Upon receipt and review of the EIR at OSI, an addendum to this CIS will be forwarded to the review division if new significant findings are discovered; otherwise, OSI's written post-inspection correspondence letter to the inspected entity (to be copied to review division) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

3. Gregory Feldman, M.D.
141 Harold Flemming Court
Spartanburg, SC 29303

Inspection dates: September 17 – 20, 2019

Study CNS7056-008, Site 004: 08 subjects were screened, 103 were enrolled, and 103 completed the study.

Case records were reviewed for all enrolled subjects, including detailed review for 40 subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuations.

No significant deficiencies were observed. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. GCP deficiencies associated with short colonoscopy times or large amounts of the study drug used were not observed. All audited NDA data were adequately verifiable against source records and CRFs.

4. Lonny Yarmus, M.D.
1800 Orleans Street
Baltimore, MD 21287

Inspection dates: September 23 – 26, 2019

Study CNS7056-008, Site 021: 111 subjects were screened, 94 were enrolled, and 91 completed the study. Three subjects were lost to follow up.

Case records were reviewed for all enrolled subjects, including detailed review for 21 subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuations.

No significant deficiencies were observed. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
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Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
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CC:

Central Document Room / NDA 212295

DAAAP / Clinical Team Leader / Martha Van Clief
DAAAP / Medical Officer / Renee Petit Scott
DAAAP / Regulatory Project Manager / Taiye Adedeji

OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
01/17/2020 11:49:59 AM

PHILLIP D KRONSTEIN
01/17/2020 12:50:57 PM

KASSA AYALEW
01/17/2020 12:53:41 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 6, 2019
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212295
Product Name and Strength:	Byfavo (remimazolam) injection, 20 mg per vial
Applicant/Sponsor Name:	Cosmo Technologies, Ltd.
OSE RCM #:	2019-789-3
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 3, 2019 for Byfavo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels for Byfavo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Johnson, C. Label and Labeling Review for Byfavo (NDA 212295). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2019-789-2.

Reference ID: 4529752

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 3, 2019

Container labels

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/s/

CAMERON D JOHNSON
12/06/2019 06:36:07 AM

OTTO L TOWNSEND
12/06/2019 10:01:08 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 12, 2019
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 212295
Product Name and Strength:	Byfavo (remimazolam) injection, 20 mg per vial
Applicant/Sponsor Name:	Cosmo Technologies, Ltd.
OSE RCM #:	2019-789-2
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 25, 2019 for Byfavo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for Byfavo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[ab]

2 CONCLUSION

The Applicant implemented all of our recommendations; however, we noted that the container labels include the package type term as [redacted] (b) (4) Since this product is a powder, we are concerned [redacted] (b) (4) could lead to confusion. We consulted with the Office of Pharmaceutical Quality (OPQ) [redacted] (b) (4) OPQ agreed that the [redacted] (b) (4) should be removed from the container labels.

[a] Johnson, C. Label and Labeling Review for Byfavo (NDA 212295). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 11. RCM No.: 2019-789.

[b] Johnson, C. Label and Labeling Review for Byfavo (NDA 212295). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 11. RCM No.: 2019-789-1.

Reference ID: 4518470

3 RECOMMENDATIONS FOR COSMO TECHNOLOGIES

We recommend the following be implemented prior to approval of this NDA:

A. We note that the package type term is included as (b) (4) Byfavo is a powder for injection, (b) (4) Furthermore, the carton labeling and Prescribing Information (b) (4) Remove the (b) (4) from the package type term and revise the (b) (4) on the container label so that the package type term reads as "Single-Patient Use Vial".

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 11, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212295
Product Name and Strength:	Byfavo (remimazolam) injection, 20 mg per vial
Applicant/Sponsor Name:	Cosmo Technologies, Ltd.
OSE RCM #:	2019-789-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 7, 2019 for Byfavo. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling for Byfavo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective for the following reasons:

A. The strength on the labels and labeling is not prominently displayed to allow for easy identification of this important information.
B. The 2D data matrix barcode and human readable serial number have been removed from the 2 x 20 mg vials carton labeling.

[a] Johnson, C. Label and Labeling Review for Byfavo (NDA 212295). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 11. RCM No.: 2019-789.

Reference ID: 4505039

C. The linear barcode has been removed from the side panel of the vial labels and appears to have been replaced by a barcode that does not have sufficient white space surrounding it.
D. The proprietary name, BYFavo, uses tallman lettering which is reserved for differentiating names of confusion.

3 RECOMMENDATIONS FOR COSMO TECHNOLOGIES, LTD.

We recommend the following be implemented prior to approval of this NDA:

A. The strength, 20 mg/vial, lacks prominence on all container labels and carton labeling. The strength should be easily identifiable and prominently displayed on the labels and labeling in accordance with 21 CFR 201.15(a)(6). To comply with 21 CFR 201.15(a)(6), increase the prominence of the strength, 20 mg/vial, on all labels and labeling.
B. The 2D data matrix barcode and human-readable serial number of the product identifier have been removed from the 2 x 20 mg vials carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[b] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If the product identifier requirements apply, add back the 2D data matrix barcode and human-readable serial number to the 2 x 20 mg vials carton labeling.
C. The vertical linear barcode has been removed from the side panel of the vial labels; however, there appears to be a horizontal barcode on the bottom portion of the Principal Display Panel (PDP). Please confirm if the barcode that has been placed on the bottom portion of the PDP is the linear barcode that can be used for scanning and product verification in the hospital setting. Barcodes placed in a horizontal position may not scan due to vial curvature. Consider reorienting the linear barcode back to a vertical position to improve the scannability of the barcode. Furthermore, ensure that the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
D. The proprietary name, BYFavo, is presented with the letters 'YF' capitalized. This mixed case type of presentation is typically reserved for differentiating known look-alike and sound-alike established name pairs or in rare circumstances for proprietary names to help reduce the risk of wrong drug name errors. Since Byfavo is not a name that has been involved in drug name confusion or wrong drug errors, the capitalization of the letter "YF" is inappropriately applied. Thus, we recommend that the proprietary name is presented as Byfavo on the container labels and carton labeling.

[b] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4505039

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 11, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 212295
Product Name and Strength:	Byfavo (remimazolam) injection, 20 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Cosmo Technologies, Ltd.
FDA Received Date:	April 5, 2019 and August 1, 2019
OSE RCM #:	2019-789
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

Reference ID: 4489851

1 REASON FOR REVIEW

As part of the approval process for Byfavo (remimazolam) injection, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed Byfavo prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
DMEPA Tracked Changes Recommendations for Section 2.2 of Prescribing Information	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We note that the vial contains 20 mg of remimazolam and the recommended dose for initiation of procedural sedation ranges from 2.5 mg to 5 mg. For maintenance of procedural sedation the patient may receive supplemental doses as needed ranging from 1.25 mg to 2.5 mg that are titrated to desired clinical response. We were initially concerned that the amount of drug in the vial exceeded the dose needed for a single dose for a single patient. Therefore, this larger quantity of drug in the vial compared to a single recommended dose could prompt users to save the remaining contents in the vial for administration to other patients (i.e., as a multiple dose vial). In addition, having more drug in the vial than required for a single dose could result in a user administering the entire contents of the vial as a single dose. We reviewed the labeling and noted that this product is labeled as a 'single patient use vial' and the unused portion should be discarded. This allows for the supplemental doses required for maintenance of procedural sedation to be withdrawn from the same vial and administered to a single patient. We also noted that after reconstitution the product should be used within (b) (4) The package type and discard statement should reduce the risk of a user administering the product to multiple patients. Also, the practicality of the 20 mg product is further supported because

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multiple doses can be administered to a single patient within (b) (4) of reconstitution so there is a possibility that the cumulative doses for both initiation and maintenance of sedation may be close to the total amount in the vial. Furthermore, since this is a controlled substance, there are additional documentation requirements that should address the risk of a user administering the drug to multiple patients. We also note that propofol products contain a similar package type term (e.g., "For Single Patient Use Only") that describes the product as intended for administration to a single patient. Therefore, in this instance, we conclude that the risk of this product being used as a multiple dose vial should be minimized through the labeling. Despite our determination from a medication error perspective, we defer to the Office of Pharmaceutical Quality to make the final determination on the appropriate package type term for this product.

Tables 2 and 3 below include other identified medication error issues with the submitted prescribing information (PI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights and Full Prescribing Information – General Issues			
1.	We note that the placeholder, "TRADENAME" is included throughout the Prescribing Information.	We reference our proprietary name review for NDA 212295 (OSE # 2019-30640132) dated June 6, 2019 concluding that the proprietary name, Byfavo, was found conditionally acceptable.	Revise the placeholder, "TRADENAME", with the conditionally acceptable proprietary name, Byfavo.
2.	The size of the glass vial, 12 mL, is included in the product's description in the Dosage Forms and Strengths section and in the Description section.	Including the vial size may cause confusion to users and has been documented in postmarket medication error reports to be error prone. For example healthcare professionals could confuse the volume after reconstitution to be 12 mL.	Remove the vial size, 12 mL, from the description and revise to "Each glass single-patient use vial contains 20 mg…".
3.	In the Dosage and Administration section, the individual strengths "2.5" and "1.25" do not	All necessary strength information must be present in proper format in order to prevent medication errors. If the unit of measure does	Add the unit of measure, "mg", after the numerals "2.5" and

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Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	contain the associated units of measure (mg) immediately following them.	not immediately follow the numeral, the lower strength in the dosage range may be overlooked.	"1.25". For example, 2.5 mg and 1.25 mg.
4.	In the Dosage and Administration section, the dose is expressed as milligrams, "mg" (b) (4)	(b) (4) may lead to misinterpretation if the healthcare professional (HCP) mistakes (b) (4)	To provide clarity and to address the risk of medication errors, remove all instances (b) (4) For example, change (b) (4) to "5 mg".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The Preparation (b) (4) section lists the reconstitution diluent 0.9% Sodium Chloride, USP as (b) (4)	(b) (4) the appropriate USP product name should be used.	Revise the name of the diluent to: "0.9% Sodium Chloride, USP".
2.	The table in section 2.1 Basic Dosing Information, contains the abbreviation, IV.	The use of abbreviations has led to misinterpretations and confusion.	Replace the abbreviation, IV, with the intended meaning, intravenously.
3.	The Preparation (b) (4) section contains the statement: "Each single-patient-use vial contains 20 mg TRADENAME (remimazolam, equivalent to 27.2 mg remimazolam besylate) lyophilized powder for reconstitution."	The inclusion of the equivalency statement may lead to confusion and, if needed, this information is included in the Dosage Forms and Strength and Description sections.	Remove the equivalency statement from the statement. For example, "Each single-patient-use vial contains 20 mg BYFAVO lyophilized powder for reconstitution."

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Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The Preparation (b) (4) section contains the statement: (b) (4) will deliver a final concentration of 2.5 mg/mL solution (b) (4) of TRADENAME." Furthermore, the order and format of the information in this section lacks clarity.	The inclusion of (b) (4) may lead to confusion. Furthermore, to improve clarity and readability of this section, the information should be rearranged and reformatted.	Remove the sentence (b) (4) and revise the statement to: "The resultant solution will deliver a final concentration of 2.5 mg/mL…." Also, see tracked changes in Appendix E below for recommended revisions to the Preparation (b) (4) section.
5.	The Administration with Other Fluids Section includes references to infusion solutions that are not common in the U.S. (b) (4)	References to infusion solutions that are not customary in the US may lead to confusion. Therefore, the appropriate product names (based on USP monograph) for these infusion solutions should be used.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine if the solutions listed in the PI are equivalent to the products listed below. We also defer to OPQ for the appropriate product names. If appropriate, we recommend revising the infusion solutions as follows: • (b) (4) to 0.9% Sodium Chloride Injection, USP • (b) (4) to 5% Dextrose Injection, USP

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Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			• [redacted] (b) (4) to 20% Dextrose Injection, USP • [redacted] (b) (4) to 5% Dextrose and 0.45% Sodium Chloride Injection, USP
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The reconstitution instructions are included in the Dosage Forms and Strengths section.	The reconstitution instructions are included in the Dosage and Administration section and thus, do not need to be included in the Dosage Forms and Strengths section.	To reduce redundancy, remove the reconstitution instruction, [redacted] (b) (4) from this section.
2.	The size of the glass vial, 12 mL, is included in the Dosage Forms and Strengths section.	Including the vial size may cause confusion to users. This presentation has been documented in postmarket medication error reports to be error prone. For example healthcare professionals could confuse the volume after reconstitution to be 12 mL.	Remove the vial size, 12 mL from the statement and revise to "Each glass single-patient-use vial contains 20 mg…".
3.	This section does not contain appropriate information to facilitate identification of the dosage form.	This information is required per 21 CFR 201.57(c)(4)(ii).	We recommend inclusion of identifying characteristics of the dosage form, such as color or any other identifying characteristics, in accordance with 21 CFR 201.57(c)(4)(ii).

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Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	This section does not contain appropriate information to facilitate identification of the dosage form.	This information is required per 21 CFR 201.57(c)(17).	We recommend inclusion of identifying characteristics of the dosage form, such as color and NDC number, in accordance with 21 CFR 201.57(c)(17).

Table 3. Identified Issues and Recommendations for Cosmo Technologies, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The container labels and carton labeling contain the placeholder, "Trade Name".	We reference our June 10, 2019 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Byfavo, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Byfavo.
2.	The finished dosage form, "for injection" is located on the bottom right or upper left corner of the PDP, away from the established name.	The finished dosage form should be located either in the same line as the established name or directly below the established name.	Relocate the dosage form next to the established name or directly below it.
3.	The strength is expressed as (b) (4) on all labels and labeling.	We note the strength that is presented on the labels and labeling (b) (4) as opposed to the quantity of the powder only as recommended by USP (see	Revise the strength statement in accordance with USP standards to 20 mg per vial.

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Table 3. Identified Issues and Recommendations for Cosmo Technologies, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		USP General Chapter <7> Labeling).	
4.	You have not included information to the user that the product requires reconstitution. (b) (4) [redacted]	We agree the end user will need to know the concentration per mL; however, the user needs to know that the product requires reconstitution and the resultant concentration after reconstitution.	Revise the statement to, "Upon reconstitution with 8.2 mL 0.9% Sodium Chloride Injection, USP, each mL contains…".
5.	The usual dose statement reads as (b) (4) [redacted]	This statement is not consistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement to read "Recommended Dosage: See prescribing information."
6.	As currently presented, the format for the expiration date is not defined.	Expiration dates have been misinterpreted and led to deteriorated drug medication errors based on confusing formats.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month,

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Table 3. Identified Issues and Recommendations for Cosmo Technologies, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Label(s)			
1.	The reconstituted product must be discarded after (b) (4) however, this important information is not included on the label and there is no space on the label for healthcare providers to write the post-reconstitution date and time.	Including this important post reconstitution storage information as well as a space for a discard date and time can reduce the risk of a healthcare provider administering expired drug product.	Allow space for healthcare providers to write post-reconstitution expiration date and time on the label. For example add a statement such as: "Discard unused portion (b) (4) (b) (4) after reconstitution. Discard after (date): __/__/__ Discard after (time): _____"
Carton Labeling			
1.	The carton labeling (b) (4) while the container label contains a lot number statement.	Consistent terminology should be used throughout the labels and labeling to reduce the risk of confusion.	Revise the carton labeling from (b) (4) to "Lot No." so that the carton labeling is consistent with the container label.

4 CONCLUSION

Our evaluation of the proposed Byfavo prescribing information (PI), container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Cosmo Technologies, Ltd. so that recommendations are implemented prior to approval of this NDA.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Byfavo that Cosmo Technologies, Ltd. submitted on August 1, 2019.

Table 4. Relevant Product Information for Byfavo	
Initial Approval Date	N/A
Active Ingredient	Remimazolam
Indication	indicated for the induction and maintenance of procedural sedation in adults.
Route of Administration	intravenous
Dosage Form	injection
Strength	20 mg per vial
Dose and Frequency	Adult Patients: • Administer an initial dose of TRADENAME intravenously as a 5 mg (2 mL) push injection over a 1-minute time period. • If necessary, administer supplemental doses of 2.5 mg (1 mL) TRADENAME over a 15-second time period. At least 2 minutes must have elapsed prior to the administration of any supplemental dose. Debilitated Patients (ASA III-IV, at the discretion of the physician): • Based on the general condition of the patient, administer 2.5 to 5 mg (1 or 2 mL) of TRADENAME over 1-minute time period. • If necessary, administer supplemental doses of 1.25 to 2.5 mg (0.5 or 1 mL) TRADENAME as a push injection over a 15 second time period.
How Supplied/container closure	sterile lyophilized powder in 12 mL glass vials containing 20 mg sterile active ingredient
Storage	Controlled room temperature

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 8, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, remimazolam. Our search did not identify any previous reviews.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – TRACKED CHANGE RECOMMMENDATIONS FOR SECTION 2.2. PREPARATION AND ADMINISTRATION OF THE PI

2.2 Preparation (b) (4)

Reconstitution of TRADENAME for injection (b) (4)

- Strict aseptic technique must (b) (4) be maintained during handling of TRADENAME.
- This product does not contain preservative.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- (b) (4) Once removed from packaging (b) (4)
- Each single-patient-use vial contains 20 mg TRADENAME (b) (4) (b) (4) lyophilized powder for reconstitution.
- To reconstitute, (b) (4) add 8.2 mL sterile 0.9% Sodium Chloride (b) (4) directing the stream of (b) (4) toward the wall of the vial (b) (4) gently swirl the vial (Do not shake), until the contents are fully dissolved. (b) (4)
  The reconstituted (b) (4) deliver a final concentration of 2.5 mg/mL solution (b) (4) of TRADENAME. (b) (4) (b) (4)
- (b) (4) The product must be prepared immediately before use. (b) (4) (b) (4) under controlled room temperature at 20°C to 25°C (68°F to 77°F). After (b) (4) any unused portion must be discarded.

(b) (4)

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Byfavo labels and labeling submitted by Cosmo Technologies, Ltd. on April 5, 2019 and August 1, 2019.

- Vial label
- Professional Sample vial label
- Carton labeling
- Professional Sample Carton Labeling
- Prescribing Information (Image not shown) but can be accessed in EDR via:
    - \\cdsesub1\evsprod\nda212295\0012\m1\us\114-labeling\draft\labeling\remimazolam-prescribing-information-draft-label-clean.pdf

F.2 Label and Labeling Images

Vial label

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA212295
Submission Number	0000
Submission Date	4/5/2019
Date Consult Received	4/22/2019
Clinical Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews under IND 102486 dated 07/17/2014 and 01/23/2015 in DARRTS;
- Study CNS7056-005 protocol and clinical trial report (Submission 0000);
- Study CNS7056-017 protocol, clinical trial report and cardiac safety report (Submission 0000);
- Proposed label (Submission 0010);
- Highlights of clinical pharmacology and cardiac safety (Submission 0002).

1 SUMMARY

A small dose- and concentration-dependent effect of remimazolam (10 mg and 20 mg IV bolus injection) on the QTc interval was detected in the TQT study.

The effect of remimazolam was evaluated in study the TQT study, CNS7056-005. The highest dose that was evaluated was 20 mg, which covers the highest dose possible with a single patient-use vial (20 mg as 7 injections in approximately 15 min). The data were analyzed using central tendency as the primary analysis, which suggest that remimazolam 20 mg is associated with small QTc prolonging effect (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), exposure-response analysis (section 4.5) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs of QTcF (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔ (ms)	90% CI (ms)
QTc	Remimazolam 10mg	0.5 min	6.7	(4.0, 9.5)
QTc	Remimazolam 20mg	0.5 min	10.7	(8.0, 13.4)
QTc	Midazolam 2.5mg	0.5 min	4.5	(1.8, 7.3)
QTc	Midazolam 7.5mg	0.5 min	8.1	(5.4, 10.8)

Remimazolam is administered as an IV bolus injection. Dose and injection/infusion rate are the most significant factors that impact the C_{max}. The proposed initial adult dose is

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5 mg push injection over a 1-minute; supplement doses of 2.5 mg over a 15-seconds can be administered at least 2 min apart. The proposed product label does not have specify an upper limit of total dose. Age, sex, race, and hepatic and renal impairment do not result in significant increase in C_{max}. No clinical DDI studies have been conducted.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Remimazolam treatment is associated with large increase in heart rate. In the thorough QT study, the largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% CI) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, after treatment with 10 mg and 20 mg remimazolam, respectively. The observation does not impact the overall conclusion that remimazolam increases the QTc interval because in a separate study (CNS7056-017) where heart rate is kept constant by using a slow IV infusion, small increases in QTc interval were detected. Furthermore, the slopes of the concentration-QTc relationship between the two studies were similar (see section 4.5).

2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0010 from the QT-IRT. Our changes are highlighted (addition, ~~deletion~~) for the Division's consideration and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology (b) (4)

(b) (4)

In a thorough QT study (b) (4), 57 healthy volunteers were given an iv push of 10 mg or 20 mg TRADENAME, intravenous midazolam (2.5 mg or 7.5 mg) or placebo, or a single tablet of moxifloxacin 400 mg given orally. (b) (4) he largest mean placebo-adjusted change-from-baseline QTc (upper bound of 2-sided 90% confidence interval) was 6.7 (9.5) ms, 10.7 (13.4) ms, 4.5 (7.3) ms, and 8.1 (10.8) ms, respectively, after treatment with 10 mg or 20 mg TRADENAME, or 2.5 mg or 7.5 mg midazolam.

TRADENAME treatment is associated with increases in heart rate. The largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% CI) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, respectively, after treatment with 10 mg and 20 mg TRADENAME.

(b) (4)

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(b) (4)

Reviewer's comments:

We do not agree (b) (4)

(b) (4)

(b) (4) *We recommend reporting study findings, including drug effect on HR and QTcF, from the TQT study, CNS7056-005.*

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3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Previously the QT-IRT reviewed the TQT study protocol and analysis plan under IND 102486 (dated 07/17/2014 and 01/23/2015 in DARRTS). The TQT study, CNS7056-005, was a single-dose, randomized, double-blind, comparative (midazolam 2.5 mg and 7.5 mg), positive (moxifloxacin 400 mg), and placebo-controlled, six-period crossover study in 57 healthy subjects. The remimazolam doses were 10 and 20 mg. Midazolam and remimazolan were given as IV injection. (b) (4) .

The results of the TQT study show an increase in heart rate. The sponsor conducted another study (CNS7056-017) where the study drug was given as IV infusion and heart rate was kept at a steady level. CNS7056-017 was a prospective, open-label, randomized, two-arm, crossover phase I study comparing a single dose of 85 mg remimazolam administered in a 35-min infusion *vs*. placebo in 20 healthy subjects. Holter ECG data were analyzed in a blinded manner. (b) (4) (b) (4) The reviewers' analyses focused on the TQT study, CNS7056-005. The reviewers use QTcF as the primary endpoint (b) (4) The primary analysis is the pre-defined, by-timepoint analysis. Data from CNS7056-017 will be included in the exploratory, concentration-QTc analysis.

It should be noted that at the time of previous review, the therapeutic dose was listed as an initial dose of 5 mg with top-up dose of 2.5 mg, (b) (4) In the current proposed label, in addition to an initial dose of 5 mg, supplemental doses can be taken as needed if at least 2 minutes elapse prior to administration of any supplemental dose. There is no mention of an upper limit to the accumulative dose.

Remimazolam shows weak inhibition of hERG tail currents with an IC_{25} of 62 uM and IC_{50} of 207 uM. The IC_{25} of its major metabolite, CNS7054, is >100 uM. No effects were seen upon calcium currents up to 30 μM remimazolam or 100 μM CNS7054, or upon inwardly or the delayed rectifying potassium channels up to 100 μM remimazolam or 300 μM CNS7054.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

Remimazolam 20 mg failed to exclude the 10 ms threshold. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3.1 for additional details.

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3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3.1.1 for additional details.

3.2.1.1.1 QT bias assessments

Not applicable.

3.2.2 Categorical Analysis

None of the subjects had absolute QTcF > 480 ms or a change from baseline QTcF >60 ms. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

There were no deaths, other serious events, or other significant AEs.

The most commonly reported AE of interest was heart rate decreased (14 subjects, 25% overall), which occurred with a similar incidence across all dose groups (4% to 6% of subjects). The next most common was BP diastolic decreased (6 subjects, 11% overall), which had the highest incidence following administration of 20 mg remimazolam (3 subjects [6%]) and occurred in 1 subject each (2%) in the placebo, 10 mg remimazolam, and 7.5 mg midazolam groups, and none in the moxifloxacin 400 mg and 2.5 mg midazolam groups.

Both remimazolam and midazolam administration resulted in transient increases in mean pulse rate that were maximal at 2 minutes post dose and had returned to baseline levels by the 2-hour postdose time point. Only 2 subjects, subject (b) (6) and (b) (6), showed heart rates >100 bpm

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

The sponsor evaluated the relationship between ΔΔQTc (i.e., QTcI, QTcF, and QTcB) and plasma concentration of remimazolan and CNS7054 using a linear mixed effect modeling approach. The results of the PK-PD model show that the slope for QTcI for remimazolam was slightly positive. The overall predicted ΔΔQTcI and the upper bound of 90% CI at Cmax for the therapeutic and supratherapeutic doses were, respectively, 4.6 (5.7 ms) and 9.4 ms (11.3 ms). The analysis suggested a flat relationship between ΔΔQTcI and CNS7054. The predictions based on QTcF were similar to QTcI (4.9 ms [5.9 ms] and 9.8 ms [11.6 ms] at the two dose levels).

Reviewer's comment: *The reviewer used QTcF as the primary endpoint. The reviewer's analysis suggest s concentration-dependent increase on the QTc interval, and a small effect could not be excluded at the supratherapeutic dose level. Please see section 4.5 for additional details.*

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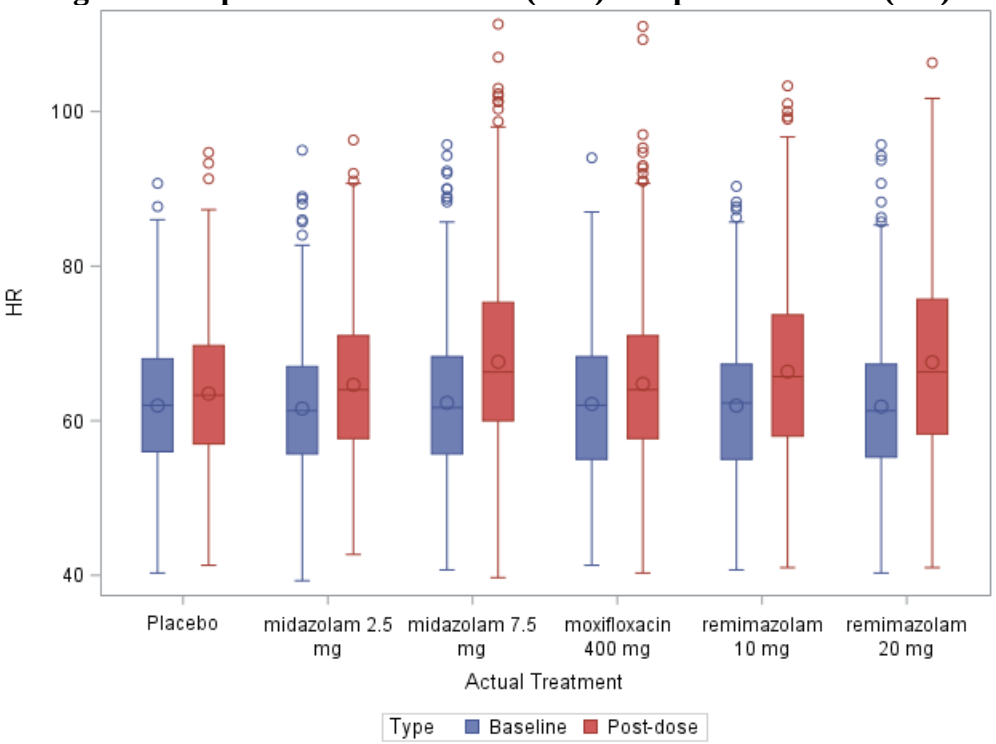
4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

Remimazolan treatment is associated with heart rate increase (sections 4.3.2 and 4.5). (b) (4) . Therefore, the reviewers default to QTcF for the analysis.

Figure 1 Boxplot of HR at baseline (blue) and post-treatment (red)



4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes time, treatment, treatment by time interaction, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate.

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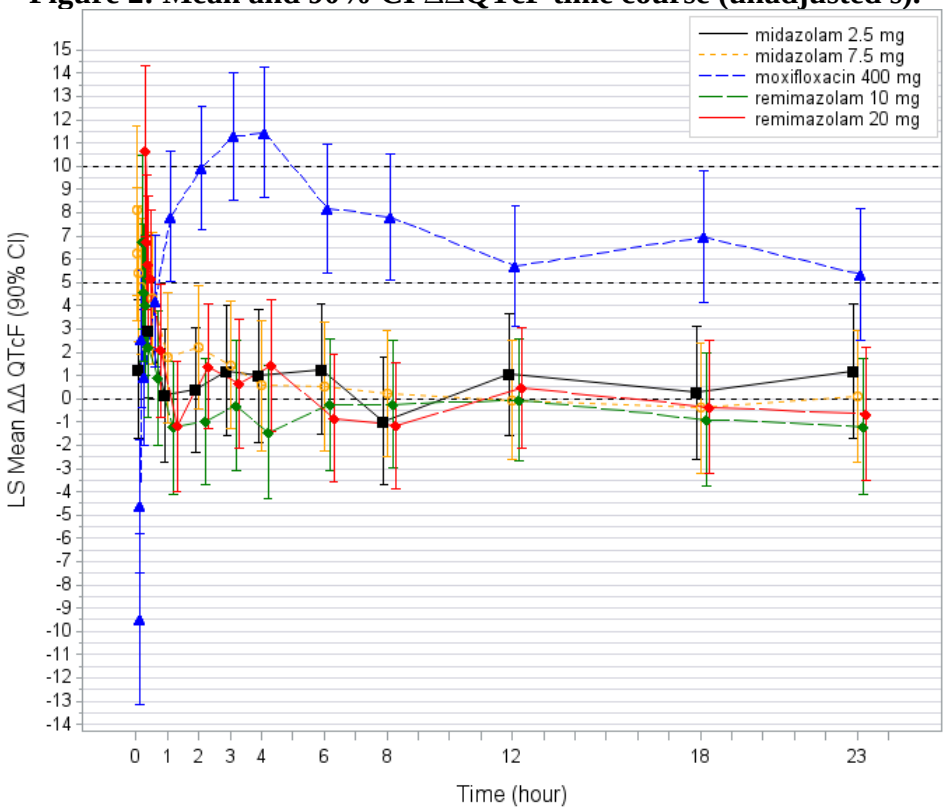
The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 2: Mean and 90% CI ΔΔQTcF time course (unadjusted s).



4.3.1.1 Assay sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Figure 2. In QTcF correction method, the largest lower bound of the unadjusted 90% confidence interval is 9.4 ms for drug moxifloxacin 400mg. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 8.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study. The time profile of moxifloxacin is consistent with ascending, peak, and descending phase of historical moxifloxacin profile. Overall, assay sensitivity was demonstrated in this study.

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 3). The largest upper limits of 90% CI for the HR mean differences between remimazolam 10 mg and placebo and remimazolam 20 mg and placebo are 14.2 bpm and 17.1 bpm, respectively.

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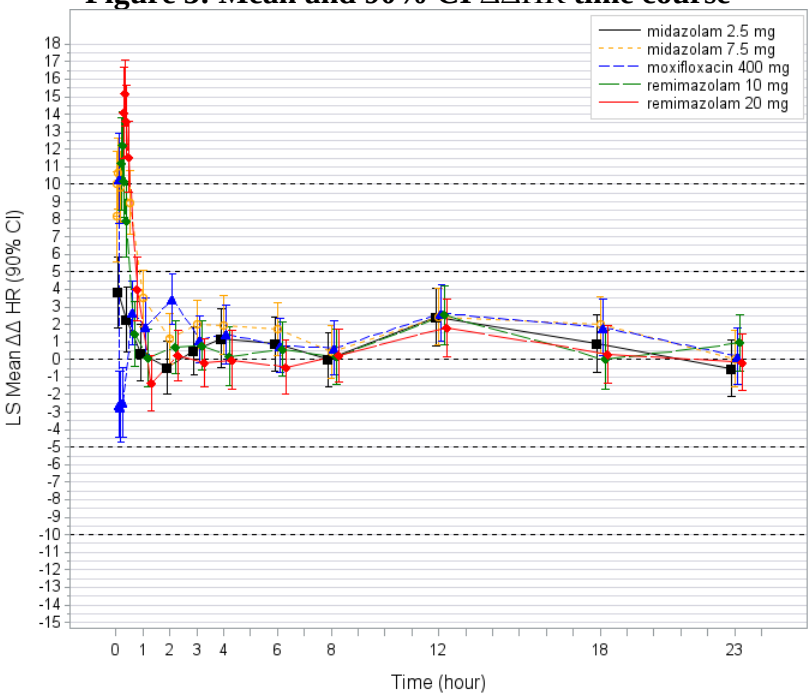
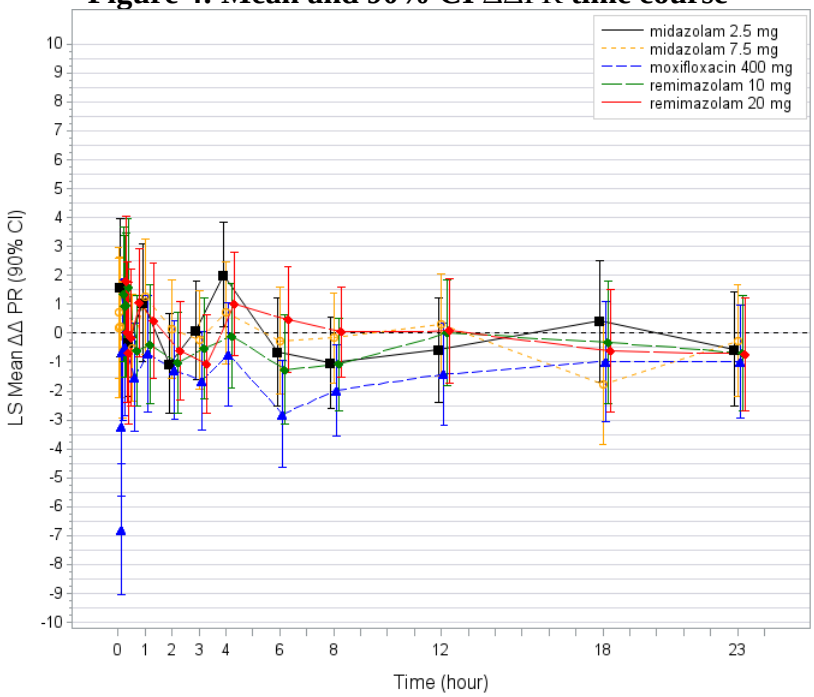
Figure 3: Mean and 90% CI ΔΔHR time course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 4). The largest upper limits of 90% CI for the PR mean differences between remimazolam10 mg and placebo and remimazolam 20 mg and placebo are 3.7 ms and 4.1 ms, respectively.

Figure 4: Mean and 90% CI ΔΔPR time course



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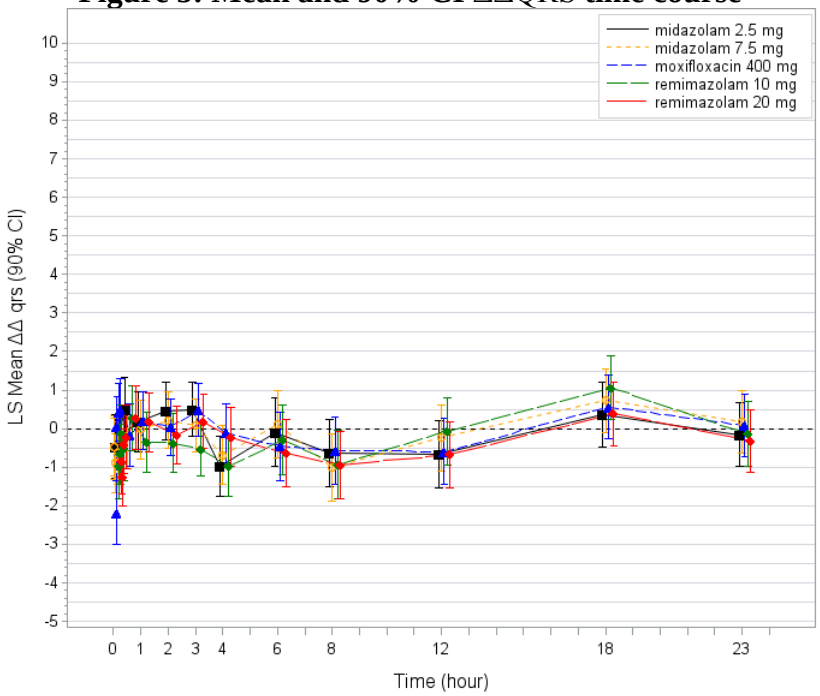
4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 5). The largest upper limits of 90% CI for the QRS mean differences between remimazolam 10 mg and placebo and remimazolam 20mg and placebo are 1.9 ms and 1.2 ms, respectively.

Figure 5: Mean and 90% CI ΔΔQRS time course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 2 lists the number of subjects and the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 2: Categorical Analysis for QTcF

Actual Treatment	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
remimazolam 10 mg	48	671	48 (100%)	671 (100%)	0 (0.0%)	0 (0.0%)
remimazolam 20 mg	52	723	52 (100%)	723 (100%)	0 (0.0%)	0 (0.0%)
midazolam 2.5 mg	49	686	49 (100%)	686 (100%)	0 (0.0%)	0 (0.0%)
midazolam 7.5 mg	53	739	52 (98.1%)	738 (99.9%)	1 (1.9%)	1 (0.1%)
Placebo	53	742	53 (100%)	742 (100%)	0 (0.0%)	0 (0.0%)

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Table 3 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 3: Categorical Analysis of ΔQTcF

Actual Treatment	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
remimazolam 10 mg	48	671	48 (100%)	671 (100%)	0 (0.0%)	0 (0.0%)
remimazolam 20 mg	52	719	52 (100%)	719 (100%)	0 (0.0%)	0 (0.0%)
midazolam 2.5 mg	49	686	49 (100%)	686 (100%)	0 (0.0%)	0 (0.0%)
midazolam 7.5 mg	53	738	53 (100%)	738 (100%)	0 (0.0%)	0 (0.0%)
Placebo	53	742	52 (98.1%)	741 (99.9%)	1 (1.9%)	1 (0.1%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. All subjects (3) experienced postdose PR>200 after receiving either remimazolam or midazolam had baseline PR<200.

Table 4: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <= 200 msec		200 msec < Value <= 220 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
remimazolam 10 mg	48	671	46 (95.8%)	666 (99.3%)	2 (4.2%)	5 (0.7%)
remimazolam 20 mg	52	723	50 (96.2%)	720 (99.6%)	2 (3.8%)	3 (0.4%)
midazolam 2.5 mg	49	686	48 (98.0%)	684 (99.7%)	1 (2.0%)	2 (0.3%)
midazolam 7.5 mg	53	739	52 (98.1%)	735 (99.5%)	1 (1.9%)	4 (0.5%)
Placebo	53	742	52 (98.1%)	741 (99.9%)	1 (1.9%)	1 (0.1%)

4.4.3 QRS

There are no subjects who experienced QRS interval greater than 110 ms in both remimazolam 10 mg and remimazolam 20 mg.

4.4.4 HR

The outlier analysis results for HR are presented in Table 5. All subjects (7) experienced postdose HR>100 after receiving either remimazolam or midazolam have baseline HR<100 (baseline HR ranging from 54 to 97).

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Table 5: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
remimazolam 10 mg	48	671	46 (95.8%)	669 (99.7%)	2 (4.2%)	2 (0.3%)
remimazolam 20 mg	52	723	49 (94.2%)	720 (99.6%)	3 (5.8%)	3 (0.4%)
midazolam 2.5 mg	49	686	49 (100%)	686 (100%)	0 (0.0%)	0 (0.0%)
midazolam 7.5 mg	53	739	50 (94.3%)	731 (98.9%)	3 (5.7%)	8 (1.1%)
Placebo	53	742	53 (100%)	742 (100%)	0 (0.0%)	0 (0.0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and drug concentration (remimazolam and CNS7054).

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of drug concentration and changes in ΔΔHR and ΔΔQTcF of studies CNS7056-005 and CNS7056-017 is shown in Figure 6.

- A single subject contributed to the predose, remimazolam concentration of >3000 ng/mL in the 20 mg treatment arm (Period 6). ΔQTcF was -5.7 ms at this time point.
- C_{max} of the metabolite increase proportionally to total remimazolam dose.
- Remimazolam treatment is associated with a maximum increase of above 10 bpm in heart rate. While the time course of HR change mirrors the shape of the PK profiles for remimazolam and CNS7054, the heart rate effect does not appear to be dose proportional.
- HR was relatively constant in the first hour in study CNS7056-017. Based on descriptive statistics, the maximum mean effect at the studied dose level in study CNS7056-017 is numerically higher than that in the TQT study (Figure 6) and is above 10 ms.
- The time course of ΔΔQTcF follows the trend in remimazolam PK profile and no apparent delayed effect was discerned. The exposure-response relationship between QTcF and CNS7054 was not evaluated further because the time to maximum QTcF change is before the time to maximum exposure of CNS7054.

Despite of an observed HR rate effect, the reviewer used QTcF as the primary endpoint because the individual heart rate correction method is not supported by available data (section 4.1).

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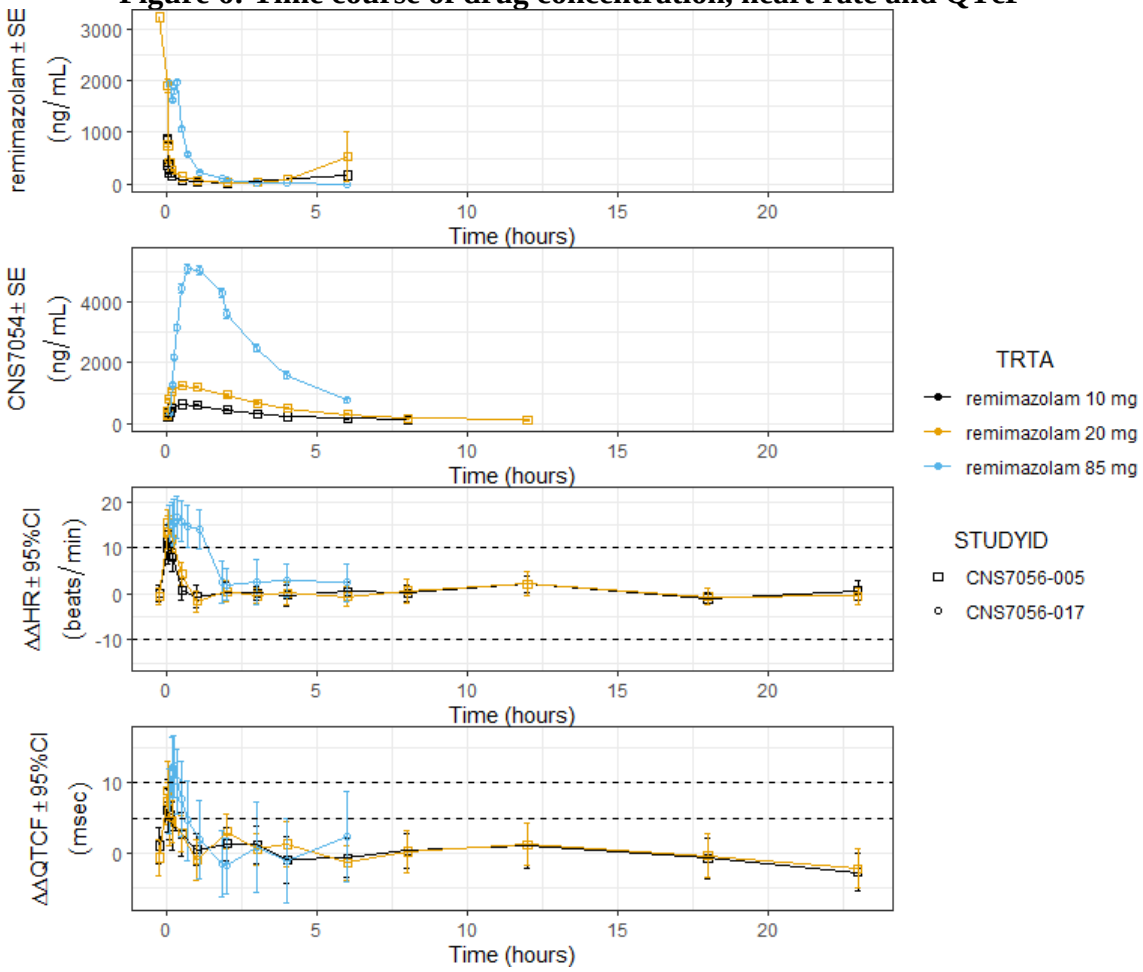
Figure 6: Time course of drug concentration, heart rate and QTcF



The relationship between drug concentration and ΔQTcF in study CNS7056-005 was evaluated to determine if a linear model would be appropriate. Figure 7 (Left) shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model. Finally, the linear model (ΔQTcF~1+CONC+adjusted_baseline+TIME, with random subject effect on slope and intercept) was applied to the data and the goodness-of-fit plot is shown in Figure 7 (Right). The analysis suggested a positive relationship between remimazolam exposure and ΔQTcF. The upper bound of 2-sided 90% CI of predicted ΔΔQTcF at C_{max} of the 10 mg and 20 mg doses are 6.5 ms and 10.9 ms. A similar conclusion was reached in an exploratory analysis where ΔΔQTcF values across the two studies were combined for linear mixed effect modeling (Figure 8).

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Figure 7: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot using data from study CNS7056-005. Purple arrow: remimazolam 10 mg injection; Yellow arrow: remimazolam 20 mg injection.

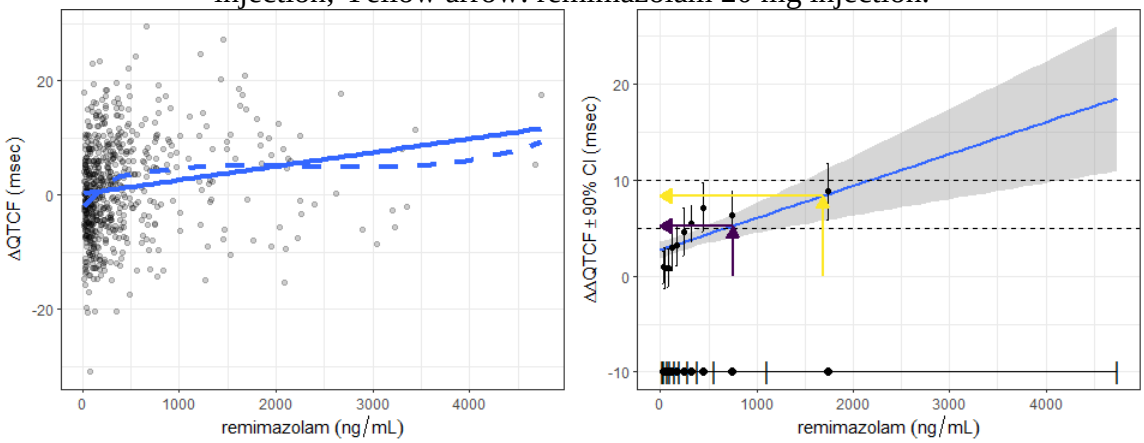
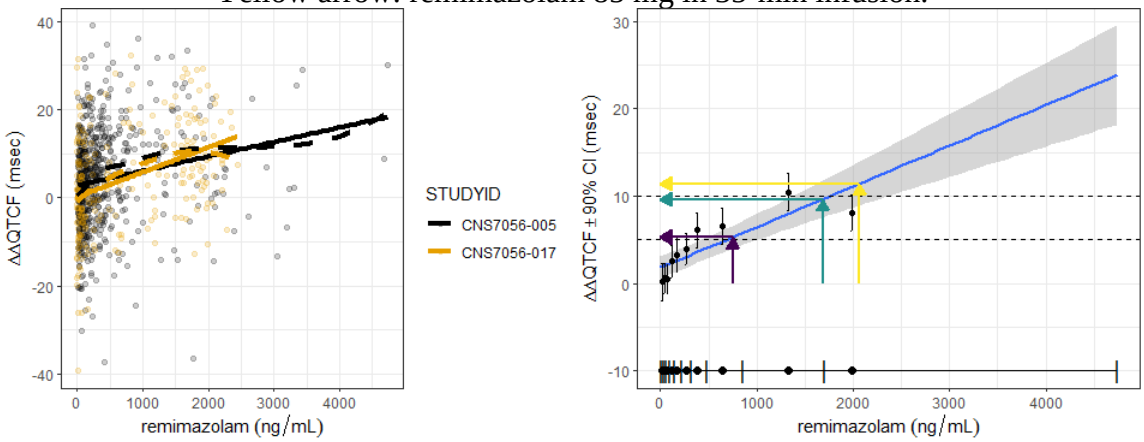


Figure 8: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot using pooled data from studies CNS7056-005 and CNS7056-017. Purple arrow: remimazolam 10 mg injection; Green arrow: remimazolam 20 mg injection; Yellow arrow: remimazolam 85 mg in 35-min infusion.



4.5.1 Assay sensitivity

Assay sensitivity was established using central tendency analysis. Please see section 4.3.1.1 for additional details.

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

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