

5.3 Discussion of Individual Studies

Study 001 was mainly to evaluate PK parameters of three doses of ZolpiMist (2.5 mg, 5 mg, and 10 mg) with 10 mg of Ambien in healthy adult male volunteers under fasting conditions. Each dosage was given separately with a period of 7 days (+/- 3 days) inbetween. By design, it determines dose linearity and/or dose proportionality over the dose range of ZolpiMist. Additionally, it determines the maximum acceptable ZolpiMist dose and evaluates its PK profile when administered over the tongue.

Blood samples were collected during all treatment visits from 10 minutes prior to dosing and immediately after dosing at 3, 6, 9, 12, 15, 20, 30, 45, 60, and 90 minutes; and then 2, 3, 4, 6, 8, 10, and 12 hours after dosing. In addition to PK parameters, PD was done thru self-assessment of drowsiness/sedation relative to pre-dosing using SSS, a scale of 1 (much more sleepy/drowsy) to 5 (much more alert) at 15, 30, and 60 minutes after dosing.

Study 002 evaluates PK parameters of two doses of ZolpiMist (5 mg and 10 mg) in comparison with the orally administered similar doses of Ambien in healthy male volunteers under fasting conditions as well as PK of 10 mg dose after standard high-fat breakfast. Each dosage was also given separately with a period of 7 days (+/- 3 days) inbetween. The study was also planned to provide assessment of PD properties of ZolpiMist as measured by the drowsiness/alertness levels associated with study drug administration.

The sponsor summarized proportions of subjects with a detectable drug concentration by 5, 10, and 15 minutes post-dosing, and proportion of subjects with a plasma level at least 20 ng/mL considered to be associated with sedation by 5, 10, 15, 20 and 30 minutes post-dosing of each treatment group. They are analyzed with pair-wise comparisons using the Wilcoxon Signed Rank test: 10 mg Ambien tablet (fasting) vs the two doses of zolpidem LS as well as 5 mg Ambien tablet; 10 mg zolpidem LS under fasting condition was also compared to the same under fed condition. For PD assessment, treatment comparisons were performed for the changes in SSS and DSST scores from baseline (measurement taken within 10 minutes prior to dosing) to the post-dosing (at 7, 13, 23, 28 minutes and 8 hours after) periods. For specific post dosing evaluation of safety, the assessments were from 20 to 39 minutes, 45 to 60 minutes, and then 2, 6, and up to 12 hours post-dosing.

Study 003 evaluates PK parameters of two doses (5- and 10-mg) of ZolpiMist in comparison with the similar doses of Ambien tablets in healthy male and female volunteers under fasting conditions, including potential gender-effect of ZolpiMist on PK parameters. It also collects safety and tolerability information of these subjects and provides PD assessment of ZolpiMist from the drowsiness/alertness levels associated with study drug using self-administered Visual Analog Scale (VAS) for each of 12 descriptors of sedation and DSST.

Blood samples were collected immediately prior to dosing, following dosing at 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and then 2, 3, 4, 6, 8, 10 and 12 hours post-dosing. The sponsor reports that data from 43 subjects, including 20 male (47%) and 23 female (53%) were evaluable for PK and pharmacodynamic analyses and data from 48 subjects were evaluable for safety.

Study 004 is the only study that evaluates PK parameters in healthy elderly male and female volunteers under fasting conditions comparing 5-mg ZolpiMist with 5-mg Ambien and thus also evaluates any potential gender-effect of ZolpiMist in the geriatric population; As other studies, safety and tolerability information was collected in this population and assessment of PD properties of ZolpiMist was measured with the drowsiness/alertness levels associated with study drug administration.

Blood sample collection was the same as that in Study 003 (see above).

Of note, test for next-day residual effect, such as next day driving or motor coordination is not reported along with any of these four studies.

6 Review of Efficacy

Efficacy has been demonstrated in clinical trials of zolpidem tartrate tablets. For this 505 b(2) application, the sponsor has no Phase 3 efficacy trial to report.

The sponsor reports that zolpidem plasma levels believed to be associated with sedation (≥ 20 ng/mL) achieved more rapidly with ZolpiMist than Ambien, but the effect is transient and clinically insignificant with no differences noted at 23 min postdose. Additionally, three studies (002, 003, and 004) provide pharmacodynamic data using DSST that were observed to be significantly decreased when comparing ZolpiMist with zolpidem tartrate at 13 min postdose. The sponsor reports that the lack of effect noted at 23 min postdose in the two definitive ZolpiMist pharmacokinetic studies. (Please see Dr. Jagan Parepally's biopharmacology review on PD.)

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The above mentioned four PK studies are reviewed for safety. There is no placebo-controlled trials for this submission.

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Table 4. Demographic Profile of Subjects Enrolled in NovaDel-Sponsored Controlled Trials

Demographics	Test Product—ZolpiMist n = 96	Active Control—Ambien n = 96
Age (years):		
Mean (SD)	39.6 (19.49)	39.6 (19.49)
Range	19–84	19–84
Groups:		
<18 years	0 (0%)	0 (0%)
18–40 years	67 (69.79%)	67 (69.79%)
41–64 years	5 (5.21%)	5 (5.21%)
65–75 years	18 (18.75%)	18 (18.75%)
>75 years	6 (6.25%)	6 (6.25%)
Sex:		
Female	45 (46.88%)	45 (46.88%)
Male	51 (53.13%)	51 (53.13%)
Race:		
Asian	2 (2.08%)	2 (2.08%)
Black	45 (46.88%)	45 (46.88%)
Caucasian	45 (46.88%)	45 (46.88%)
Hispanic	4 (4.16%)	4 (4.16%)
Other	0 (0%)	0 (0%)
Other Factors:		
Height (m):		
Mean (SD)	1.69 (0.105)	1.69 (0.105)
Range	1.47–1.96	1.47–1.96
Weight (kg):		
Mean (SD)	74.41 (11.97)	74.41 (11.97)
Range	49.90–100.90	49.90–100.90
BMI (kg/m ²):		
Mean (SD)	25.94 (2.790)	25.94 (2.790)
Range	20.00–30.00	20.00–30.00

7.1.2 Adequacy of Data

The data is adequate for this 505 b (2) application.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The major safety items, deaths, SAEs, and discontinuation cases are collected across the four studies. Since there is no placebo-controlled trials, the common AEs are listed for reference comparing to the active control formulation, zolpidem tartrate tablet doses.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations Explorations for Dose Response

The sponsor reports a total of 96 unique subjects were enrolled in the four studies. Among these, 24 were geriatric patients who were exposed to 5mg ZolpiMist only.

The numbers of Subjects who were exposed to each dose group in these four studies are summarized in the table below:

Table 5. The Numbers of Subject Exposed to Dose Groups of ZolpiMist in Four PK-PD Studies

Doses & Formulations	Study 001	Study 002	Study 003	Study 004	Total
10 mg Ambien	10	14	46	-	70
5 mg Ambien	-	9	45	24	78
Total exposure to Ambien					148
10mg ZolpiMist	10	10*	47	-	67
5 mg ZolpiMist	10	10	45	24	89
2.5mg ZolpiMist	10	-	-	-	10
Total exposure to ZolpiMist					166

*Of note, in Study 002, 10 subjects received ZolpiMist 10mg twice, one in fed state and one in fasting state.

These studies are all PK studies and though overall, studies lasted up to 35 - 50 days, each single treatment was separated from 7 +/- 3 days.

7.2.2 Special Animal and/or In Vitro Testing

Effect on oral mucosa was tested in animals in studies up to 28 days. Please see Dr. Melissa Banks' Pharmacology-toxicology review for details.

7.2.3 Routine Clinical Testing

Routine clinical testing included PK evaluation and PD testing using self-assessment measures. Clinical safety evaluations included reporting of adverse events, blood chemistry, physical examination (including oral soft tissue examination in studies 002, 003, and 004), vital signs, radial pulse, and systolic and diastolic blood pressure. Information on adverse events was collected during the 12-hour observation period. Blood pressure and pulse rate were determined immediately before dosing and at 20-30, 45-60 min and 2, 6, and 12 h post-dose at each visit. Physical examinations were performed and samples for clinical chemistry determinations were collected only at screening and the final visit.

7.2.4 Metabolic, Clearance, and Interaction Workup

The sponsor reports no significant changes in clinical laboratory test results, including renal or liver function tests.

7.2.5 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As a formulation of zolpidem, the evaluation for next-day residual effect evaluation, such as driving test or other motor coordination test, is not reported in the submission. The sponsor states that effects of ZolpiMist on the ability to drive are not expected to be different from those of Ambien.

7.3 Major Safety Results

7.3.1 Deaths

There was no death in all four PK studies submitted.

7.3.2 Nonfatal Serious Adverse Events

There was no SAE in Study 001, Study 003 or Study 004; however, there was one SAE in Study 002 (torsion testis) which is considered unrelated to the drug and I agree.

7.3.3 Dropouts and/or Discontinuations

No subject discontinued from Study 001; among the four subjects who dropout from Study 002, only one was due to adverse event (vomiting) in Ambien tablet 10 mg group while two of them withdrew the consent and one was discontinued due to protocol deviation. In Study 003, two of the three subjects discontinued from the study due to vomiting, one in each formulation group of 10mg dose; the other was after a severe animal bite. No subject discontinued from Study 004 due to AEs.

7.3.4 Other Significant Adverse Events

There was no other significant adverse event.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Oral Mucosa

There was no specific examination of oral mucosa in protocols of Studies 001. Oral soft tissue examination was performed in Studies 002, 003, and 004 at screening and at the final visit and at all treatment visits when ZolpiMist was administered. Examinations were performed within 30

min pre-dose and 120 min post-dose with ZolpiMist during these studies and in studies 003 and 004, it was also conducted 12 h post-dose.

The sponsor states that no one reported oral-related symptoms in Study 003 and only one subject reported mild pharyngolaryngeal pain after zolpidem LS administration in Study 004, but the sponsor reports that there were no objective signs of oral irritation on examination.

6.3.5.2 Onset of Action (based on T_{max})

The sponsor reports that ZolpiMist initially reaches higher zolpidem blood levels more rapidly, at about 10 and 20 min post-dose than Ambien but transient and there is no significant difference in zolpidem blood levels noted at 30 min post-dose, and clinically insignificant.

6.3.5.3 Maximum Effect (based on C_{max})

The C_{max} is bioequivalent to zolpidem tartrate. (See biopharmacology review.)

6.3.5.4. Duration of Action (based on residual effect and slope of decrease)

There is no residual effect study data reported. The drug is judged as with bioequivalent values in the two definitive ZolpiMist pharmacokinetic studies. (See biopharmacology review.)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

There is no placebo controlled trials in the submission but active control, open-label trials. Below is a table submitted by the sponsor comparing the AE incidences in different dose groups among all these trials. (See Table 6 on next page.)

AE listing in Ambien labeling was coded by modified WHO Terms, while AE listing in ZolpiMist trials were coded by MedDRA Terms, Though used two different coding systems, no new treatment-related adverse events were reported with ZolpiMist.

Comparing with placebo, in studies with zolpidem tartrate (up to 10 mg), drowsiness, dizziness, and diarrhea are recognized as the most common AEs with short-term (<10 nights) treatment; Dizziness and drugged feelings are the most common ones seen with long-term (28-35 nights) treatment.

Table 6. Incidence of Adverse Events by Treatment Exposure in Pooled Active Controlled Trials

Body System Preferred Term	Test Drug—ZolpiMist					Active Control—Ambien		
	2.5 mg (fasted) n = 16 ^a	5 mg (fasted) n = 39 ^a	10 mg (fasted) n = 67 ^a	10 mg (fed) n = 18 ^a	All doses of ZolpiMist n = 176 ^b	5 mg (fasted) n = 75 ^c	10 mg (fasted) n = 78 ^c	All doses of Ambien (fasted) n = 148 ^d
Subjects with any Adverse Events	0	19 (21%)	18 (27%)	3 (30%)	40 (22.7%)	9 (12%)	21 (30.0%)	30 (20.3%)
Eye Disorders	0	2 (2%)	7 (10%)	0	9 (5.1%)	2 (3%)	9 (13%)	11 (7.4%)
Diplopia	0	1 (1%)	6 (9%)	0	7 (4.0%)	2 (3%)	5 (7%)	7 (4.7%)
Vision Blurred	0	1 (1%)	2 (3%)	0	3 (1.7%)	0	2 (3%)	2 (1.4%)
Visual Disturbance	0	0	0	0	0	0	2 (3%)	2 (1.4%)
Gastrointestinal Disorders	0	0	2 (3%)	1 (10%)	3 (1.7%)	0	5 (7%)	5 (3.4%)
Dry Mouth	0	0	0	1 (10%)	1 (0.6%)	0	0	0
Nausea	0	0	1 (1%)	0	1 (0.6%)	0	4 (6%)	4 (2.7%)
Vomiting	0	0	1 (1%)	0	1 (0.6%)	0	2 (3%)	2 (1.4%)
General Disorders and Administration Site Conditions	0	1 (1%)	2 (3%)	1 (10%)	4 (2.3%)	0	2 (3%)	2 (1.4%)
Fatigue	0	0	0	0	0		1 (1%)	1 (0.7%)
Feeling Abnormal	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Feeling Drunk	0	0	1 (1%)	0	1 (0.6%)	0	1 (1%)	1 (0.7%)
Feeling Hot	0	0	1 (1%)	0	1 (0.6%)		0	0
Gait Disturbance	0	0	0	0	0	0	1 (1%)	1 (0.7%)
Thirst	0	0	0	1 (10%)	1 (0.6%)	0	0	0
Infections and Infestations	0	2 (2%)	0	0	2 (1.2%)	0	0	0
Herpes Simplex	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Nasopharyngitis	0	1 (1%)	0	0	1 (0.6%)		0	0
Injury, Poisoning and Procedural Complications	0	0	1 (1%)	0	1 (0.6%)	0	0	0
Animal Bite	0	0	1 (1%)	0	1 (0.6%)	0	0	0
Investigations	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Heart Rate Increased	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Musculoskeletal and Connective Tissue Disorders	0	2 (2%)	0	0	2 (1.1%)	1 (1%)	1 (1%)	2 (1.4%)
Musculoskeletal Pain	0	0	0	0	0	0	1 (1%)	1 (0.7%)
Pain in Extremity	0	2 (2%)	0	0	2 (1.1%)	1 (1%)	0	1 (0.7%)
Nervous System Disorders	0	4 (4%)	7 (10%)	1 (10%)	12 (6.8%)	3 (4%)	11 (16%)	14 (9.5%)
Dizziness	0	1 (1%)	7 (10%)	1 (10%)	9 (5.1%)	1 (1%)	4 (6%)	5 (3.4%)
Headache	0	3 (3%)	0	0	3 (1.7%)	2 (3%)	4 (6%)	6 (4.1%)
Somnolence	0	0	0	0	0	0	6 (9%)	6 (4.1%)
Psychiatric Disorders	0	5 (6%)	4 (6%)	2 (20%)	11 (6.3%)	4 (5%)	3 (4%)	7 (4.7%)
Euphoric Mood	0	5 (6%)	4 (6%)	2 (20%)	11 (6.3%)	4 (5%)	3 (4%)	7 (4.7%)

Table 6. Incidence of Adverse Events by Treatment Exposure in Pooled Active Controlled Trials (Cont'd)

Body System Preferred Term	Test Drug—ZolpiMist					Active Control—Ambien		
	2.5 mg (fasted) n = 10 ^a	5 mg (fasted) n = 39 ^a	10 mg (fasted) n = 67 ^a	10 mg (fed) n = 10 ^a	All doses of ZolpiMist n = 176 ^b	5 mg (fasted) n = 78 ^a	10 mg (fasted) n = 70 ^a	All doses of Ambien (fasted) n = 148 ^b
Reproductive Systems and Breast Disorders	0	0	0	0	0	0	1 (1%)	1 (0.7%)
Testicular Torsion	0	0	0	0	0	0	1 (1%)	1 (0.7%)
Respiratory, Thoracic and Mediastinal Disorders	0	2 (2%)	1 (1%)	0	3 (1.7%)	0	1 (1%)	1 (0.7%)
Hiccups	0	0	1 (1%)	0	1 (0.6%)	0	1 (1%)	1 (0.7%)
Pharyngolaryngeal Pain	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Throat Tightness	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Skin and Subcutaneous Tissue Disorders	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Echymosis	0	1 (1%)	0	0	1 (0.6%)	0	0	0
Vascular Disorders	0	1 (1%)	0	0	1 (0.6%)	0	1 (1%)	1 (0.7%)
Hot Flash	0	1 (1%)	0	0	1 (0.6%)	0	1 (1%)	1 (0.7%)
Hypotension	0	1 (1%)	0	0	1 (0.6%)	0	0	0

^a = Number of subjects receiving treatment.

^b = Total number of single doses administered across four NovaDel studies collected after administration of ZolpiMist doses under both fasted (n = 166) and fed (n = 10) conditions.

Note: Data on adverse event incidence are based on the number of subjects exposed to each treatment in these crossover studies.

Data sources: Table 14.3.1, Final Clinical Report Study NVD-ZOLP-PFI-002; Table 14.3.1, Final Clinical Report Study NVD-ZOLP-PFI-003; Table 12.2, Final Clinical Report Study NVD-ZOLP-PFI-004.

7.4.2 Special Safety Studies

No special safety study was conducted.

7.4.3 Immunogenicity

There is no immunogenicity concern for this drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No subjects reporting adverse events at 2.5 mg. The highest incidence of adverse events occurred at the 5- and 10-mg doses of either ZolpiMist or Ambien.

7.5.2 Time Dependency for Adverse Events

These PK studies do not show time-dependent for AEs.

7.5.3 Drug-Demographic Interactions

Please see biopharmacology review by Agency Biopharmaceutical Science Reviewer, Jagan Parepally, Ph.D.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

There is no new study data. (Please see biopharmacology review by Agency Biopharmaceutical Science Reviewer, Jagan Parepally, Ph.D.)

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

There is no human carcinogenicity data.

7.6.2 Human Reproduction and Pregnancy Data

There is no new human reproduction or pregnancy data.

7.6.3 Pediatrics and Effect on Growth

The study was waived in pediatric population up to 16 years of age.

According to the sponsor, Zolpidem excretion in milk is not reported in animals but has been demonstrated in lactating women (<0.5 ng/mL) and yet did not exceed 0.4% of the administered dose (20 mg).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.4.1 Overdose

Reports of intentional overdose with zolpidem involve a wide range of doses, between 10 and 1400 mg. About 50% reports indicated concomitant ingestion of other substances (psychotropic

drugs and alcohol). As expected, drowsiness is the main symptom of overdose, but coma (4 cases), and respiratory failure (1 case) were also reported.

Treatment essentially involves gastric lavage and supportive measures. Most (91%) were able to achieve symptom remission spontaneously. A total of 6% of cases were fatal but involving multiple drugs.

7.6.4.2 Drug Abuse Potential, Withdrawal and Rebound

ZolpiMist is considered as bioequivalent to Zolpidem tartrate. There is no increased abuse potential compared to the tablet form from pharmacological point of view.

Below summarizes the issues that maybe related to risk of potential abuse in the Division review meetings and the response from the sponsor during the tele-conference on Aug. 6, 2008 (personally communication with PM Cathy Mi

- 1) Child-resist mechanism on the device – Unfortunately, based on the current regulation, we don't have authority to regulate; However, the sponsor states that they are aware of this and will not launch on the product till they put on a child-resist cap on the top.
- 2) The lack of _____ on this metered pump making it easier for people to misuse it – Though it is agreed in the meetings that the solution does have cherry flavor that the patient should be able to taste the dose and the spray is strong enough for patients to feel inside the mouth, the sponsor states that they will have _____
- 3) The ease of using this solution spray formulation with potential to be used as an abusive substance and added to drinks since the solution has little color – Though in the risk management plan, the company states that there will be a statement on the carton stating, "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it is prescribed," the risk exists. The sponsor agrees and will submit more information on this issue.

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There is no new information regarding withdrawal or rebound.

For more detailed information on Abuse Potential, please see CSS review.

7.7 Additional Submissions

Additional submissions since the original include:

- 1) Amendment 0001 of Jan. 9, 2008 is a response to Office of Compliance regarding legal name change of the manufacturer, from Ferring AB to Rechon Life Science AB. The submission reports that "an agreement was reached for the purchase Ferring AB, Malmo manufacturing operations by the Swedish subsidiary of Shanghai Dongbao Biopharmaceutical Co. Ltd. (DBC), China" and became effective on Jan. 1, 2007.

- 2) Amendment 0002 of Jan. 9, 2008 is the submission of Zolpimist sample package per our request.
- 3) Amendment 0003 of Jan. 18, 2008 is about clarification of parameters of the dataset in the original submission
- 4) Amendment 0004 of Feb. 15, 2008 includes the resubmission of literature review and CMC information on batch stability, environmental assessment, and packaging based on our 74-day letter.
- 5) 120-Day Safety Update – No new clinical trial data but nine relevant articles (see Literature Review in Appendices)
- 6) During the teleconference this morning, the sponsor stated that they will soon send in more materials with regard to prevention of abuse potential and explain the issue of not swallowing the spray. —

8 Postmarketing Experience

There is no postmarketing experience for ZolpiMist.

9 Appendices

9.1 Literature Review/References

The sponsor didn't submit the summary of literature reference appropriately in the original submission and again was not proper when resubmitted in their response on Feb. 15, 2008, to the Agency 74-day letter. Request for correct submission sent on Feb. 21, 2008.

Newly submitted literature review reports that literature search to update the NDA was performed by _____

_____ All subsequent literature searches were performed by _____
_____ The following search strategy was used in support of the ZolpiMist NDA 022196 submitted on November 20, 2007, and is presented below as pre- and post-NDA activities:

The database used is PubMed database. The covering time period was from January 1, 2006, through September 30, 2007. The original search only used "Zolpidem" as the key word but the subsequent search expanded with the following key words together with zolpidem after the teleconference regarding literature search submission in late Jan, 2008, with time frame also extended to end of February 2008: Drug interactions, safety, adverse events, side effects, serious adverse events, sleep driving, anterograde amnesia, nocturnal eating, pseudohallucinations, somnambulism, fatalities, deaths, suicidality, suicidal ideation.

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