

SUMMARY OF CLINICAL TRIAL RESULTS

A. CLINICAL TRIAL INFORMATION	
Clinical trial identification:	
Title: Efficacy and tolerability of tasipimidine after 3 repeated bed-time doses with 4-week extension part in patients with insomnia disorder	
Trial code: 3110012	
Trial identifiers:	
EU Trial Number: 2022-502483-21-00	
IND number: 174612	
Sponsor details:	
Sponsor: Orion Corporation	
Scientific/public contact point: clinicaltrials@orionpharma.com	
Paediatric regulatory details: This trial is not part of a Paediatric Investigation Plan.	
Result analysis stage: Final analysis (date of global end of the clinical trial 24 September 2025)	
General information about the clinical trial: This was the first trial with tasipimidine in patients with insomnia disorder. Insomnia disorder patients with short sleep duration were enrolled because hyperarousal involving hyperactivity of the sympathetic nervous system seemed to be prominent in this population and as targeting this group by an alpha-2 agonist is theoretically attractive. Specifically, alleviation of the hyperarousal by an alpha-2 agonist was expected to promote sleep and also tolerability was expected to be better in this population than for healthy participants. Main objective was to evaluate efficacy of tasipimidine in participants with insomnia disorder. This was a randomised, double-blind, placebo-controlled, dose-escalation, multisite, exploratory, adaptive, phase 2 trial in sleep laboratory setting with an extension part at home. In Part 1, 4 escalating dose levels of tasipimidine were administered to 4 sequential cohorts of participants in a sleep laboratory setting. Dose escalations were decided by the Data and Safety Monitoring Board (DSMB) after reviewing the safety data of previous dose level. Based on the results an interim analysis, 3 tasipimidine dose levels were decided by the DSMB for Part 2. In Part 2 the participants were randomised to 3 parallel groups receiving one of the selected dose levels of tasipimidine and matching placebo. The trial was conducted in accordance with the protocol, local requirements and the Declaration of Helsinki. Before entering the trial, the informed consent was read by and explained to all the participants. Participants signed the informed consent form and could withdraw from the trial at any time. Trial period: Date of first participant first visit: 28 July 2023 Date of last participant completed: 24 September 2025	
Population of participants:	
Country/region (EU)	Actual number of participants enrolled
Finland	19
Germany	136
Poland	17
Total number of participants in the EU	172
Countries outside the EU	US
Total number of participants in the rest of the world	18
Total number of participants worldwide	190
Age range	Actual number of participants enrolled
Adults (18-64 years)	188
Elderly (65-84 years)	2
Very elderly (≥85 years)	0

Sex	Actual number of participants enrolled					
Female	126					
Male	64					
B. Participant disposition						
Recruitment, disposition and analysis sets: 814 participants signed the informed consent form (ICF), 190 were enrolled and 189 treated, 18 discontinued (including 4 who withdrew consent) and 172 completed the trial. See Table 1 for number of participants in each analysis set by trial part and treatment group.						
Table 1. Disposition of participants (ITT population)						
	PBO (N = 48)	TAS A (N = 13)	TAS B (N = 43)	TAS C (N = 35)	TAS D (N = 51)	Total (N = 190)
	n (%)					
Part 1						
Randomised (ITT)	20 (41.7)	13 (100)	15 (34.9)	9 (25.7)	18 (35.3)	75
Safety analysis set (SAF)	20 (41.7)	13 (100)	14 (32.6)	9 (25.7)	18 (35.3)	74
Full analysis set (FAS)	20 (41.7)	13 (100)	14 (32.6)	9 (25.7)	18 (35.3)	74
Per-protocol set (PP)	19 (39.6)	13 (100)	13 (30.2)	9 (25.7)	18 (35.3)	72
Discontinued trial	2 (4.2)	1 (7.7)	2 (4.7)	-	-	5
Completed	18 (37.5)	12 (92.3)	13 (30.2)	9 (25.7)	18 (35.3)	70
Part 2						
Randomised (ITT)	28 (58.3)	-	28 (65.1)	26 (74.3)	33 (64.7)	115
Safety analysis set (SAF)	28 (58.3)	-	28 (65.1)	26 (74.3)	33 (64.7)	115
Full analysis set (FAS)	28 (58.3)	-	28 (65.1)	26 (74.3)	33 (64.7)	115
Per-protocol set (PP)	28 (58.3)	-	28 (65.1)	25 (71.4)	32 (62.7)	112
Discontinued trial	1 (2.1)	-	1 (2.3)	3 (8.6)	8 (15.7)	13
Completed	27 (56.3)	-	27 (62.8)	23 (65.7)	25 (49.0)	102
PBO = placebo, TAS A = tasipimidine A group, TAS B = tasipimidine B group, TAS C = tasipimidine C group, TAS D = Tasipimidine D group, ITT = intend-to-treat						
Inclusion and exclusion criteria:						
Inclusion criteria:						
1. Signed IC for participation in the trial.						
2. Male or female participants with age between 18 and 65 years (inclusive) at screening visit.						
3. Insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition Text Revision (DSM-5-TR®).						
4. Self-reported history of the following on at least 3 nights per week and for at least 3 months prior to the screening: ≥ 30 minutes to fall asleep, self-reported total sleep time (sTST) ≤ 6 hours at screening visit.						
5. Insomnia Severity Index (ISI®) score ≥ 15 in Part 1 and ≥ 11 in Part 2.						
6. Usual bedtime between 21:00 and 02:00.						
7. Regular time in bed between 6 and 9 hours.						
8. Meeting the following sleep parameter criteria in polysomnography (PSG) on the 2 screening PSG nights: mean latency to persistent sleep (LPS) ≥ 25 minutes (with none of the 2 nights < 15 minutes) and mean total sleep time (TST) ≤ 6 h in Part 1 and ≤ 6.5 h in Part 2.						
9. Female participants with fertile male partner, and male participants with female partners of child-bearing potential, had to adhere to a highly effective form of contraception, if sexually active and not permanently sterilised. Additionally, women who were postmenopausal (1 year since last menstrual cycle) were considered not to be reproductive and could be included.						
Exclusion criteria:						
1. A predictable poor compliance or inability to understand and comply with protocol requirements, instructions and protocol-stated restrictions, or communicate well with the investigator.						
2. Body mass index below 18.5 or above 40.0 kg/m ² .						
3. Self-reported usual daytime napping ≥ 1 hour per day, and ≥ 3 days per week.						
4. Shift work within 2 weeks prior to the screening visit, or planned shift work during the trial.						

5. Travel across ≥ 3 time zones within 2 weeks prior to the screening visit, or planned travel across ≥ 3 time zones during the trial.
6. Use of medications with known relevant alpha-2 AR affinity (e.g. mirtazapine, mianserine, dexmedetomidine, clonidine, guanfacine or tizanidine) or known strong or moderate CYP2D6 inhibitors (e.g. in Part 1 paroxetine, fluoxetine, bupropion, in both parts quinidine) within 14 days or 5 times the half-life, whichever is longer, prior to the 1st screening PSG.
7. Use of benzodiazepines, z-drugs (zolpidem, zopiclone, eszopiclone, zaleplon), melatonin, sedative H1 antagonists, sedative antidepressants (e.g. doxepine and trazodone), orexin receptor antagonists (e.g. daridorexant) or antipsychotics within 7 days or 5 times the half-life, whichever is longer, prior to 1st screening PSGs.
8. Use of amphetamine derivatives like methylphenidate, dexamphetamine and lisamphetamine within 14 days, or 5 times the half-life, whichever is longer, prior to the 1st screening PSG.
9. Use of other central nervous system active drugs, including over-the-counter or herbal medicines, for 7 days or 5 times the half-life, whichever is longer, prior to the 1st screening PSG. In Part 2, the use of one of the following antidepressants was allowed: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, duloxetine, milnacipran, venlafaxine, vortioxetine, providing that the dose had been stable at least 4 weeks prior to the 1st screening PSG and planned to be stable throughout the trial.
10. Start of other new chronic medication within 14 days or 5 times the half-life, whichever is longer, prior to the 1st screening PSG and in Part 2 also a planned change to an ongoing chronic medication during the trial.
11. Cognitive behavioural therapy (CBT) for any indication was allowed only if the CBT started at least 1 month prior to the 1st screening PSG and the participant agreed to continue the CBT throughout the trial.
12. Any lifetime history of a diagnosed sleep-related breathing disorder, including chronic obstructive pulmonary disease and sleep apnoea.
13. Acute or unstable psychiatric conditions as judged by the investigator (including but not restricted to current bipolar disorder, schizophrenia or obsessive compulsive disorder) that were diagnosed by the Mini International Neuropsychiatric Interview[®] (MINI[®]) or that required pharmacological treatment for these disorders. N.B.: participants with a history of major depressive disorder or anxiety disorder that were currently stable, and without requiring pharmacological treatment were eligible. In Part 2, antidepressants specified in exclusion criterion 9 were allowed.
14. Part 1: positive answer to item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) or current risk of suicide based on the investigator's judgement at screening visit. Part 2: positive answer to item 4 or 5 in the past 6 months or any suicidal behaviour in the past 10 years or current risk of suicide based on the investigator's judgement at screening visit.
15. Diagnosis of alcohol or substance use disorder within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days.
16. Myocardial infarction or other clinically significant ischemic cardiac disease, heart failure, sick-sinus syndrome or arrhythmia tendency within the past 2 years.
17. History of clinically significant orthostatic hypotension, syncope or syncopal attacks within the past 2 years.
18. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, neurological (e.g. epilepsy or dementia) or psychiatric disorder or any other major concurrent illness that in the opinion of the investigator could interfere with the interpretation of the trial results or constitute a health risk for the participant if he/she took part in the trial.
19. Heavy tobacco use (at least one pack of cigarettes a day or corresponding heavy use of other nicotine containing products or inability to refrain from smoking during the night).
20. Caffeine consumption ≥ 600 mg per day or regular caffeine consumption after 4 p.m.
21. Supine heart rate < 50 bpm or > 100 bpm after a 5-minute rest at screening visit.
22. Systolic blood pressure (BP) < 100 or > 160 mmHg or diastolic BP < 50 or > 100 mmHg after a 5-minute rest at screening visit.
23. Orthostatic hypotension (decrease of ≥ 20 mmHg for systolic BP or decrease of ≥ 10 mmHg for diastolic BP) or dizziness in orthostatic test at screening visit.
24. Abnormal 12-lead electrocardiogram (ECG) finding of clinical relevance at the screening visit, (after 5 min rest in supine position, confirmed by a repeat measurement) for example:
 - QTc (calculated through the Fridericia's formula) repeatedly > 450 ms in males or > 470 ms in females at screening visit. Pacemaker rhythm as such did not need to lead to exclusion. (If QTc interval measured by

the ECG machine algorithm was > 450 ms in males or > 470 ms in females, 2 additional recordings were done and QTcF values confirmed) • 2° or 3° AV block.						
25. Part 1: AST and/or ALT $> 2 \times$ ULN and/or direct bilirubin $> 1.5 \times$ ULN. Part 2: AST and/or ALT $> 2 \times$ ULN and/or direct bilirubin $> 1.5 \times$ ULN and/or Child-Pugh score > 6.						
26. Positive urine drug screen or presence of alcohol in exhaled breath at screening visit, screening PSG nights or on Day 1.						
27. Any other abnormal value in laboratory tests, vital signs or 12-lead ECG which could in the opinion of the investigator interfere with the interpretation of the trial results or cause a health risk for the participant if he/she took part in the trial.						
28. Pre-planned elective surgery for the trial period.						
29. Known hypersensitivity to the active substance or to any of the excipients of the trial treatment.						
30. Pregnant or lactating females.						
31. Blood donation or loss of significant amount of blood within 60 days prior to the screening.						
32. Participation in a drug trial within 60 days prior to the screening or earlier participation in clinical trial with tasipimidine.						
33. Periodic limb movement disorder with arousal index (PLMAI) $\geq 15/h$ (assessed on the 1st screening PSG night), restless legs syndrome, circadian rhythm disorder, REM behaviour disorder, or narcolepsy.						
34. Apnoea/hypopnea index (AHI) $\geq 15/h$ according to American Academy of Sleep Medicine criteria or event associated with blood oxygen saturation level by pulse oximetry (SpO₂) $< 80\%$, as assessed on the 1st screening PSG night.						
35. Any other condition that in the opinion of the investigator could interfere with the interpretation of the trial results or constitute a health risk for the participant if he/she took part in the trial.						
36. Part 2: Body surface area corrected eGFR < 60 ml/min/1.73 m².						
Randomisation and blinding: In Part 1, participants were allocated at random to tasipimidine and placebo groups in a ratio of 3:1 for each escalating dosing cohort. In Part 2, the participants were randomly assigned to the 3 parallel tasipimidine dosing groups and corresponding placebo within the dose group in a ratio 3:1. Investigators, participants and trial personnel remained blinded to trial treatment throughout the course of the trial. For practical reasons, investigators and other trial personnel knew the dose level of tasipimidine. Service provider personnel responsible for bioanalytics were unblinded and had access to the randomisation list.						
Investigational medicinal products, dose and mode of administration: • Test product: Tasipimidine 0.3 mg/ml oral solution 15 ml in Part 1 and Tasipimidine 0.05 mg/ml oral solution 15 ml in Part 2. The selected dose levels were targeted to produce a tasipimidine plasma C_{max} of 0.075 (treatment group A), 0.150 (treatment group B), 0.300 ng/ml (treatment group C) and 0.450 ng/ml (treatment group D). The dose for each participant was adjusted with a population pharmacokinetic (PK) model -based equation. Actual doses varied from 20 to 380 µg. • Reference product: Placebo Tasipimidine oral solution 15 ml (placebo group).						
Pre-assignment period: See Disposition and analysis sets in Section B.						
Post-assignment period(s): See Disposition and analysis sets in Section B.						
C. Baseline characteristics						
See Table 2 for baseline demographic characteristics.						
Table 2. Demographic characteristics (FAS population)						
	PBO (N = 48)	TAS A (N = 13)	TAS B (N = 42)	TAS C (N = 35)	TAS D (N = 51)	Total (N = 189)
Sex						
Female	33 (68.8)	11 (84.6)	31 (73.8)	20 (57.1)	30 (58.8)	125 (66.1)
Male	15 (31.3)	2 (15.4)	11 (26.2)	15 (42.9)	21 (41.2)	64 (33.9)
Age						
Mean (SD)	48.3 (10.1)	49.1 (11.7)	50.3 (11.5)	48.1 (10.8)	48.9 (12.5)	48.9 (11.2)
Range	24-63	20-65	23-65	27-64	22-64	20-65

D. Variables.

Variable definitions:

Primary variables: Wake after sleep onset (WASO) and LPS assessed with PSG for Day 1 and Day 2 data combined from Part 1 and Part 2.

Secondary variables: WASO and LPS assessed with PSG for Day 1 and Day 2 data separately from Part 1 and Part 2; in Part 2 WASO and LPS assessed with PSG for Day 27 and Day 28.

Adverse events (AEs), heart rate, diastolic and systolic BP, mean arterial pressure, orthostatic changes in BP, morning sleepiness, safety laboratory tests, ECG conduction times

PK variables

Other/Additional/Exploratory variables:

TST, sleep efficiency (SE), sleep architecture (the duration and proportion of sleep spent in each sleep stage), and number of awakenings assessed with PSG; sTST, subjective WASO (sWASO) and subjective latency to sleep onset (sLSO) assessed with morning questionnaire; in Part 2, also Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score, other IDSIQ domain scores and total IDSIQ score, variables assessed by the home EEG device and C-SSRS.

Efficacy variables: Mean WASO decreased from baseline in all treatment groups. There were no clinically significant differences in mean changes from baseline in WASO on Day 1-2 between placebo and any active treatment groups. In statistical analysis, there was no statistically significant difference in WASO between any active treatment groups and pooled placebo on Day 1-2 (primary efficacy analysis) or on Day 27-28 (secondary efficacy analysis).

Mean LPS decreased from baseline in all treatment groups. The mean changes from baseline in LPS on Day 1-2 tended to be larger in tasipimidine groups B, C and D compared to placebo approaching threshold of clinical significance. However, these differences did not reach statistical significance (primary efficacy analysis). Furthermore, these effects were clearly smaller and not clinically or statistically significant on Day 27-28 (secondary efficacy analysis) between placebo and any of the active treatment groups.

Mean TST increased from baseline in all treatment groups. There were no clinically significant differences in mean changes from baseline in TST between any of the active treatment groups and placebo. Statistically, there were no significant differences in mean changes from baseline in TST between any of the treatment groups and placebo on Day 1-2 or on Day 27-28.

No clear evidence for efficacy was seen in other assessed efficacy endpoints either.

The sum of N2 and N3 sleep stages was increased and REM sleep stage was decreased in the two highest tasipimidine dose groups compared to placebo on Day 1-2 time point providing indication of detectable pharmacodynamic effects.

The results of the trial do not support efficacy of tasipimidine in insomnia disorder at studied dose levels.

Pharmacokinetic variables: The observed geometric mean C_{max} of tasipimidine remained below the target C_{max} level in all treatment groups. The mean $C_{max}/\text{target } C_{max}$ ratio in each treatment group was approximately 80%, except in treatment group C, where it was approximately 70%. The exposures of tasipimidine and ORM-18662 increased from treatment groups A to D approximately in proportion to the target C_{max} .

The t_{max} of tasipimidine was 1-2 h across the treatment groups, and the elimination half-life was approximately 3 h. Individual $t_{1/2}$ values varied considerably, ranging from 1.62 h to 9.14 h. The $t_{1/2}$ of ORM-18662 was slightly shorter, and t_{max} was reached slightly earlier than those of the parent compound.

Within the C_{max} target cohorts A-D, the exposure and elimination of tasipimidine varied between participants with different CYP2D6 phenotypes. The largest AUC values and longest $t_{1/2}$ values were observed in poor CYP2D6 metabolizers, and the smallest AUC values and shortest $t_{1/2}$ values in ultrarapid metabolizers. The ORM-18662/tasipimidine AUC ratio was largest in ultrarapid metabolizers, whereas the metabolite/parent ratio was almost negligible in poor metabolizers, consistent with the major role of CYP2D6 in tasipimidine metabolism and elimination and in ORM-18662 formation.

The PK results support the major role of CYP2D6 in tasipimidine metabolism and elimination and in ORM-18662 formation.

E. Adverse events
Adverse events information and adverse event reporting groups: All AEs were elicited, documented and reported by the investigator to the sponsor from the time that a trial participant signed the IC form until the end-of-trial visit (5-10 days after the last trial treatment administration). Serious adverse events (SAEs) and other significant AEs were followed up also after the end-of-trial visit until resolved or until the event was considered a chronic or stable outcome, or both. AE could be notified to the investigator by the trial participant or observed by the investigator clinically or be an adverse change in laboratory assessment results. Orthostatic events were considered as AEs of special interest (AESIs) in this trial. AEs reported during the trial were classified by system organ class and preferred terms using the MedDRA coding system version 27.1. All randomised participants who had taken at least one dose of trial treatment were included in the safety evaluations. AEs and treatment emergent AEs (TEAEs) were summarised by the treatment and dose. TEAEs were displayed as event and participant counts in a frequency table by the treatment and dose. The number and proportion (%) of participants having each TEAE as well as the TEAE severity (mild, moderate, severe) and causality (related, not related) to the trial treatment were given. AESIs were reported separately similar to TEAEs. SAEs, other significant AEs and special situations were evaluated case-by-case.
Serious and non-serious adverse events: A total of 187 TEAEs were reported in 89 participants (47.1%) during the treatment period. The most common TEAE was orthostatic hypotension with 27 events reported by 24 (12.7%) of all participants, followed by headache with 29 events reported by 17 (9.0%) of all participants. In placebo group, orthostatic hypotension with 7 events was reported by 7 (14.6%) participants and headache with 4 events reported by 2 (4.2%) participants. There was a total of 43 AESIs in 36 participants. One SAE (appendicitis) occurred after the start of the trial treatment. 103 AEs in 59 participants (31.2%) were considered related to the trial treatment by the investigator. The most common related AE was orthostatic hypotension with 26 events reported in 23 participants (12.2%). Most of the reported AEs were mild or moderate in intensity but there were 2 events which were classified as severe (appendicitis and headache). 5 participants (2.6%) discontinued the trial due to an AE. In statistical analysis, there was no significant differences between placebo and treatment groups in supine and orthostatic BP. Tasipimidine was well tolerated in all dose levels administered in this trial.
F. Additional information
Global substantial modifications: The original protocol was approved on 26 Jan 2023. The trial commenced with Protocol Amendment 1 (26 Apr 2023) in which requests from competent authorities were addressed. In Protocol Amendment 2 (05 Jan 2024), trial period was extended and number of sites increased. In Protocol Amendment 3 (03 Apr 2024), request from the competent authorities was addressed. In Protocol Amendment 4 (14 Sep 2024), extension part, Part 2, (3-day treatment period in sleep laboratory was extended to 4-week treatment period in sleep laboratory and at home) was added. In Protocol Amendment 5 (14 Jan 2025), request from competent authorities was addressed. In Protocol Amendment 6 (25 Feb 2025), requests from the FDA were addressed as the trial was to start in the USA. In Protocol Amendment 7 (02 Jul 2025), extension part, Part 3, to include participants with insomnia disorder and significant anxiety symptoms and/or comorbid generalised anxiety disorder. In Protocol Amendment 8 (08 Aug 2025), a trial procedure which was added in Protocol Amendment 7, was removed. Part 3 of the trial was not started because the interim analysis results of the Part 1 and 2 on the primary efficacy endpoint for all participants did not indicate significant efficacy for any of the tasipimidine doses compared to placebo.
Global interruptions and re-starts: The trial was not interrupted or re-started.
Limitations: Not applicable.
Declaration on the accuracy of the submitted information: The sponsor declares that the data provided in this document are accurate as of the time the document was finalised.