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ORIGINAL ARTICLE

Administration of oxathridine, a first-in-class histamine-3 receptor partial agonist in healthy male volunteers: Central nervous system depression and pseudo-hallucinations

Francis M. Dijkstra^{1,2}  | Rob G. J. A. Zuiker^{1,2}  | Jules A. A. C. Heuberger¹  |
Kawita M. S. Kanhai^{1,2}  | Marieke De Kam¹ | Thierry Duvauchelle³  |
Jeanne-Marie Lecomte³ | Olivier Labeeuw⁴ | Laurent Landais⁴ |
Xavier Ligneau⁴ | Philippe Robert⁴ | Marc Capet⁴ | Jean-Charles Schwartz³ |
Joop M. A. van Gerven^{1,2}

¹Centre for Human Drug Research, Leiden, the Netherlands

²Leiden University Medical Center, Leiden, ZA, the Netherlands

³Bioprojet Pharma, Paris, France

⁴Bioprojet Biotech, Saint Gregoire, France

Correspondence

Francis M. Dijkstra, MD, Centre for Human Drug Research, Zernikedreef 8, 2333CL Leiden, the Netherlands.
Email: fdijkstra@chdr.nl

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Aims: To characterise the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending doses of oxathridine, a first-in-class histamine-3 receptor partialagonist, in healthy male volunteers.

Methods: A randomised, double-blind, placebo-controlled study including the NeuroCart, consisting of a battery of drug sensitive neurophysiological tests, was performed. Oxathridine was administered orally as an aqueous solution. After dosing, safety and NeuroCart tests (adaptive tracking [AT], body sway [BS], saccadic peak velocity [SPV], smooth pursuit [SP] eye movements, VAS according to Bond and Lader, VAS according to Bowdle [VAS B&L, Bowdle], pharmaco-electroencephalogram [pEEG], Sustained Attention to Response Task [SART]) were performed at set times.

Results: Forty volunteers completed the study. Given doses were: 0.5, 2.5, 5, 0.25 and 1.5 mg. At 5 mg, unacceptable and unanticipated adverse events (AEs) of (orthostatic) hypotension and pseudo-hallucinations were reported. Statistically significant effects ([CI]; *p*-value) of 2.5 mg and 5 mg oxathridine were observed on AT ([−8.28, −1.60]; *p* = 0.0048), ([−8.10, −1.51]; *p* = 0.00530), BS ([0.6, 80.2]; *p* = 0.0455), ([5.9, 93.1]; *p* = 0.0205) and SPV ([−59.0, −15.9]; *p* = 0.0011), ([−43.9, −1.09]; *p* = 0.0399), respectively. Oxathridine 5 mg significantly increased all three VAS Bowdle subscale scores; VAS external ([0.183, 0.476]; *p* = <.0001), VAS internal ([0.127, 0.370]; *p* = 0.0001) and VAS feeling high ([0.263, 0.887]; *p* = 0.0006).

Conclusion: NeuroCart tests indicated central nervous system (CNS) depressant effects. Oxathridine also unexpectedly caused pseudohallucinations. Although this led to the decision to stop further development of oxathridine, these observations suggest that the H3R system could be an interesting new target for the development of novel antipsychotics.

KEYWORDS

first-in-man, histamine-3 partial agonist, pharmacodynamics, pharmacokinetics, tolerability, translatability

1 | INTRODUCTION

Since its discovery in 1983, the **histamine-3 receptor (H3R)**, has been a target of interest for central nervous system (CNS) drug development.^{2–4} The H3R is an autoreceptor modulating histamine synthesis and release.^{2,3} It also functions as a heteroreceptor regulating the release of important other neurotransmitters, such as serotonin, acetylcholine, noradrenaline and dopamine.⁴ H3Rs are primarily expressed in the CNS in brain regions associated with cognition, pain, sleep and homeostatic regulation, such as the cerebral cortex, hippocampal formation, basal ganglia and hypothalamus.⁴ Although there have been several studies with investigational compounds targeted at the H3R, such as cipralisant, to date pitolisant, an H3R antagonist/inverse agonist, is the only drug targeted at the H3R that the European Medicines Agency (EMA) and Food and Drug Administration have approved.^{5,6} Pitolisant is registered for treating excessive daytime sleepiness and cataplexy in adults with narcolepsy and to improve wakefulness and reduce excessive daytime sleepiness in adults with obstructive sleep apnoea.^{5,7}

Oxathridine or 4-(1H-imidazol-4-ylmethyl)-pyridine sesquioxalate, is a highly selective partial agonist of the H3R with high potency (half maximal effective concentration = 1.5 nM) and intrinsic activity (0.7). Oxathridine behaves as a full agonist in vivo, inhibiting brain histaminergic neuron activity at low oral doses, and is therefore regarded as first-in-class. Preclinical studies demonstrated that oxathridine easily crosses the blood–brain barrier (data on file, [Supporting Information](#)). In animal models of sleeping disorders, oxathridine had sleep-promoting effects, without overt sedative reactions or anxiolytic properties as observed with GABAergic compounds. Preclinical safety experiments demonstrated a favourable effect profile. At high dose levels, undesired effects were observed starting with reduced arterial blood pressure and at higher doses piloerection and increased reactivity to touch and at the highest given doses initial decreased activity followed by increased activity, increased reactivity to touch and stereotypies. It was further noticed that at relatively low exposure levels monkeys demonstrated a change in behaviour with accepting and looking for human contact. The preclinical data supported further development of oxathridine, and a first-in-human (FIH) study was set up (Figure [S1](#)).

The starting dose for the FIH study was set at 0.5 mg (0.007 mg/kg for a 70 kg individual), which was >70 times lower than the no observed adverse effect level (NOAEL) in the most sensitive species (dogs; data on file). This NOAEL was based on a telemetry study which demonstrated increased heart rate and decreased arterial blood pressure at a dose of 1 mg/kg with a maximum exposure ($C_{\max}$) of 609 ng/mL/h, corresponding to a human equivalent dose (HED) of 0.54 mg/kg. Although a minimum anticipated biological effect level or pharmacologically active dose (PAD) was not formally established, at HED values of 0.024 mg/kg brain histamine neuron activity in mice

What is already known about this subject

- The histamine-3 receptor (H3R) is an interesting, but complex target for central nervous system drug development as it regulates several neurotransmitters such as serotonin, acetylcholine, noradrenaline and dopamine, and is hypothesized to play a role in the pathophysiology of disorders involving cognition, pain and sleep.
- Oxathridine or 4-(1H-imidazol-4-ylmethyl)-pyridine sesquioxalate is a first-in-class H3R agonist in humans. It is a highly selective partial agonist of the H3R with high potency (half maximal effective concentration = 1.5 nM) and intrinsic activity (0.7), behaving as a full agonist in vivo.
- It is important to characterize the full pharmacokinetic and pharmacodynamic profile of compounds in the early phases of clinical drug development, particularly for substances with new action mechanisms.

What this study adds

- This study adds to the knowledge about the functional effects of H3R agonism. Notably, oxathridine caused unexpected pseudo-hallucinations indicating that the H3R system could be an interesting new target for the development of novel antipsychotics.
- In line with recommendations by the European Medicines Agency, this study demonstrates the importance of considering the predictions of minimum anticipated biological effect level, pharmacologically active dose and anticipated therapeutic dose when designing a study, particularly for compounds with a new mechanism of action.¹
- This study illustrates that systematic repeated assessments of central nervous system effects of new drugs in a first-in-man study (using the NeuroCart) not only serves to profile the functional pharmacological effects of the compound, but also to sensitively detect and characterize unexpected adverse central nervous system effects.

was significantly reduced as measured by decreased levels of the main metabolite of histamine, N⁺-methylhistamine (data on file). In cats, desirable effects on sleep were observed from $C_{\max}$ values of 30 ng/mL/h and higher. Therefore, pharmacological activity could be expected from HED values of 0.024 mg/kg (1.68 mg for a 70 kg individual) and $C_{\max}$ values of 30 ng/mL/h. A dose range was selected,

which was expected to show significant pharmacological and functional effects, and to explore the large safety window that was also observed preclinically (Figure S2).

In addition to assessing tolerability, safety and pharmacokinetics (PK) in this FIH study, pharmacodynamics (PD) were explored using the NeuroCart.⁸ The NeuroCart consists of a battery of drug-sensitive neurophysiological tests and has been applied to a broad spectrum of CNS active drugs, making it possible to compare the effect profile of a novel compound on the different NeuroCart tests, to known profiles of other compounds.⁸ By doing so, the pharmacological characteristics of a novel compound can be mapped and held against predictions based on preclinical data in an early phase of clinical drug development.⁸ Oxathridine was the first partial H3R agonist to be tested on the NeuroCart, so it was not yet known which NeuroCart test would be sensitive to oxathridine. Therefore NeuroCart tests sensitive to the sedative effects of **GABAergic agonists** were selected, such as visual analogue scales (VASs), saccadic eye movement measurements and adaptive tracking.^{9–11}

Overall, this FIH study aimed to assess the PK, safety, tolerability and PD effects of single ascending doses of oxathridine in healthy male volunteers.

2 | METHODS

2.1 | General

The study was performed according to ICH GCP guidelines as laid down in the Declaration of Helsinki and its latest amendments. The Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO), Assen, the Netherlands approved the study, and the study was registered at ToetsingOnline under number NL44541.056.13. Bioprojet Pharma sponsored the study, and the study was conducted at the Centre for Human Drug Research (CHDR), Leiden, the Netherlands. All volunteers gave written informed consent prior to the study start.

2.2 | Study population

Healthy male volunteers aged between 18 and 45 years at screening were included. Health status was assessed by medical history, laboratory assessments and physical examination. Volunteers with a history or clinical evidence of alcohol or drug abuse within the 3 years prior to screening were excluded. Volunteers were not allowed to use any prescribed medications or over-the-counter medications within 2 weeks prior to the first study drug administration except for paracetamol (maximum 1 g/day; Figure S3).

2.3 | Study design

This was a randomized, double-blind, placebo-controlled, single ascending dose study. The study consisted of 5 cohorts of

8 volunteers each (active/placebo ratio: 6:2). Before escalating to the next dose level, a blinded interim safety review, consisting of safety data (adverse events [AEs], echocardiograms [ECGs], laboratory tests, vital signs), PD data and PK data of the first 24 h after dosing was performed. In the first group, a sentinel scheme was used: 2 volunteers were dosed on the first day (active/placebo ratio: 1:1) and on the second day, the remaining 6 volunteers were dosed.

The study consisted of an inpatient study visit, a medical screening within 3 weeks prior to admission and a follow-up visit a week after discharge from the clinical unit. At check-in of the study visit an eligibility check consisting of concomitant medication use and AE review, body weight and height measurement, urine drug screening, alcohol breath test, 12-lead ECG, vital signs and body temperature measurement was performed. During the dosing day (Day 1), volunteers were dosed in the morning, and throughout the day, safety, PK and PD measurements were performed at set times. Volunteers were discharged about 24–27 h after dosing (Day 2).

2.4 | Treatments

Treatments consisted of 25 mL oxathridine solution or a matching placebo for oral administration. The solution was administered with purified water and blackcurrant syrup to a volume of 100 mL for masking purposes. Planned dose levels were 0.5, 2.5, 10, 25, 40, 60, 80 and 100 mg. Volunteers were in a fasted state from 10 h prior to dosing and were allowed to eat from 3 h after dosing. Volunteers were allowed to drink water ad libitum, except for 1 h before and 2 h after dosing when drinking water was not allowed.

2.5 | PK assessments

Blood samples for PK measurements were collected prior to dosing (1 sample) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after dosing. Serum oxathridine concentrations were measured using the validated analytical ultraperformance liquid chromatography–tandem mass spectrometry method in the Bioprojet Biotech Laboratory in accordance with the guideline EMEA/CMPH/EWP/192217/2009 Rev. 1 and the rules of Good Laboratory Practice. The lower limit of quantification was 0.1 ng/mL. At the lower limit of quantification, the intra-assay coefficient of variation was 10.8% and the interassay coefficient of variation was 12.4%, respectively.

2.6 | Tolerability and safety assessments

After dosing, the following safety assessments were performed at set times throughout the study day: vital signs, physical examination, laboratory tests consisting of biochemistry, haematology, urinalysis and 12-lead ECG measurements.

2.7 | PD assessments

NeuroCart measurements consisted of adaptive tracking, body sway, saccadic eye movements, smooth pursuit eye movements, VAS according to Bond and Lader, VAS according to Bowdle and pharmacoelectroencephalogram (EEG) and the Sustained Attention to Response Task (SART). The measurements were performed twice prior to dosing and were then repeated at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 22 h after dosing. In addition, the Visual Verbal Learning Test (VVL) was performed 3 h after dosing (immediate recall) and 6 h after dosing (recognition and delayed recall).

As part of the screening visit, volunteers underwent a NeuroCart test training to prevent learning effects during study conduct. During all test sessions, there was only 1 volunteer in each room, illumination settings were standardized between the rooms. When performing the tests, volunteers were comfortably seated behind a computer screen, except during body sway measurements, when they were standing.

2.8 | Adaptive tracking

The adaptive tracking test was performed as described initially by Borland and Nicholson,¹² using customized equipment and software (based on TrackerUSB hard-/software [Hobbs, 2004, Hertfordshire, UK]). During the test, a dot inside a circle is randomly moving on a screen. Volunteers are instructed to try to keep the dot inside the circle by operating a joystick. If the volunteer succeeds in this task, the speed of the moving circle increases; conversely, the speed of the circle decreases if the volunteer fails at the task. The outcome of the test is the average speed of the moving circle as a percentage of the maximum speed of the circle over a 3.5-min period.

2.9 | Body sway

Body sway is a measure of postural stability, during measurements, volunteers are instructed to stand as still as possible with closed eyes. Body sway was performed as previously described by others.^{13,14} The anteroposterior body sway was measured using a body sway meter based on the Wright ataxiometer.¹⁵ All body movements over a 2-min period were integrated and expressed as millimetres of sway and recorded.

2.10 | Saccadic eye movements

The primary outcome of saccadic eye movement measurements was saccadic peak velocity (SPV) in degrees per second ($^{\circ}/s$). During the test, volunteers were instructed to follow a dot jumping approximately 15° to either side on a computer screen with their eyes, while head movements were restrained using a fixed head support at 58 cm from the computer screen. Fifteen saccades were recorded with

interstimulus intervals varying randomly between 3 and 6 s. Saccadic eye movements were recorded using a computer-based system, customized Cambridge Electronics Design software for data sampling and analysis (Cambridge Electronics Design, Cambridge, UK), and disposable surface electrodes for registration of the electro-oculographic signals (Medicotest N-OO-S, Olstykke, Denmark).

2.11 | Smooth pursuit eye movements

For smooth pursuit eye movements, the target moves sinusoidally at frequencies ranging from 0.3 to 1.1 Hz, by steps of 0.1 Hz. The amplitude of target displacement corresponds to 22.5° eyeball rotation to both sides. Four cycles for each stimulus frequency were recorded. The time during which the eyes are in smooth pursuit of the target was calculated for each frequency and expressed as a percentage of stimulus duration. The average percentage of smooth pursuit for all stimulus frequencies was used as a parameter.

2.12 | Pharmacoelectroencephalogram

Each EEG measurement duration was 2 min. EEG recordings were made using 4 gold electrodes, fixed with EC2 paste at Fz, Cz, Pz and Oz, with the common ground electrode for the eye movement registration (international 10/20 system). The electrode resistance was kept below 5 k Ω . EEG signals were obtained from leads Fz-Cz and Pz-Oz and a separate channel to record eye movements. The signals were amplified with a time constant of 0.3 s and a low pass filter at 100 Hz. Data collection and analysis were performed using customized CED and Spike2 for Windows software (Cambridge Electronics Design, Cambridge, UK). Per session, 8 consecutive blocks of 8 s were recorded. The signal was AD-converted using a CED 1401 Power (Cambridge Electronics Design, Cambridge, UK) and stored on hard disc for subsequent analysis. Data blocks containing artefacts were identified by visual inspection and excluded from the analysis. For each lead, a fast Fourier transform analysis was performed to obtain the sum of the amplitudes in the very low (0.5–2 Hz), delta (2–4 Hz), theta (4–7.5 Hz), alpha (7.5–13.5 Hz), beta (13.5–35 Hz) and gamma (35–48.9 Hz) frequency ranges.

2.13 | VAS according to Bond and Lader and VAS Bowdle

VAS in this study were used as originally described by Norris.¹⁶ We used Dutch versions of the scales that have been frequently used at our research institute.⁸ For VAS Bond and Lader, volunteers indicate (with vertical marks) on 16 horizontal 100-mm VAS how they feel. From these measurements, 3 main factors were calculated; *subjective alertness* (from 9 scores), *contentedness or mood* (from 5 scores) and *calmness* (from 2 scores).¹⁷

VAS Bowdle evaluates psychedelic effects with 13 10-cm VAS lines ranging from 0 (*Not at all*) to 100 mm (*Extremely*).¹⁸ From these scores, 3 sum scores were calculated; *internal perception* (reflects inner feelings that do not correspond with reality, including mistrustful feelings), *external perception* (reflects a misperception of an external stimulus or a change in the awareness of the volunteer's surroundings) and *feeling high*.¹⁸

2.14 | VVLT

The VVLT tests the whole scope of learning behaviour, i.e. acquisition, consolidation, storage and retrieval.¹⁹ Volunteers were presented with 30 words in 3 consecutive word trials. At each of these trials, an immediate recall was performed. Delayed recall was assessed 6 h after dosing. Immediately after delayed recall, a recognition test was performed, consisting of 15 previously presented words and 15 new words in which the volunteer had to verbally indicate recognition of the word as quickly as possible. An operator behind a computer screen recorded the volunteer's response by clicking on the named word in a list with all 30 presented words and clicking on a bar stating *different word* if an unlisted word was mentioned. Words mentioned twice or more were recorded as duplications. After 3 trials, a script automatically counted the scores per trial as: number correct, number incorrect, number double. If a correct word was mentioned twice, the overall score included 1, *Correct response* and 1, *Double response*. Similarly, an incorrect word, which was mentioned twice, was scored as 1, *Incorrect response* and 1, *Double response*.

2.15 | SART

This test was performed as a measurement of improved cognitive functioning, as H3R antagonists are hypothesized to have beneficial effects on cognition.⁴ The SART is similar in many respects to a standard vigilance task, in that a single infrequent target is presented among a background of frequent nontargets. Unlike a traditional vigilance task, however, the volunteer is required to push the space bar to the nontarget and inhibit their response to the target. To perform this task correctly, the volunteer must remain sufficiently attentive to their responses, such that at the appearance of a target they can substitute the directly antagonistic response.²⁰

2.16 | Statistical analysis

Statistical analyses were performed using the SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). The repeatedly measured PD endpoints were analysed separately by mixed model analyses of covariance (ANCOVA) with treatment-and-dose, time, and treatment-and-dose by time as fixed effects, subject as random effect, and with the (average) baseline value as covariate. Baseline was defined as the average of the 2 measurements performed prior to dosing. Measurements of VAS Bowdle, all EEG parameters, body sway and SART total omission errors were logarithmically transformed (after 0 was changed to 0.01). Log-transformed parameters were back-transformed after analysis where the results may be interpreted as percentage change.

Contrasts for all dose levels of oxathridine vs. placebo were calculated within the model up to the 3-h measurement after dosing. This

TABLE 1 Demographics.

Demographic variables	Placebo n = 10	Oxa 0.25 mg n = 6	Oxa 0.5 mg n = 6	Oxa 1.5 mg n = 6	Oxa 2.5 mg n = 6	Oxa 5 mg n = 6
Age, years						
Mean	23.7	21.0	22.5	24.0	23.3	22.8
SD	3.9	3.1	2.6	4.6	3.9	2.4
Range	20–32	18–25	18–26	19–31	19–28	20–26
Height (cm)						
Mean	183.6	181.1	182.7	183.8	186.0	186.8
SD	5.0	9.2	6.7	8.7	11.2	4.0
Range	175.8–192.3	171.8–195.0	175.9–191.4	170.0–191.7	174.4–204.2	181.6–191.1
Weight (kg)						
Mean	77.7	73.1	79.4	71.9	73.8	76.8
SD	8.4	10.9	11.3	9.0	11.1	5.6
Range	67.7–94.9	61.7–84.9	68.4–96.5	61.2–86.2	60.2–85.8	68.5–82.8
Body mass index (kg/m ²)						
Mean	23.1	22.4	23.7	21.3	21.2	22.0
SD	1.9	3.7	2.3	1.6	1.3	1.0
Range	19.9–26.8	18.3–27.2	21.5–26.8	19.6–24.1	19.8–22.9	20.8–23.0

Abbreviations: Oxa, oxathridine; SD, standard deviation.

timepoint was based on *posthoc* inspection of the time profiles of the concentrations in this clinical study, showing that for all doses a 3-h period covered most of the exposure. Assuming that the PD effects would be closely related to the PK profile, this analysis was considered most relevant.

The VVLT endpoints were analysed separately by mixed model analyses of variance (ANOVA) with treatment-and-dose as fixed effect. Treatment effects are reported as the contrasts specified below where the average of the measurements up to last time point will be calculated within the statistical model.

Contrasts are reported for all NeuroCart tests along with 95% confidence intervals and analyses are 2-sided with a significance level of 0.05.

PK calculations were performed using R (V2. 12.0, R Core Team). Standard noncompartmental methods were used in the calculations. Data below the limit of quantification before $t_{\max}$ was replaced with zero. Data below the limit of quantification after $t_{\max}$ was replaced with not applicable, i.e., excluded from analysis.

2.17 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.^{21,22}

3 | RESULTS

3.1 | Subject disposition

In total 40 healthy male volunteers participated; all completed the study. The cohorts were comparable with regards to age, weight, height and body mass index (Table 1).

3.2 | PK

Maximum median serum concentrations were reached at about 1.00–1.26 h after dosing across the dose levels (Table 2, Figure 1). The median half-life of oxathridine varied between 1.20 and 1.45 h across the dose levels. Exposure to oxathridine increased more than dose proportionally in the higher dose range.

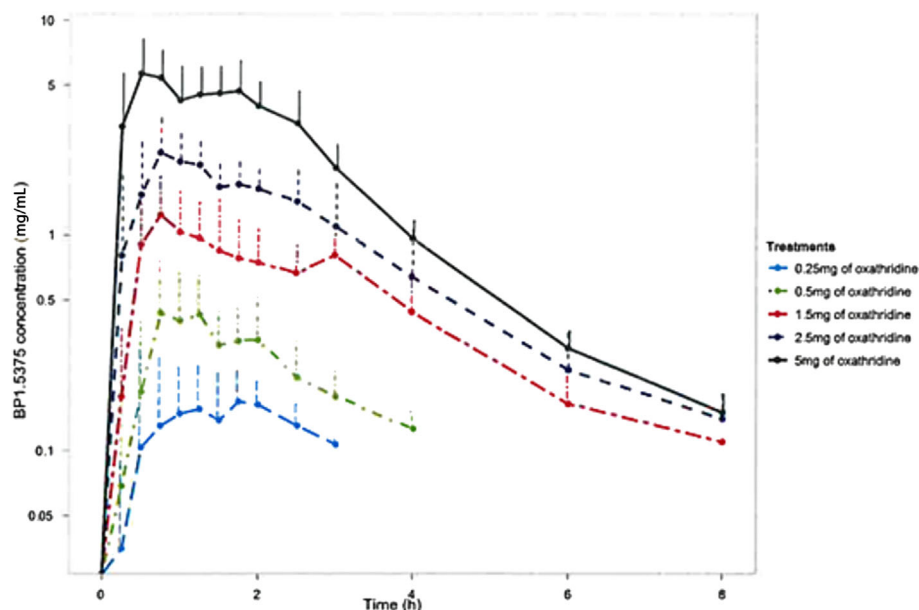
3.3 | Tolerability and safety

An overview of AEs by dose group is provided in Table 3. All observed AEs were self-limiting. There were no serious AEs in the study. Doses could not be escalated as planned due to safety concerns about subjective effects. In cohort 1 (0.5 mg), 1 AE of somnolence was reported and classified as mild. As this dose was well

TABLE 2 Pharmacokinetics of oxathridine.

Dose (mg)	Oxathridine				AUC ₀₋₂₄ (ng/mL*h)				AUC _{0-∞} (ng/mL*h)				T _{max} (h)		T _{1/2} (h)	
	C _{max} (ng/mL)		Mean/dose		Mean		SD		Mean		SD		Median		Median	
	Mean	range	Mean/dose	SD	range	Mean/dose	SD	range	Mean	range	SD	range	Median	Range	Median	Range
0.25 (n = 6)	0.22 (0.12; 0.47)		0.88	0.13	0.29 (0.04; 0.65)	1.16	0.23		0.57 (0.35; 0.79)		0.21		1.13	0.12–0.47	1.22	0.93–1.50
0.5 (n = 6)	0.5 (0.23; 0.92)		1.00	0.28	0.92 (0.37; 1.78)	1.84	0.51		1.20 (0.64; 1.95)		0.46		1.26	0.75–1.78	1.45	0.94–2.33
1.5 (n = 6)	1.4 (0.73; 1.81)		0.93	0.48	3.55 (2.42; 4.54)	2.37	0.77		3.83 (2.66; 4.76)		0.77		1.15	0.75–3.00	1.20	1.14–1.42
2.5 (n = 6)	2.73 (1.22; 3.69)		1.09	0.87	6.54 (3.44; 9.63)	2.62	2.21		6.84 (3.69; 9.96)		2.24		1.12	0.75–2.00	1.29	0.83–1.47
5 (n = 6)	7.12 (4.32; 10.05)		1.42	1.99	14.97 (12.81; 19.45)	2.99	2.33		15.26 (13.07; 19.79)		2.36		1.00	0.50–2.00	1.31	1.15–1.51

FIGURE 1 Pharmacokinetics (serum concentrations) of oxathridine (BP1.5375).



tolerated and the next planned dose of 2.5 mg was still <10 times lower than the HED of the NOAEL and had a predicted C_{max} that was far below the exposure observed at the NOAEL in the most sensitive species, it was decided to escalate the dose to 2.5 mg as initially planned. In cohort 2 (2.5 mg), all volunteers who received oxathridine reported 1 or more AEs. The most frequently reported AEs were nausea, fatigue, somnolence, blurred vision, dizziness and orthostatic hypotension. All these AEs were mild, whereas 2 AEs of balance disorder and dizziness, were reported as moderate. Because of these observations, the dose for the next cohort was escalated to 5 mg instead of the planned 10 mg.

At a dose of 5 mg, all volunteers who received oxathridine reported 1 or more adverse events. The most frequent events were dizziness and visual (pseudo)-hallucinations. For this study, it was chosen to use the term *pseudo-hallucination* to describe the AEs experienced by the volunteers, as in contrast to *typical hallucinations* the volunteers reported that they were aware that the perceived images were not real and that they could change the content of the visual phenomena.²³ The pseudo-hallucinations started on average 40 min after dosing and lasted 50 min up to 2 h, in all volunteers, the effects disappeared completely without treatment and did not reoccur. One volunteer had orthostatic hypotension and fainted about 30 min after dosing and felt light-headed for the following 3 h. Three single AEs of nausea, dizziness and syncope were reported as moderate, and the others were reported as mild.

The occurrence of these AEs led to the decision to halt further dose escalation. Two additional cohorts with low dose levels of 0.25 and 1.5 mg to better characterize the PD and PK of oxathridine were performed instead.

At a dose level of 0.25 mg, 2 of the volunteers receiving oxathridine reported AEs. AEs consisted of dizziness, somnolence, feeling of relaxation and paraesthesia, which all were of mild severity.

All volunteers receiving a dose of 1.5 mg oxathridine reported 1 or more AEs. The most frequent reported AEs were nausea, vision blurred, dizziness and hypotension. Four events of dizziness, 2 events of hypotension and 1 of orthostatic hypotension were reported as moderate, and the others were reported as mild. No pseudo-hallucinations were reported with these additional low doses.

As expected with AEs of dizziness, hypotension and orthostatic hypotension, decreases in supine and standing blood pressure, mostly diastolic, were observed with dose levels of 1.5 mg oxathridine or higher (Supporting Information). A compensatory increase in standing heart rate was observed.

There were no clinically relevant changes in laboratory assessments (clinical chemistry, haematology and urinalysis). Also, there were no clinically relevant observations on any ECG parameters.

3.4 | PD

A dose-dependent decrease in performance on adaptive tracking was observed, which was statistically significant for the 2 highest dose levels (Table 4). At these dose levels, a statistically significant increase in body sway was observed as well (Table 4). Additionally, a decrease in SPV and increased saccadic inaccuracy were observed with these dose levels (Table 4). In the highest dose group of 5 mg oxathridine, statistically significant effects were observed on all 3 VAS Bowdle subscales (VAS external, VAS internal and VAS feeling high; Table 5, Figure 2). In the lowest dose levels (0.25 and 0.5 mg), oxathridine decreased the reaction time of correct responses of the delayed word recognition task of the VVLT (Table 5). No statistically significant effects were observed on the other NeuroCart measurements.

TABLE 3 Adverse events per dose group.

System organ class/preferred term	Number (%) of subjects					
	Placebo n = 10	Cohort 4 Oxa 0.25 n = 6	Cohort 1 Oxa 0.5 n = 6	Cohort 5 Oxa 1.5 n = 6	Cohort 2 Oxa 2.5 n = 6	Cohort 3 Oxa 5.0 n = 6
Any event	2 (20)	2 (33)	1 (16.7)	6 (100)	6 (100)	6 (100)
Ear and labyrinth disorders						
Tinnitus					1 (16.7)	
Eye disorders						
Asthenopia					1 (16.7)	1 (16.7)
Gastrointestinal disorders						
Nausea	1 (10.0)			3 (50.0)	2 (33.3)	2 (33.3)
Vomiting				1 (16.7)		
General disorders and administration site conditions						
Asthenia				1 (16.7)		
Fatigue	1 (10.0)				3 (50.0)	1 (16.7)
Feeling abnormal				1 (16.7)		1 (16.7)
Feeling of relaxation		1 (16.7)				
Nervous systems disorders						
Balance disorder					1 (16.7)	
Disturbance in attention				1 (16.7)		
Dizziness		1 (16.7)			1 (16.7)	
Dysarthria					1 (16.7)	
Headache	1 (10.0)			1 (16.7)	1 (16.7)	
Paraesthesia		1 (16.7)				
Somnolence	2 (20.0)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)
Tremor				1 (16.7)		
Vision blurred				2 (33.3)	2 (33.3)	2 (33.3)
Psychiatric disorders						
Disturbance in attention						1 (16.7)
Euphoric mood					1 (16.7)	2 (33.3)
Hallucination, visual						4 (66.7)
Vascular disorders						
Dizziness		1 (16.7)		4 (66.7)	3 (50.0)	6 (100.0)
Flushing				1 (16.7)		
Hypotension				3 (50.0)		
Orthostatic hypotension				1 (16.7)	2 (33.3)	
Pallor				1 (16.7)		
Syncope						1 (16.7)

4 | DISCUSSION

This FIH, randomized, double-blind, placebo-controlled study investigated the safety, PK and PD of the first-in-class H3 agonist oxathridine. As expected, the effects of 2.5 and 5 mg oxathridine on the NeuroCart tests of adaptive tracking, body sway and saccadic eye movements were indicative of CNS-depressant effects. However, the safety profile of oxathridine in healthy volunteers was different than expected based on the preclinical data, with mild to moderate

orthostatic hypotension and pseudo-hallucinations at the 2 highest administered dose levels. This led to the decision to halt further dose escalation at 5 mg and to expand the dose range with 0.25 and 1.5 mg of oxathridine to characterize its safety, PK and PD profile more thoroughly.

In retrospect, the planned dose range of 0.5–100 mg was too large, especially when taking into account the PAD and anticipated therapeutic doses as recommended by current EMA guidelines.¹ Pre-clinical experiments demonstrated pharmacological effects from HED

TABLE 4 Pharmacodynamic effects.

Parameter	Treatment P-value	Contrasts up to 3 h				
		Estimate of difference (confidence interval) P-value				
		OXA-0.25 vs. placebo	OXA-0.5 vs. placebo	OXA-1.5 vs. placebo	OXA-2.5 vs. placebo	OXA-5 vs. placebo
Adaptive tracking (%)	.6422	−0.873 (−4.16, 2.409) P = .5939	−1.28 (−4.58, 2.017) P = .4368	−2.51 (−5.83, 0.817) P = .1357	−4.94 (−8.28, −1.60) P = .0048	−4.81 (−8.10, −1.51) P = .0053
		−7.4% (−31.4%, 25.1%) P = .6099	5.7% (−21.1%, 41.4%) P = .7047	29.2% (−4.2%, 74.2%) P = .0915	34.6% (−0.6%, 80.2%) P = .0455	43.0% (5.9%, 93.1%) P = .0205
Body sway (mm)	.4571	0.41 (−0.60, 1.42) P = .4207	−0.19 (−1.20, 0.81) P = .7043	0.63 (−0.54, 1.79) P = .2877	2.00 (0.97, 3.04) P = .0003	1.49 (0.47, 2.52) P = .0050
		3.07 (−18.3, 24.41) P = .7733	−7.08 (−29.4, 15.25) P = .5252	−10.8 (−33.8, 12.13) P = .3487	−37.4 (−59.0, −15.9) P = .0011	−22.5 (−43.9, −1.09) P = .0399
Saccadic peak velocity (°/s)	.3217	2.29 (−2.23, 6.82) P = .3113	−0.01 (−4.07, 4.04) P = .9954	0.89 (−3.34, 5.12) P = .6742	0.27 (−3.77, 4.31) P = .8928	−0.77 (−4.99, 3.45) P = .7135
		4.627 (−2.23, 6.82) P = .3113	−0.01 (−4.07, 4.04) P = .9954	0.89 (−3.34, 5.12) P = .6742	0.27 (−3.77, 4.31) P = .8928	−0.77 (−4.99, 3.45) P = .7135
Smooth pursuit (%)	.4627	−1.89 (−8.73, 4.95) P = .5812	2.44 (−4.36, 9.25) P = .4738	−4.43 (−11.6, 2.77) P = .2235	−0.70 (−8.04, 6.64) P = .8482	−5.83 (−13.2, 1.50) P = .1167
		1.938 (−0.37, 13.98) P = .0626	−1.05 (−8.93, 6.84) P = .7897	3.07 (−4.34, 10.49) P = .4075	2.32 (−5.36, 10.00) P = .5445	4.82 (−2.56, 12.19) P = .1944
VAS Alertness (mm)	.1270	2.60 (−3.25, 8.46) P = .3740	5.38 (−0.46, 11.21) P = .0700	2.32 (−3.67, 8.31) P = .4389	1.40 (−4.81, 7.61) P = .6513	4.51 (−1.53, 10.55) P = .1394
		2.423 (−3.25, 8.46) P = .3740	5.38 (−0.46, 11.21) P = .0700	2.32 (−3.67, 8.31) P = .4389	1.40 (−4.81, 7.61) P = .6513	4.51 (−1.53, 10.55) P = .1394
VAS Calmness (mm)	.1938	6.80 (−0.37, 13.98) P = .0626	−1.05 (−8.93, 6.84) P = .7897	3.07 (−4.34, 10.49) P = .4075	2.32 (−5.36, 10.00) P = .5445	4.82 (−2.56, 12.19) P = .1944
		2.423 (−3.25, 8.46) P = .3740	5.38 (−0.46, 11.21) P = .0700	2.32 (−3.67, 8.31) P = .4389	1.40 (−4.81, 7.61) P = .6513	4.51 (−1.53, 10.55) P = .1394
VAS Mood (mm)	.2423	−0.020 (−0.168, 0.128) P = .7850	0.016 (−0.127, 0.159) P = .8213	0.096 (−0.049, 0.241) P = .1914	−0.014 (−0.156, 0.127) P = .8376	0.330 (0.183, 0.476) P ≤ 0.0001
		.0031 (−0.168, 0.128) P = .7850	0.016 (−0.127, 0.159) P = .8213	0.096 (−0.049, 0.241) P = .1914	−0.014 (−0.156, 0.127) P = .8376	0.330 (0.183, 0.476) P ≤ 0.0001
VAS External log (mm)	.0031	−0.006 (−0.127, 0.116) P = .9249	0.075 (−0.044, 0.194) P = .2084	0.087 (−0.033, 0.207) P = .1528	0.051 (−0.064, 0.167) P = .3751	0.249 (0.127, 0.370) P = .0001
		.0226 (−0.127, 0.116) P = .9249	0.075 (−0.044, 0.194) P = .2084	0.087 (−0.033, 0.207) P = .1528	0.051 (−0.064, 0.167) P = .3751	0.249 (0.127, 0.370) P = .0001
VAS Internal log (mm)	.0226	−0.156 (−0.471, 0.160) P = .3249	0.049 (−0.258, 0.355) P = .7488	0.013 (−0.295, 0.322) P = .9310	0.014 (−0.286, 0.314) P = .9242	0.575 (0.263, 0.887) P = .0006
		.0468 (−0.471, 0.160) P = .3249	0.049 (−0.258, 0.355) P = .7488	0.013 (−0.295, 0.322) P = .9310	0.014 (−0.286, 0.314) P = .9242	0.575 (0.263, 0.887) P = .0006
EEG Alpha Fz-Cz (uV)	.6320	−8.5% (−28.6%, 17.3%) P = .4739	−14.8% (−33.4%, 9.2%) P = .1996	0.1% (−23.5%, 31.0%) P = .9934	−8.5% (−28.8%, 17.5%) P = .4761	−2.2% (−24.2%, 26.1%) P = .8581
		.6320 (−28.6%, 17.3%) P = .4739	−14.8% (−33.4%, 9.2%) P = .1996	0.1% (−23.5%, 31.0%) P = .9934	−8.5% (−28.8%, 17.5%) P = .4761	−2.2% (−24.2%, 26.1%) P = .8581

(Continues)

TABLE 4 (Continued)

Parameter	Treatment P-value	Contrasts up to 3 h				
		Estimate of difference (confidence interval) P-value				
		OXA-0.25 vs. placebo	OXA-0.5 vs. placebo	OXA-1.5 vs. placebo	OXA-2.5 vs. placebo	OXA-5 vs. placebo
EEG Alpha Pz-Oz (uV)	.4700	-17.5% (-45.1%, 24.1%) P = .3462	-35.2% (-56.4%, -3.6%) P = .0331	-6.0% (-38.8%, 44.6%) P = .7753	-26.9% (-51.3%, 9.6%) P = .1255	-20.0% (-46.5%, 19.5%) P = .2675
EEG Beta Fz-Cz (uV)	.4216	10.0% (-14.3%, 41.2%) P = .4424	-15.3% (-34.0%, 8.5%) P = .1822	7.4% (-17.5%, 39.9%) P = .5868	5.4% (-18.0%, 35.5%) P = .6751	16.6% (-10.0%, 51.0%) P = .2372
EEG Beta Pz-Oz (uV)	.6551	-12.6% (-38.5%, 24.2%) P = .4430	-29.4% (-50.1%, -0.0%) P = .0498	-13.3% (-40.7%, 26.7%) P = .4535	-14.2% (-39.8%, 22.3%) P = .3873	-12.9% (-38.7%, 23.6%) P = .4296
EEG Delta Fz-Cz (uV)	.5773	-1.4% (-22.7%, 25.7%) P = .9072	-10.0% (-29.3%, 14.5%) P = .3807	13.7% (-12.1%, 47.1%) P = .3206	-5.3% (-26.0%, 21.3%) P = .6589	1.9% (-20.7%, 31.0%) P = .8776
EEG Delta Pz-Oz (uV)	.5890	-4.1% (-34.0%, 39.4%) P = .8222	-27.6% (-50.1%, 4.9%) P = .0858	1.6% (-31.7%, 51.1%) P = .9366	14.0% (-21.9%, 66.4%) P = .4887	-0.1% (-31.7%, 45.9%) P = .9941
EEG Gamma Fz-Cz (uV)	.6472	14.9% (-9.8%, 46.4%) P = .2519	-10.6% (-29.8%, 13.7%) P = .3500	5.8% (-17.8%, 36.2%) P = .6523	6.6% (-16.5%, 36.2%) P = .5979	9.0% (-15.2%, 40.2%) P = .4906
EEG Gamma Pz-Oz (uV)	.6894	2.7% (-31.3%, 53.6%) P = .8938	-24.7% (-49.5%, 12.2%) P = .1581	-2.8% (-36.7%, 49.3%) P = .8945	8.2% (-27.8%, 62.2%) P = .6946	14.6% (-24.2%, 73.2%) P = .5092
EEG Theta Fz-Cz (uV)	.6453	11.6% (-13.5%, 43.9%) P = .3876	-11.9% (-31.6%, 13.4%) P = .3157	11.9% (-14.3%, 46.2%) P = .4007	5.4% (-18.3%, 36.1%) P = .6777	10.5% (-15.3%, 44.0%) P = .4517
EEG Theta Pz-Oz (uV)	.5617	-13.2% (-41.5%, 28.6%) P = .4689	-31.0% (-53.3%, 1.9%) P = .0612	-4.3% (-36.7%, 44.9%) P = .8332	10.9% (-25.2%, 64.3%) P = .5978	-7.6% (-38.1%, 38.1%) P = .6939
SART total commission errors	.4500	-3.57 (-8.01, 0.88) P = .1122	-0.46 (-4.64, 3.71) P = .8228	-0.47 (-4.76, 3.82) P = .8267	-3.68 (-8.45, 1.09) P = .1261	-3.69 (-7.90, 0.52) P = .0840
SART mean RT correct	.9940	18.80 (-67.2, 104.8) P = .6596	-0.97 (-82.2, 80.23) P = .9807	6.87 (-77.3, 91.00) P = .8692	53.86 (-38.4, 146.1) P = .2434	11.66 (-70.8, 94.06) P = .7755
SART total omission errors	.2723	-71.9% (-95.3%, 68.9%) P = .1609	-64.6% (-93.6%, 96.4%) P = .2283	-7.7% (-84.1%, 436.5%) P = .9277	-72.6% (-96.0%, 88.5%) P = .1832	8.5% (-80.5%, 503.8%) P = .9242

TABLE 4 (Continued)

Parameter	Treatment P-value	Contrasts up to 3 h				
		Estimate of difference (confidence interval) P-value				
		OXA-0.25 vs. placebo	OXA-0.5 vs. placebo	OXA-1.5 vs. placebo	OXA-2.5 vs. placebo	OXA-5 vs. placebo
SART post error slowing	.7256	−0.052 (−0.177, 0.072) P = .4037	−0.008 (−0.122, 0.106) P = .8897	−0.077 (−0.194, 0.040) P = .1943	−0.079 (−0.212, 0.053) P = .2332	−0.038 (−0.155, 0.079) P = .5192
SART RT variability	.4898	−8.87 (−19.1, 1.352) P = .0869	−0.664 (−10.3, 8.969) P = .8895	4.566 (−5.27, 14.41) P = .3532	−4.23 (−15.2, 6.787) P = .4412	−3.83 (−13.7, 6.011) P = .4351
SART total error score	.6362	−6.87 (−15.5, 1.72) P = .1135	−1.83 (−9.92, 6.25) P = .6477	1.87 (−6.42, 10.15) P = .6506	−6.07 (−15.4, 3.24) P = .1941	−4.91 (−13.1, 3.26) P = .2310

Abbreviations: EEG, electroencephalogram; Oxa, oxathridine; SART, Sustained Attention to Response Task; VAS, visual analogue scale.

TABLE 5 Visual Verbal Learning Test.

Parameter	Treatment P-value	Contrasts all measurements				
		OXA-0.25 vs. placebo	OXA-0.5 vs. placebo	OXA-1.5 vs. placebo	OXA-2.5 vs. placebo	OXA-5 vs. placebo
Word recall correct 1	.5126	−0.90 (−4.33, 2.53) P = .5975	−0.73 (−4.17, 2.70) P = .6668	−0.90 (−4.33, 2.53) P = .5975	−1.57 (−5.00, 1.87) P = .3601	−3.40 (−6.83, 0.03) P = .0520
Word recall correct 2	.6855	2.17 (−2.03, 6.37) P = .3017	−0.50 (−4.70, 3.70) P = .8102	1.00 (−3.20, 5.20) P = .6315	−1.00 (−5.20, 3.20) P = .6315	−1.17 (−5.37, 3.03) P = .5760
Word recall correct 3	.7095	2.53 (−2.48, 7.55) P = .3117	−1.63 (−6.65, 3.38) P = .5123	0.87 (−4.15, 5.88) P = .7275	−0.63 (−5.65, 4.38) P = .7989	−0.97 (−5.98, 4.05) P = .6976
Delayed word recall correct	.8847	1.93 (−3.62, 7.48) P = .4837	0.10 (−5.45, 5.65) P = .9710	0.77 (−4.78, 6.32) P = .7806	−1.90 (−7.45, 3.65) P = .4912	−0.23 (−5.78, 5.32) P = .9324
Delayed word recognition correct	.8967	0.33 (−2.74, 3.41) P = .8268	−0.50 (−3.57, 2.57) P = .7428	−0.83 (−3.91, 2.24) P = .5850	0.83 (−2.24, 3.91) P = .5850	−0.83 (−3.91, 2.24) P = .5850
Delayed word recognition RT correct (ms)	.0235	−102 (−202, −1.43) P = .0470	−172 (−273, −71.6) P = .0014	−24.6 (−125, 75.90) P = .6224	−32.4 (−133, 68.07) P = .5166	−30.1 (−131, 70.40) P = .5471

Abbreviation: Oxa, oxathridine.

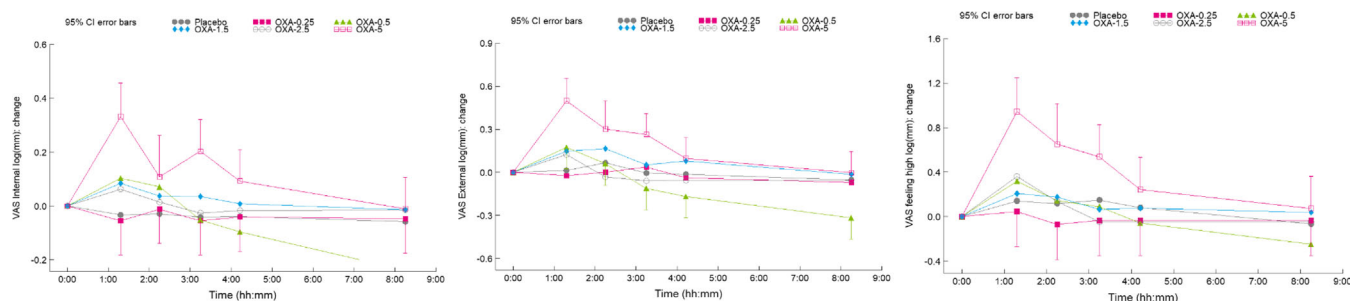


FIGURE 2 Visual analogue scale Bowdle sum scores (internal, external, feeling high). Oxa, oxathridine.

levels of 1.68 mg and $C_{\max}$ values of 30 ng/mL and higher. However, predictions of sleep-inducing doses were mainly based on cats, which is an unusual species in preclinical research. Moreover, the NOAEL was about 20-fold higher, and determined by cardiovascular effects in dogs, which can be adequately monitored in humans. Since CNS-depression can also be measured accurately in healthy volunteers, a large dose range was selected for the FIH study.

The occurrence of pseudo-hallucinations was entirely unexpected. The time courses of the occurrence and resolving of pseudo-hallucinations and the increased scores on all 3 subscales of the VAS Bowdle (VAS internal, VAS external, VAS feeling high; Figure 2) closely followed the PK profile (Figure 1), providing a strong argument that pseudo-hallucinations are a pharmacological effect of oxathridine. In view of the high selectivity of oxathridine, this effect is likely related to stimulation of H3R. However, to our knowledge there are no other reports of clinical studies with H3R agonists, so without replication we cannot be absolutely certain that the pseudo-hallucinations are a class effect. Due to their nature, pseudo-hallucinations could not be observed preclinically, although some non-specific behavioural symptoms such as increased reactivity to touch and monkeys accepting and looking for human contact, were observed in the animal studies, which retrospectively could have been indicative of cognitive, behavioural or perceptive dysregulations. These behavioural effects were observed at considerably higher exposure levels than for pseudo-hallucinations in humans. This could be due to different sensitivities, to detect spontaneous behavioural observations in animals, compared to subjective VAS-scores in humans. It could also be that humans are more sensitive to H3R-agonism, since cardiovascular effects of (orthostatic) hypotension also occurred at lower exposure levels in healthy volunteers than observed preclinically, indicating that humans are more sensitive to the effects of H3R agonists than animals.

The mechanism of action underlying pseudohallucinatory effects is uncertain. A stage of dreaming without being asleep might be an explanation. Pseudo-hallucinations have also been reported after use of drugs targeted at the GABA-ergic system, the main inhibitory neurotransmitter system in the brain.^{24,25} In some healthy volunteers, but not all, zolpidem (a GABA_A-agonist with high α_1 subtype selectivity) caused concentration-related pseudo-hallucinations.^{26,27} In the current study, all volunteers reported being able to change their visual pseudo-hallucinations intentionally. This is reminiscent of that

hypnagogic hallucinations that occur in narcolepsy.²⁸ This condition is characterized by a deficiency of orexin (hypocretin), an important neuropeptide for—among others—the regulation of the sleep–wake cycle, in which histamine plays a prominent role.²⁸ Within this system, H3R pharmacology is complex and involved in the regulation of many other neurotransmitter systems such as serotonergic (5HT), dopaminergic and cholinergic systems.⁴ Several CNS-penetrating compounds affecting these systems, like antimuscarinics and 5HT_{2a}- or D₂-agonists, are well-known psychomimetics, suggesting that the pseudo-hallucinations may have been caused by dysregulation of these systems by oxathridine. Abnormal H3R expression is observed in the brain of patients with schizophrenia, which further points in the direction of a role for the H3R in the occurrence of hallucinations.²⁹ It therefore seems that pharmacological interference on homeostatic brain processes of sleep can lead to a disruption of different aspects of sleep onset, leading to phenomena of pseudo-hallucinations.

From dose levels of 2.5 mg and higher, oxathridine demonstrated CNS-depressant effects on the NeuroCart. In Table 6 the NeuroCart effects of oxathridine are compared with several other sleep-promoting and (anti)histaminergic compounds: lorazepam (GABA-A-agonist), diphenhydramine (H₁-R antagonist and some anti-muscarinic/anticholinergic action) and CEP-26401 (investigational H3R antagonist/inverse agonist).^{9,30–32} The effect size of oxathridine on adaptive tracking was approximately half the effect size of 2-mg lorazepam, and twice as large as the effect of diphenhydramine. On body sway oxathridine's effect was approximately half the effect size of 2-mg lorazepam and 4 times larger than the effect size of 50-mg diphenhydramine. The effect size of oxathridine on SPV was approximately 3 times smaller than the effect size of 2-mg lorazepam, but larger than the effect size of diphenhydramine. Comparable to diphenhydramine, oxathridine did not affect smooth pursuit, while lorazepam did. Overall, the NeuroCart profile of oxathridine is indicative of a CNS-depressant compound with less sedative capacity than 2-mg lorazepam, but more than 50-mg diphenhydramine. Furthermore, in line with their mechanisms of action, the effects of oxathridine on the NeuroCart tests are opposite to the effects observed with the H3R-inverse agonist CEP-26401.³² Compared with placebo, the groups with the 2 lowest doses of oxathridine showed lower reaction times in the delayed word recognition task of the VVLT. This might be indicative of improved cognitive functioning. However, no CNS stimulating effects were observed on the other NeuroCart tests, which in contrast

TABLE 6 Summary NeuroCart effects for different central nervous system active compounds.

	Lorazepam 2 mg (GABA _A -agonist) ^{9,30}	Diphenhydramine 50 mg (H1R antagonist, with some antimuscarinic/anticholinergic action) ³¹	CEP-26401 125 ug (H3R antagonist/inverse agonist) ³²	Oxathridine 5 mg (H3R partial agonist)
Adaptive tracking (%)	−9.53 (−11.9; −7.21) <i>P</i> < .0001	−2.64 (−3.92; −1.13) <i>P</i> = .0001	1.20 (0.42; 1.98) <i>P</i> = .0029	−4.81 (−8.10; −1.51) <i>P</i> = .0053
Body sway (%)	89.0 (62.8; 119.6) <i>P</i> < .0001	12.25 (−2.35; 29.03) .1021	−28.72 (−61.94; 4.51) <i>P</i> = .0895	43.0 (5.9; 93.1) <i>P</i> = .0205
Saccadic peak velocity (°/s)	−59.23 (−46.05; −72.41) <i>P</i> < .001	−13.8 (−21.7; −5.9) .0010	16.99 (9.73; 24.24) <i>P</i> < .0001	−22.5 (−43.9; −1.09) <i>P</i> = .0399
Smooth pursuit (%)	−10.8 (−14.2; −7.3) <i>P</i> < .0001	−0.5 (−3.1; 2.1) <i>P</i> = .7149	−0.31 (−2.10; 1.48) <i>P</i> = .7310	−0.77 (−4.99; 3.45) <i>P</i> = .7135
pEEG	All frequencies of EEG bands were statistically significantly affected	Not reported	No effect	No effect
VAS Bond & Lader alertness (mm)	−1.80 (−3.52; −0.08) <i>P</i> = .041	−1.0 (−4.4; 2.3) <i>P</i> = .5377	No effect	−5.83 (−13.2; 1.50) <i>P</i> = .1167
VAS Bond & Lader calmness (mm)	−0.10 (−0.41; 0.22) <i>P</i> = .529	1.1 (−1.0; 3.2) <i>P</i> = .3066	No effect	4.82 (−2.56; 12.19) <i>P</i> = .1944
VAS Bond & Lader mood (mm)	−0.24 (−0.96; 0.49) <i>P</i> = .510	0.4 (−0.8; 1.7) <i>P</i> = .5059	No effect	4.51 (−1.53; 10.55) <i>P</i> = .1394
VAS Bowdle internal	0.07 (0.03; 0.11) <i>P</i> = .0007	Not reported	No effect	0.249 (0.127; 0.370) <i>P</i> = .0001
VAS Bowdle external	0.10 (0.05; 0.16) <i>P</i> = .0004	Not reported	No effect	0.330 (0.183; 0.476) <i>P</i> < .0001
VAS Bowdle Feeling high	0.12 (0.02; 0.22) <i>P</i> = .0168	Not reported	No effect	0.575 (0.263; 0.887) <i>P</i> = .0006
Visual Verbal Learning Test	Not reported	Not reported	No effect	Effect on word recall correct 1 −3.40 (−6.83; 0.03) <i>P</i> = .0520

Abbreviations: pEEG, pharmaco-electroencephalogram; VAS, visual analogue scale.

to the VVLT are baseline corrected. Therefore, these effects may well have been false positive findings.

Although further development of oxathridine was ceased based on the findings of this study, important lessons can be learned from it. This study demonstrates how the NeuroCart can be used in early phase clinical trials to measure important pharmacological characteristics of novel CNS compounds and compare these to existing compounds.⁸ In line with recommendations by the EMA this study demonstrates the importance of considering the predictions of minimum anticipated biological effect level, PAD and anticipated therapeutic dose when designing a study, particularly for compounds with a new mechanism of action.¹ This study also shows that there is

inherent uncertainty in the translation from preclinical to human studies. Although the preclinical data of oxathridine indicates an appropriate *therapeutic window* with desired effects at lower dose levels than undesired effects, in humans there was no therapeutic window as dose levels with desired effects were associated with unacceptable AEs. This study emphasizes that not all AEs are translatable between animals and humans, as some psychiatric AEs, such as hallucinations, cannot be observed in animals. However, nonspecific changes in behaviour observed preclinically might indicate that animals experience disruptive cognitive or perceptive symptoms and, therefore, should make investigators aware of potential psychiatric symptoms in humans. A final intriguing lesson of the clearly drug-related and fully

reversible pseudo-hallucinations in this study was, that the H3R system could be an interesting new target for the development of novel antipsychotics. Moreover, there is an increasing interest in the therapeutic effect of psychomimetic agents targeted at other receptor systems, such as psilocybin (5HT_{2A}-partial agonist) and esketamine (NMDA-antagonist).^{33,34} It could be speculated that H3R-antagonists could serve a similar role in psychomimetic assisted psychotherapies.

In conclusion, this study demonstrates how the PD of a novel compound can be investigated in early phase clinical trials. The findings of this study contribute to the field of knowledge about H3R pharmacology and delineate its complexity as already described by others.³⁵ This knowledge can be used for the future development of compounds targeted at the H3R, including potential antipsychotics or therapeutic psychomimetics.

AUTHOR CONTRIBUTIONS

Rob G.J.A. Zuiker, Jules A.A.C. Heuberger, Kawita M.S. Kanhai, Thierry Duvauchelle, Jeanne-Marie Lecomte, Jean-Charles Schwartz, and Joop M.A. van Gerven contributed to the study design. Rob G.J.A. Zuiker, Jules A.A.C. Heuberger, Kawita M.S. Kanhai, and Joop M.A. van Gerven contributed to the acquisition of data. All authors contributed to analysis and interpretation of data, drafting and review of the manuscript.

CONFLICT OF INTEREST STATEMENT

T.D., J.L., O.L., L.L., X.L., P.R., M.C. and J.S. are current or former employees of Bioprojet Pharma and may own stock or stock options. The other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data collected in this study are proprietary to Bioprojet Pharma. Bioprojet Pharma is committed to public sharing of data in accordance with applicable regulations and laws.

ORCID

Francis M. Dijkstra  <https://orcid.org/0000-0001-5804-0708>

Rob G. J. A. Zuiker  <https://orcid.org/0000-0001-5604-0157>

Jules A. A. C. Heuberger  <https://orcid.org/0000-0001-7202-5088>

Kawita M. S. Kanhai  <https://orcid.org/0000-0002-4503-6467>

Thierry Duvauchelle  <https://orcid.org/0000-0002-4762-588X>

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