A Single-Dose, Randomized, Open-Label, Parallel Design Study to Characterize the Pharmacokinetics of an Investigational Olanzapine Intranasal Spray Compared to a Reference Dose of Olanzapine Intramuscular Injection in Healthy Adult Males

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Abstract

Objective: Injectable olanzapine for acute agitation in psychiatric disorders is limited to delivery by health care professionals in supervised settings. Intranasal (IN) administration offers a potential needle-free route of delivery with favorable pharmacokinetics and patient experience, including the possibility of self-administration in community settings. Two IN formulations of olanzapine containing the permeation enhancer dodecyl maltoside (DDM) were assessed, with intramuscular (IM) olanzapine as a reference.

Methods: In this randomized phase 1 trial (conducted October 2023), healthy volunteers (N = 24) were randomized 1:1:1 to receive 1 dose of IN olanzapine 7.5 mg + 0.25% DDM, IN olanzapine 7.5 mg + 0.50% DDM, or olanzapine 7.5 mg IM. Plasma olanzapine concentrations were measured over time, and safety and tolerability were assessed.

Results: Mean peak plasma olanzapine concentrations were 31.5, 32.3, and 20.5 ng/mL for 0.25% and 0.50% DDM sprays and IM dosing, respectively. Median times to peak plasma concentration were 4.8, 10.2, and 37.8 minutes. After a single dose of the 0.25% and 0.50% DDM formulations, bioavailability was 88.8% and 83.3% of a single IM dose. All reported treatment-emergent adverse events were mild, transient, and deemed possibly related to the study drug, with the most frequent being sedation (n = 24) and nasal discomfort lasting seconds (n = 16, IN treatments). Nasal irritation scores were grade 0 (no sign of nasal irritation or mucosal erosion), and suicide risk assessment was negative for all time points.

Conclusion: Two novel investigational IN formulations of olanzapine containing the permeation enhancer DDM showed favorable pharmacokinetics and an acceptable safety profile presenting no unexpected signals in healthy adults. Continued study is warranted.

Trial Registration: ClinicalTrials.gov identifier: NCT06600477.

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Acute agitation is a common clinical management issue most recently defined in the glossary contained in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), as "excessive motor activity associated with a feeling of inner tension" and nonproductive, repetitive behaviors.[1] Acute agitation is a unique state but may on occasion evolve into aggression or violence[2] and thus requires prompt treatment to avert escalation. It is also distressing to patients,[3] who are at risk of harming themselves or others. Acute agitation may occur in a range of settings from emergency departments (EDs), inpatient psychiatric

Clinical Points

- Intramuscular treatments are available for the treatment of acute agitation in supervised settings; however, there is an unmet clinical need for noninvasive treatment that can be used by patients or caregivers in the community. A nasally administered spray has the potential to offer a new option.
- Formulations of an investigational nasal spray of olanzapine to treat acute agitation were generally safe in healthy volunteers and led to drug levels in the blood similar to levels after intramuscular injection. Continued study of olanzapine nasal spray is planned.

units, long-term care, and community settings.[3–5] In the US, an estimated ~2 million ED visits annually involve agitation.[6] In one study[7] at an urban county ED, the overall prevalence of agitation was 2.6%, where it was associated with alcohol and drug use, medical conditions, and psychiatric conditions. Although most patients with psychiatric disorders are not violent, schizophrenia and bipolar disorder can increase the risk of violence.[8] In 1 psychiatric ED, aggression was present in 26% of patients.[9]

Treatment guidelines for acute agitation support a flexible approach that combines observation and verbal de-escalation techniques with pharmacologic intervention when needed, with patient consent being critical.[4,6,10,11] Current pharmacologic formulations approved by the US Food and Drug Administration (FDA) for agitation associated with schizophrenia (with most also approved for agitation associated with bipolar disorder) include intramuscular (IM) aripiprazole, olanzapine, and ziprasidone; inhaled loxapine; and dexmedetomidine sublingual film.[2,12] These formulations provide rapid drug action but require trained staff in controlled settings for administration, and some routes of administration can be perceived as coercive and carry a risk of needlestick and other injuries to health care staff or the individual. There remains an unmet clinical need for noninvasive treatment options that support verbal de-escalation strategies and can be used by patients or caregivers in the community, with a result of decreased ED visits and potentially associated lower costs.

Intranasal (IN) delivery is currently used in clinical care for several acute treatments targeting the central nervous system.[2] IN formulations offer relatively rapid onset, avoidance of first-pass metabolism, and good bioavailability, possibly resulting in reduced dose-related side effects.[2] Potential patient benefits include noninvasive ease of delivery in community settings and patient experience, including ability for self-administration.[2] IN formulations are specifically designed to address the challenges of the anatomy and physiology of the nose, including the addition of excipients to increase drug solubility or mucosal absorption.[13] One example is the alkylsaccharide excipient dodecyl maltoside (DDM; Intravail A3), which acts to transiently open tight cell junctions and disrupt cell membranes in the nasal mucosa and promotes systemic bioavailability. It is Generally Recognized as Safe (GRAS) for oral administration and has been shown to be generally nonirritating to the nose.[14] It is a component of the immediate-use seizure medication diazepam nasal spray for the treatment of seizure cluster in epilepsy,[15] sumatriptan nasal spray for migraine,[16] epinephrine for anaphylaxis,[17] and nalmefene nasal spray for opioid overdose.[18]

To address the treatment gap for a noninvasive, easy-to-use treatment for acute agitation with adequate safety and tolerability, and potentially, a more rapid onset of action, an IN formulation of olanzapine that includes the FDA-accepted excipient DDM is in development. The primary objective of this phase 1 study was to characterize the pharmacokinetics of 2 IN formulations of olanzapine plus DDM relative to a clinically available olanzapine IM formulation. The secondary objective was to assess the safety and tolerability of the formulations.

METHOD

The study (NCT06600477) used an open-label, randomized, single-dose, parallel design to assess the pharmacokinetics and safety of IN olanzapine 7.5 mg + 0.25% DDM and olanzapine 7.5 mg + 0.5% DDM in healthy male adults. A commercially available IM formulation of olanzapine 7.5 mg served as the reference. The concentrations of DDM were determined based on previous preclinical and clinical studies.[19]

Study Participants and Interventions

Participants were healthy males, aged 18–55 years, and nonsmokers or ex-smokers, as olanzapine metabolism is mediated by CYP1A2, which is induced by the polycyclic aromatic hydrocarbons found in cigarette smoke.[20,21] Exclusion criteria included a history of a major health condition, including asthma, sinusitis, cardiovascular, and psychiatric disorder, specifically schizophrenia, schizoaffective disorder, bipolar I disorder, or major depressive disorder; a history of suicide attempt or at significant risk for suicide, violence, or homicide; and any acute (≥2 weeks) intranasal problems (eg, common cold or hay fever) or history of nasal pathology, surgery, disorders, or abnormality that might affect intranasal spray administration and absorption.

The study was conducted in October 2023 at the International Pharmaceutical Research Center (IPRC, Amman, Jordan) clinic site in accordance with the Declaration of Helsinki and in compliance with the International Committee on Harmonisation tripartite guidelines. The institutional review board of the IPRC

granted approval for the study, and written informed consent was obtained from each participant prior to study screening.

Enrolled participants were randomized to 1 of the 3 treatments in equal proportions. A single dose was administered by study staff to fasted participants on study day 1. Prior to IN administration, participants' nasal cavities were examined for any obstructions, and after administration, the nose was examined for dripping of drug solution. The IN formulations were delivered as a single spray in 1 nostril. IM administration in this experimental context was to the gluteal muscle. Assessments of nasal irritation, sedation, and pain related to injection were carried out at baseline and at regular intervals after drug administration. Blood samples were collected for plasma olanzapine concentration assay immediately before drug administration at 0 hour (predose) and at 5, 10, 15, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 4, 8, 12, 24, 36, 48, 72, 96, 144, 192, and 240 hours after administration. Plasma olanzapine concentration was assayed using a liquid chromatography-tandem mass spectrometry (Agilent, Waldbronn, Germany [liquid chromatography]; Applied Biosystems Sciex, Toronto, Canada [mass spectrometry]) developed at the IPRC and validated in accordance with FDA guidelines.[22]

Treatment-emergent adverse events (TEAEs) were collected, summarized, and reviewed throughout the study and included any TEAE, serious TEAE (SAEs), treatment-related TEAE, treatment-related SAEs, discontinuations, and deaths. Nasal irritation for IN formulations was assessed by trained professional observers using a 6-point scoring system of the nasal mucosa (ie, grade 0, no sign of nasal irritation or mucosal erosion; grade 1A, focal nasal mucosal irritation or inflammation; grade 1B, superficial mucosal erosion; grade 2, moderate mucosal erosion; grade 3, ulceration; grade 4, septal perforation). Pain from the IM administration was assessed by participants using an 11-point numeric rating scale (0–10), with 0 representing "no pain" and 10 signifying "worst pain imaginable." For all formulations, sedation was assessed using a previously published 6-point system by participants (if awake) and trained staff (ie, grade 0: alert, not drowsy, normal conversation; grade 1: awake, talking, but somewhat drowsy; grade 2: napping or sleeping, but easily awakened; grade 3: sleeping, awaken only with loud voice or shaking; grade 4: sleeping, very difficult to awaken, promptly returns to sleep; grade 5: sleeping, cannot awaken).[23,24] Suicidal ideation and behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS).[25] Blood pressure and heart rate were assessed at baseline, hourly from 1 to 8 hours, and 11 and 24 hours following administration; body temperature and respiratory rate were measured at baseline and 4 and 24 hours. Complete physical examination, clinical laboratory tests, and electrocardiogram were also performed at screening/baseline and at day 11 follow-up.

Pharmacokinetic Evaluation and Statistical Analyses

Pharmacokinetic parameters were estimated using standard noncompartmental methods, with peak plasma olanzapine concentration (C_{max}) and time to peak concentration (T_{max}) taken directly from measured data. The area under the curve from time zero to the last measurable concentration (AUC_{0-t}) was calculated from measured data points by the linear trapezoidal rule, and elimination half-life ($t_{1/2}$) was calculated as the slope of the linear regression of the ln-transformed plasma concentrations in the terminal period of the curve. Missing data for drug concentrations were not included in calculations, and any value below the lower limit of quantitation was treated as zero.

Statistical analyses were performed using WinNonlin Statistical Software, v8.3.4 (Certara, Inc, Princeton, NJ). Statistical evaluation of pharmacokinetic parameters included an analysis of variance of ln-transformed C_{max}, AUC_{0-t}, AUC extrapolated to infinity ($AUC_{0-\infty}$), and calculation of formulations ratios (point estimates) to assess the effect of DDM concentration on pharmacokinetic parameters. Treatment effects were tested at a significance level of 0.05. For the parametric analysis of bioequivalence, as recommended by Steinijans and Diletti,[26] the 90% CI for the ratio of the IN and IM formulations was calculated for ln-transformed C_{max} (reflecting rate of absorption), AUC_{0-t} (defining extent of absorption), and $AUC_{0-\infty}$. No formal determination of sample size was undertaken for this study; 24 participants were deemed adequate to obtain meaningful pharmacokinetic results.

RESULTS

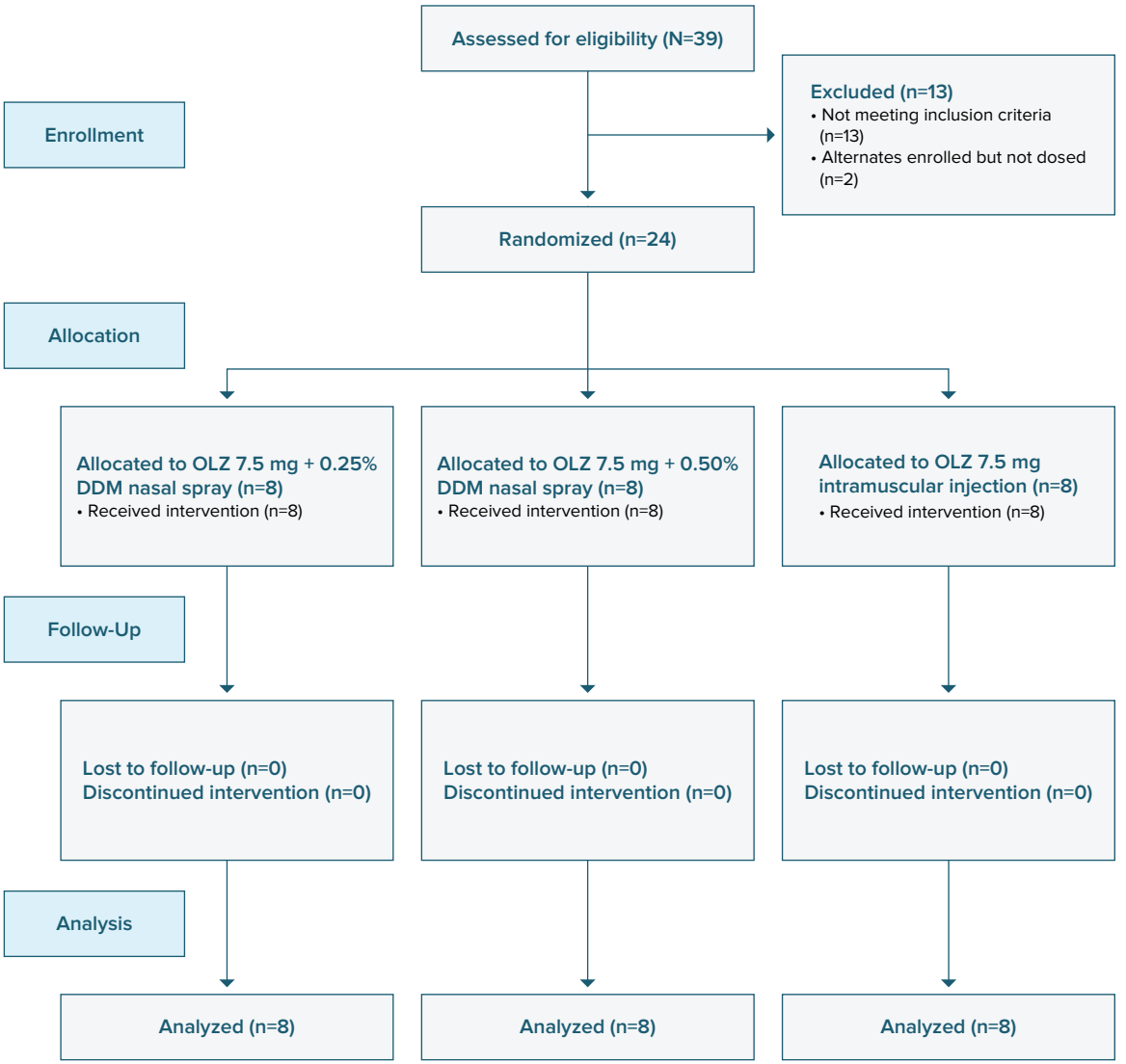
Disposition and Demographics

A total of 39 participants were screened, with 13 failing screening (Figure 1). Two participants were screened and enrolled as alternates. The remaining 24 participants were enrolled, dosed, and completed the study. The alternate participants were not required as replacements and thus were excluded as per protocol. All participants (N = 24) were male, Middle Eastern, and nonsmokers, with a mean age (SD) of 34.8 (7.0) years and a mean BMI (SD) of 26.2 (2.1) kg/m^2.

Pharmacokinetics

Mean plasma olanzapine concentration vs time plots (0–2 hours and 0–240 hours, Figure 2) showed a rapid rise in plasma drug concentrations following nasal administration of both DDM-containing formulations,

Figure 1.
CONSORT Participant Flow Diagram



Abbreviations: DDM = dodecyl maltoside, OLZ = olanzapine.

with comparable mean peak plasma concentration (C_{max}) of ~30 ng/mL (Table 1). Peak mean plasma concentration with IM administration was ~20 ng/mL. Median time to peak plasma concentration (T_{max}) was 0.08 hour (~5 minutes) and 0.17 hour (~10 minutes) with the 0.25% and 0.50% DDM formulations, respectively, while median T_{max} with IM administration was 0.63 hour (~38 minutes). The plasma olanzapine concentrations with all formulations were similar at times >2 hours after administration. Bioequivalence assessments using a parametric approach showed that the IN formulations resulted in a faster rate of absorption and a ~1.5-fold higher mean C_{max} and a short median T_{max}, relative to IM olanzapine (Table 2). The extent of absorption, measured by $AUC_{0-\infty}$, was 88.8% and 83.3% for the 0.25% and 0.50% DDM formulations, respectively, of that measured with IM administration.

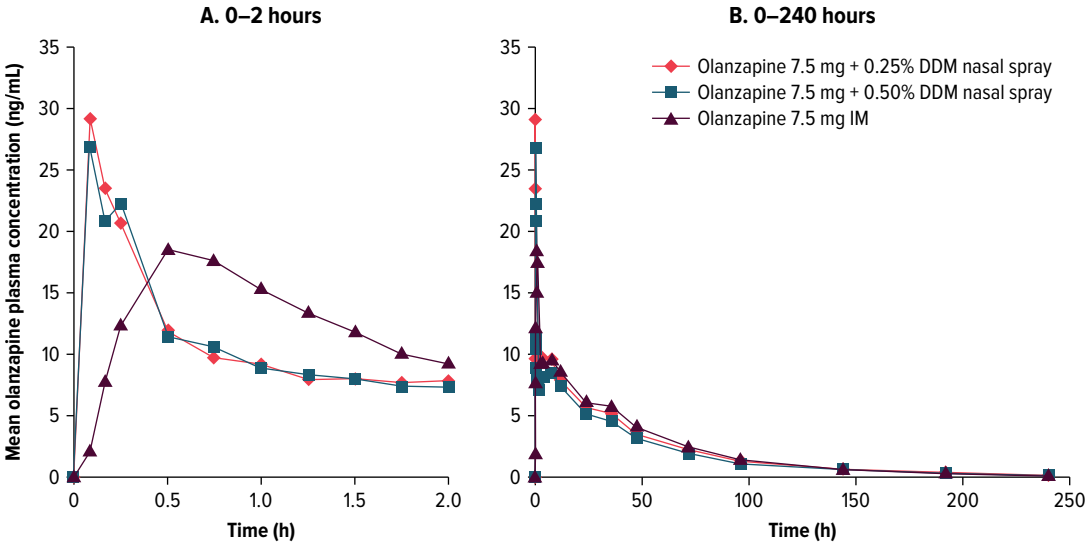
Safety

There were a total of 40 TEAEs reported; 24 participants (100%) had ≥1 TEAE (Table 3). TEAEs in ≥2 participants consisted of sedation and nasal discomfort. All TEAEs were mild in severity and deemed as possibly related to the study drug by the investigator. No moderate or severe TEAEs were reported in any participant. There were no deaths, no SAEs, and no TEAEs that resulted in study discontinuation.

All 24 participants experienced maximal sedation between grade 2 (napping or sleeping, but easily awakened) and grade 4 (sleeping, very difficult to

Figure 2.

Mean Plasma Olanzapine Concentration–Time Profiles



Abbreviations: DDM = dodecyl maltoside, IM = intramuscular.

Table 1.

Pharmacokinetic Parameters (Mean ± SD) of 2 Intranasal Olanzapine Formulations and Reference IM Formulation

Parameter	OLZ + 0.25% DDM nasal spray (n = 8)	OLZ + 0.50% DDM nasal spray (n = 8)	IM OLZ (n = 8)
C_{max} (ng/mL)	31.5 ± 11.3	32.3 ± 18.8	20.5 ± 6.7
AUC_{0-t} (ng·h/mL)	509.8 ± 185.9	463.5 ± 74.6	568.1 ± 183.7
$AUC_{0-\infty}$ (ng·h/mL)	526.5 ± 197.3	474.9 ± 75.8	591.8 ± 197.1
T_{max}[a] (h)	0.08 (0.08–0.17)	0.17 (0.08–0.25)	0.63 (0.50–1.00)
$T_{1/2}$ (h)	47.7 ± 11.3	48.2 ± 6.8	55.1 ± 12.6

[a]Median (range).
Abbreviations: AUC_{0-t} = area under the curve from time zero to the last measurable concentration, $AUC_{0-\infty}$ = area under the curve extrapolated to infinity, C_{max} = peak plasma concentration, DDM = dodecyl maltoside, IM = intramuscular, OLZ = olanzapine, T_{max} = time to reach maximum plasma concentration, $T_{1/2}$ = elimination half-life.

awaken, promptly returns to sleep), with no apparent differences between the IN and IM groups (Figure 3). Highest scores were grade 2 in 4 participants (16.7% overall), grade 3 in 13 participants (54.2%), and grade 4 in 7 participants (29.2%). Sedation resolved in all participants within 24 hours.

Mild, transient nasal discomfort lasting seconds was reported in all 16 participants in the IN groups. All nasal discomfort TEAEs resolved by the time of discharge from the clinical research unit. Nasal irritation assessment scores were grade 0 (no sign of nasal irritation or mucosal erosion) in all participants who received an IN dose at all time points assessed. There were no reports of epistaxis, nasal discharge, or sneezing during the study.

There were no clinically significant abnormalities for any laboratory parameter or clinically significant changes from baseline. There were also no clinically significant abnormal vital sign measurements and no clinically significant changes from baseline, including any significant hypotension.

C-SSRS results were negative for all participants at all time points.

DISCUSSION

Intranasal delivery of central nervous system drugs offers the potential for favorable pharmacokinetics and

Table 2.

Bioequivalence CIs, Power, and Interparticipant Variability of IN Olanzapine Formulations vs Reference IM Formulation

Parameter	IM OLZ Geo LSM	OLZ nasal spray Geo LSM	Point estimate (%)	90% CI lower limit	90% CI upper limit	Interparticipant CV%	Power%
OLZ + 0.25% DDM nasal spray vs IM OLZ							
C_{max}	19.6	29.7	151.5	111.3	206.2	36.1	32.2
AUC_{0-t}	541.8	485.1	89.5	67.0	119.7	33.9	34.9
$AUC_{0-\infty}$	562.9	499.7	88.8	66.0	119.5	34.7	33.8
OLZ + 0.50% DDM nasal spray vs IM OLZ							
C_{max}	19.6	28.4	145.1	99.1	212.3	45.3	24.6
AUC_{0-t}	541.8	457.6	84.5	66.7	106.9	27.2	46.6
$AUC_{0-\infty}$	562.9	469.0	83.3	65.6	105.9	27.7	45.6

Abbreviations: AUC_{0-t} = area under the curve from time zero to the last measurable concentration, $AUC_{0-\infty}$ = area under the curve extrapolated to infinity, CI = confidence interval, C_{max}=peak plasma concentration, CV% = coefficient of variation (%), DDM = dodecyl maltoside, Geo LSM = geometric least squares mean, IM = intramuscular, IN = intranasal, OLZ = olanzapine.

Table 3.

Safety Summary[a]

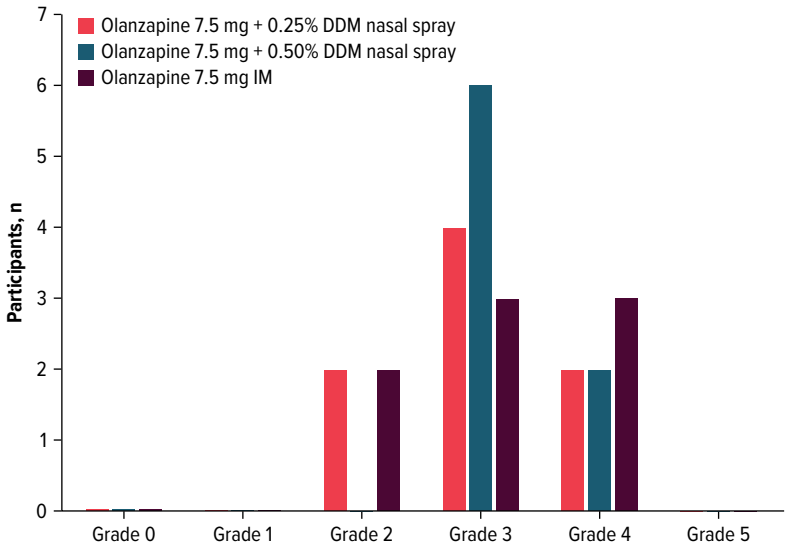
	OLZ + 0.25% DDM nasal spray (n = 8)	OLZ + 0.50% DDM nasal spray (n = 8)	IM OLZ (n = 8)
Any TEAE	8 (100)	8 (100)	8 (100)
Mild	8 (100)	8 (100)	8 (100)
Moderate or severe	0	0	0
Serious TEAE	0	0	0
Treatment-related TEAE	8 (100)	8 (100)	8 (100)
TEAE leading to discontinuation	0	0	0
TEAE resulting in death	0	0	0
Most frequent TEAEs (≥2 participants)			
Sedation	8 (100)	8 (100)	8 (100)
Nasal discomfort	8 (100)	8 (100)	0

[a]Data are n (%).
Abbreviations: DDM = dodecyl maltoside, IM = intramuscular, OLZ = olanzapine, TEAE = treatment-emergent adverse event.

bioavailability along with good safety and positive patient attributes (eg, noninvasive, with potential for self-administration), which may be beneficial during the treatment of acute agitation. We have assessed for the first time the pharmacokinetics and safety of a novel investigational nasal spray containing the atypical antipsychotic olanzapine plus a permeation enhancer, DDM. When comparing the pharmacokinetic parameters of olanzapine nasal spray and IM injection formulations, the IN formulation resulted in a higher rate of absorption with a higher (~l. 5-fold) mean C_{max} and a short median T_{max} relative to the IM injection formulation, supporting a potential for the IN formulation to be a favorable option. The extent of absorption (as measured by $AUC_{0-\infty}$) following a single dose of IN formulation with 0.25% DDM or 0.50% DDM was comparable with the IM injection formulation (~89% and 83%, respectively), bolstering an expectation of similar long-term safety with both IN and IM formulations. Results showed the IN formulations to be generally safe and well tolerated with no SAEs and no unexpected TEAEs.

Both nasal spray formulations resulted in favorable pharmacokinetics, with the 0.25% DDM formulation associated with the faster T_{max}, a comparable C_{max}, and higher overall exposure, AUC, of the 2 IN formulations. When testing for bioequivalence with olanzapine IM, the 0.25% DDM formulation resulted in a higher point estimate for C_{max} and better comparative bioavailability. The slightly higher and faster drug absorption seen with the 0.25% DDM formulation aligns with the 0.1%–0.2% formulation range reported elsewhere for alkylsaccharide absorption enhancers[19] and potentially suggests a dose-limiting effect on absorption with DDM. At the same time, alkylsaccharides have been tested in the Draize test at concentrations up to 25% and have been shown to be safe, nontoxic, and nonsensitizing.[19]

Figure 3.
Sedation Assessment by Maximum Severity



Grade	Sedation severity
0	Alert, not drowsy, normal conversation
1	Awake, talking, but somewhat drowsy
2	Napping or sleeping, but easily awakened
3	Sleeping, awakened only with loud voice or shaking
4	Sleeping, very difficult to awaken, promptly returns to sleep
5	Sleeping, cannot awaken

Abbreviations: DDM = dodecyl maltoside, IM = intramuscular.

The safety profile in this group of healthy volunteers was favorable, with TEAEs being mild, transient, and consistent with olanzapine and nasal delivery. The safety profiles were comparable between the two 7.5-mg nasal spray formulations. No unexpected TEAEs were observed, and there were no SAEs or TEAEs leading to discontinuation. Somnolence was similar between IN and IM formulations, and there was no observed nasal irritation with IN administration. All TEAEs resolved by study completion. As expected with olanzapine in an antipsychotic-naive population, sedation was reported by all patients but with no differences between those receiving the IN and IM formulations. There was no noted hypotension and no signals of suicide risk. Nasal discomfort was minimal and transient, as was seen in the long-term, repeat-dose safety study of intermittent-use diazepam nasal spray with DDM,[27] in which no evidence of olfactory changes and no impact of seasonal allergies/rhinitis were observed.[28] There were no reports of epistaxis, nasal discharge, or sneezing.

The pharmacokinetic profiles for the IN olanzapine formulations indicated improved absorption kinetics with similar overall drug exposure as with olanzapine IM. These profiles reasonably suggest a potentially improved therapeutic profile and comparable safety profile for the IN formulations compared with studies of the IM formulation, including sustained effect over time.[29–32] In one pivotal trial, inpatients with agitation meeting *DSM-IV* criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder received a single dose of olanzapine 10 mg IM or placebo. At 2 hours after injection, olanzapine was statistically superior to placebo in reducing agitation as measured by mean (SD) decreases on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC), −7.7 (6.1) vs −3.6 (5.2; $P < .05$).[29] Significant differences were observed starting at 15 minutes, the first measured time point after dosing. Statistically superior reductions in PANSS-EC have also been observed with a single 10-mg IM dose, vs placebo, when tested in agitated inpatients meeting *DSM-IV* criteria for bipolar I disorder.[31] Similarly, lower doses, 2.5 mg and 5 mg, tested in acutely agitated patients with dementia were also statistically superior to placebo.[32] In these studies, repeat dosing rates of ~25% were reported with 10-mg IM dosing.[30,31]

Outpatients experiencing acute agitation may present to the ED for treatment, and when nonpharmacologic interventions are insufficient, parental formulations may be used. They remain the most appropriate choice in some patients, such as patients with severe agitation who may be less receptive to participating in administration. At the same time, a large proportion of agitation episodes treated in psychiatric EDs involve restraint or seclusion, suggesting that there may be an opportunity to treat some episodes at an earlier, lower-acuity stage with less coercive, needle-free interventions,[33] potentially prior to arrival in an acute health care setting. In a study of community-dwelling patients with schizophrenia or bipolar disorder, 71% were always or sometimes aware of becoming agitated, and over half (55% of patients with schizophrenia, 66% with bipolar disorder) reported taking prescribed medications to cope with an episode.[3]

The noninvasive, investigational olanzapine nasal spray formulation tested here represents a potentially substantial step forward in treatment options for acute agitation. Olanzapine is extensively studied and was identified in a

systematic review and meta-analysis as among the most efficacious and safe treatments for agitation.[34] The unidose nasal delivery system that is part of the investigational formulation is familiar and widely used to delivery therapy for acute conditions of the central nervous system, such as migraine, opioid overdose, and seizure cluster in epilepsy.[15–17] The system is easy to learn and to use for both health care professionals and community members,[35,36] and it can be self-administered or administered by a caregiver/care partner in the community setting.

Investigations into a powdered formulation of olanzapine support our findings of favorable pharmacokinetics with IN delivery. Powdered olanzapine is being tested in a drug-device combination for IN delivery.[37] The device is a handheld investigational administration device that requires a gas cartridge to propel powder into the nasal cavity following manual activation. A phase 1 pharmacokinetic dose-escalating study (5-, 10-, and 15-mg olanzapine) found similar exposure with the powder formulation and equivalent doses of the IM formulation. Median T_{max} was 9.5–15 minutes with powdered olanzapine, with increasing time associated with lower doses. The incidence of TEAEs was 67%–80%, with the most common (>2 patients across all groups receiving powdered olanzapine) being dizziness (including postural dizziness), orthostatic symptoms, and nasal congestion.

As is common with phase 1 pharmacokinetic studies involving healthy participants, the results observed here have limited generalizability to the potential target population of patients with schizophrenia or bipolar disorder who experience acute agitation. In terms of safety, the study did not specifically assess for orthostatic hypotension (ie, vital signs were not measured under orthostatic stress). Orthostatic hypotension has been associated with antipsychotic treatments[38] and may occur with olanzapine, particularly during initial dose titration.[39] Investigation is needed to further characterize the use of olanzapine nasal spray in patients with psychiatric conditions.

In conclusion, a gap remains for rapid, noninvasive, noncoercive treatment options for acute agitation that may be used in both the hospital and the community. A novel investigational IN formulation of olanzapine containing the permeation enhancer DDM has favorable pharmacokinetics with higher maximum plasma concentration and shorter time to maximum concentration that suggest a potentially favorable therapeutic effect profile in reference to the commercially available IM formulation. This, along with an acceptable safety profile in healthy adults, supports the continued study of this IN formulation of olanzapine with DDM.

Article Information

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*. American Psychiatric Publishing; 2013.

2. Citrome L, Correll CU, San L, et al. Alternative approaches for addressing acute agitation in schizophrenia and bipolar disorder. *Prim Care Companion CNS Disord*. 2024;26(1):23nr03596.
3. Roberts J, Gracia Canales A, Blanthorn-Hazell S, et al. Characterizing the experience of agitation in patients with bipolar disorder and schizophrenia. *BMC Psychiatry*. 2018;18(1):104.
4. Garriga M, Pacchiarotti I, Kasper S, et al. Assessment and management of agitation in psychiatry: expert consensus. *World J Biol Psychiatry*. 2016;17(2): 86–128.
5. Fillit H, Aigbogun MS, Gagnon-Sanschagrin P, et al. Impact of agitation in long-term care residents with dementia in the United States. *Int J Geriatr Psychiatry*. 2021;36(12):1959–1969.
6. Holloman GH Jr, Zeller SL. Overview of project BETA: best practices in evaluation and treatment of agitation. *West J Emerg Med*. 2012;13(1):1–2.
7. Miner JR, Klein LR, Cole JB, et al. The characteristics and prevalence of agitation in an urban county emergency department. *Ann Emerg Med*. 2018;72(4):361–370.
8. Correll CU, Yu X, Xiang Y, et al. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. *Ann Clin Psychiatry*. 2017;29(2):92–107.
9. Dhossche DM, Ghani SO. Who brings patients to the psychiatric emergency room? Psychosocial and psychiatric correlates. *Gen Hosp Psychiatry*. 1998;20(4):235–240.
10. Baldacara L, Ismael F, Leite V, et al. Brazilian guidelines for the management of psychomotor agitation. Part 1. Non-pharmacological approach. *Braz J Psychiatry*. 2019;41(2):153–167.
11. Patel MX, Sethi FN, Barnes TR, et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: de-escalation and rapid tranquillisation. *J Psychopharmacol*. 2018;32(6):601–640.
12. Faden J, Citrome L. Examining the safety, efficacy, and patient acceptability of inhaled loxapine for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. *Neuropsychiatr Dis Treat*. 2019;15:2273–2283.
13. Chung S, Peters JM, Detyniecki K, et al. The nose has it: opportunities and challenges for intranasal drug administration for neurologic conditions including seizure clusters. *Epilepsy Behav Rep*. 2023;21:100581.
14. Rabinowicz AL, Carrazana E, Maggio ET. Improvement of intranasal drug delivery with Intravail® alkylsaccharide excipient as a mucosal absorption enhancer aiding in the treatment of conditions of the central nervous system. *Drugs R D*. 2021; 21(4):361–369.
15. VALTOCO® (diazepam nasal spray). Full Prescribing Information. Neurelis Inc. 2023.
16. TOSYMRA® (sumatriptan). Full Prescribing Information. Upsher-Smith Laboratories, LLC. 2021.
17. Neffy (epinephrine nasal spray). Full Prescribing Information. ARS Pharmaceuticals Operations, Inc. 2024.
18. Opvee (nalmefene nasal spray). Full Prescribing Information. Indivior Inc. 2023.
19. Maggio ET, Pillion DJ. High efficiency intranasal drug delivery using Intravail® alkylsaccharide absorption enhancers. *Drug Deliv Transl Res*. 2013;3(1):16–25.
20. Schoretsanitis G, Kane JM, Correll CU, et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie. *J Clin Psychiatry*. 2020; 81(3):19cs13169.
21. Horvat M, Kadija M, Scavnicar A, et al. Association of smoking cigarettes, age, and sex with serum concentrations of olanzapine in patients with schizophrenia. *Biochem Med (Zagreb)*. 2023;33(3):030702.
22. US Food and Drug Administration. *Bioanalytical Method Validation Guidance for Industry*. US Food and Drug Administration; 2018.
23. Agarwal SK, Kriel RL, Brundage RC, et al. A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers. *Epilepsy Res*. 2013;105(3):362–367.
24. Hogan RE, Gidal BE, Koplowitz B, et al. Bioavailability and safety of diazepam intranasal solution compared to oral and rectal diazepam in healthy volunteers. *Epilepsia*. 2020;61(3):455–464.
25. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277.
26. Steinijans VW, Diletti E. Statistical analysis of bioavailability studies: parametric and nonparametric confidence intervals. *Eur J Clin Pharmacol*. 1983;24(1):127–136.
27. Wheless JW, Miller I, Hogan RE, et al. Final results from a phase 3, long-term, open-label, repeat-dose safety study of diazepam nasal spray for seizure clusters in patients with epilepsy. *Epilepsia*. 2021;62(10):2485–2495.
28. Vazquez B, Wheless J, Desai J, et al. Lack of observed impact of history or concomitant treatment of seasonal allergies or rhinitis on repeated doses of diazepam nasal spray administered per seizure episode in a day, safety, and tolerability: interim results from a phase 3, open-label, 12-month repeat-dose safety study. *Epilepsy Behav*. 2021;118:107898.
29. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry*. 2001;158(7):1149–1151.
30. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry*. 2002;59(5):441–448.
31. Meehan K, Zhang F, David S, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol*. 2001;21(4):389–397.
32. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology*. 2002;26(4): 494–504.
33. San L, Marksteiner J, Zwanzger P, et al. State of acute agitation at psychiatric emergencies in Europe: the STAGE study. *Clin Pract Epidemiol Ment Health*. 2016; 12:75–86.
34. Bak M, Weltens I, Bervoets C, et al. The pharmacological management of agitated and aggressive behaviour: a systematic review and meta-analysis. *Eur Psychiatry*. 2019;57:78–100.
35. Santilli N, Dewar S, Guerra C, et al. Use of intranasal rescue therapy for seizure clusters in students with epilepsy: nurses' knowledge, perceptions, and practice. *Epilepsy Behav Rep*. 2023;22:100604.
36. Penovich PE, Buelow J, Steinberg K, et al. Burden of seizure clusters on patients with epilepsy and caregivers: survey of patient, caregiver, and clinician perspectives. *Neurologist*. 2017;22(6):207–214.
37. Shrewsbury SB, Hocevar-Trnka J, Satterly KH, et al. The SNAP 101 double-blind, placebo/active-controlled, safety, pharmacokinetic, and pharmacodynamic study of INP105 (nasal olanzapine) in healthy adults. *J Clin Psychiatry*. 2020;81(4): 19m13086.
38. Bhanu C, Nimmons D, Petersen I, et al. Drug-induced orthostatic hypotension: a systematic review and meta-analysis of randomised controlled trials. *PLoS Med*. 2021;18(11):e1003821.
39. Zyprexa (olanzapine). Full Prescribing Information. Lilly USA; 2021.