A Randomized Phase 1 Safety Study of Repeated Doses of Intranasal OP0201 Metered Dose Inhaler Compared to Placebo in Healthy Adults: A Potential Treatment for Otitis Media

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Abstract

Background OP0201 Nasal Aerosol is a novel drug-device surfactant product being developed for treatment and prevention of otitis media. The active ingredients in OP0201, dipalmitoylphosphatidylcholine (DPPC) and cholesteryl palmitate (CP), are endogenous to the human nasal and respiratory systems. This phase 1 study evaluated the safety and tolerability of OP0201 in healthy adults.

Methods This was a randomized, double-blind, placebo-controlled, parallel-group study with a dose-escalation cohort design to evaluate 30 mg/day (Cohort A) and 60 mg/day (Cohort B) of OP0201. Subjects were randomized 4:1 to receive either OP0201 or placebo 3 times per day for 14 consecutive days. Treatment was administered via a metered dose inhaler and sprayed directly backwards into each nostril. Primary endpoints were adverse events, otoscopy, tympanometry, nasal and epipharynx endoscopy, University of Pennsylvania Smell Identification Test (UPSIT), audiology pure-tone hearing test, 12-lead electrocardiography, physical examination, vital signs, and clinical laboratory tests. Exploratory endpoints included baseline-adjusted maximum serum concentration (Cmax) and time to maximum concentration (tmax) of DPPC and CP on Day 14 in Cohort B.

Results 101 participants were screened, and 30 were randomized (15 per cohort; n=12 OP0201, n=3 placebo). No deaths, serious adverse events, or treatment-emergent adverse events leading to study discontinuation were reported. No clinically significant deviations from baseline were found in any of the primary endpoints. Serum DPPC and CP concentrations on Day 14 were comparable to baseline in the OP0201 group and numerically higher in the placebo group. Mean baseline-corrected serum DPPC Cmax on Day 14 was 0.82 µg/mL with OP0201 and 4.51 µg/mL with placebo, with a median tmax observed at 0.05 hours for both groups. Mean baseline-corrected serum CP Cmax on Day 14 was 14.89 µM with OP0201 and 89.50 µM with placebo, with a median tmax observed at 0.05 and 0.22 hours for OP0201 and placebo, respectively.

Conclusions OP0201 was safe and well tolerated in healthy adults. There were no supraphysiologic systemic concentrations of DPPC or CP after local intranasal administration of a 60 mg/day dose of OP0201. These outcomes support continued development of OP0201 with future studies in a patient population.

Background

Otitis media, or inflammation of the middle ear, is a highly prevalent disorder and the most common disease seen in pediatric practices in the United States.[1,2] Otitis media can be classified as acute otitis media, with signs and symptoms of short-term ear infection including possible suppuration, or as otitis media with effusion, characterized by fluid in the middle ear without signs and symptoms of acute ear infection.[3] Worldwide, there are an estimated 700 million cases of acute otitis media diagnosed each year, with approximately half of cases occurring in children less than 5 years of age.[1]

An important underlying contributor to otitis media is Eustachian tube dysfunction.[3,4] The Eustachian tube is a compliant, liquid-lined tube connecting the middle ear to the nasopharynx.[4] The Eustachian tube functions to regulate pressure in the middle ear, clear fluid from the middle ear, and protect against pathogens in the nasopharynx.[3,5] Normally, the Eustachian tube is collapsed and opens occasionally, which equalizes pressure in the middle ear.[4] Eustachian tube dysfunction is often triggered by a viral infection of the upper respiratory system, which leads to diminished mucociliary clearance within the Eustachian tube and nasopharynx, and negative middle ear pressure.[3] The negative middle ear pressure promotes the transmission of pathogens into the middle ear and can result in otitis media.[3] Children are at increased risk of otitis media because of their immature immune systems and underdeveloped Eustachian tubes, which are shorter, floppier, and more horizontal than those of adults.[3]

OP0201 Nasal Aerosol is a novel, drug-device surfactant delivery product being developed by Novus Therapeutics, Inc., for the treatment and prevention of otitis media. OP0201 is a 20:1 fixed combination of dipalmitoylphosphatidylcholine (DPPC, a phospholipid surfactant) and cholesteryl palmitate (CP, a neutral phospholipid spreading agent) suspended in a chlorofluorohydrocarbon-free propellant (hydrofluoroalkane-134a [HFA 134a]). None of the ingredients contain animal or human derivatives, and both active ingredients are endogenous to the human Eustachian tube, nasopharynx, and respiratory system.[6–8] Together, the two active ingredients reduce the interfacial surface tension of the Eustachian tube, which reduces the pressure required to passively open the Eustachian tube and restores normal functioning of the Eustachian tube.[4,9] Animal studies related to this product have been previously described.[4,10,11] OP0201 is administered intranasally via a metered dose inhaler. It is supplied in mechanical packaging parts that include a pressurized canister with a securely attached metering valve where the drug product is contained, an actuator into which the canister is seated, the valve that connects with the device body, and a tip to deliver the drug to the nostril. This phase 1 trial evaluated the safety and tolerability of OP0201 administered 3 times daily for 14 consecutive days in healthy adults.

Methods

Study Design

This study was a phase 1, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation trial in healthy adults at a single center (Altasciences/Vince and Associates, Overland Park, KS, USA) (Fig. 1). The trial was approved by MidLands Independent Review Board (Overland Park, Kansas) and complied with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent before any study-related procedure took place. This study adheres to CONsolidated Standards of Reporting Trials (CONSORT) guidelines.

Subjects

Eligible subjects were healthy adults aged 18–50 years who were willing and able to provide informed consent, had a body mass index of 18–30 kg/m^2 and weighed at least 50 kg, agreed to the use of contraception and to refrain from submerging their head fully underwater during the study, and had a physiologic tympanogram classified as Type A (normal).

Subjects were excluded if they: had a history of a significant medical condition; had a clinically significant abnormal olfactory test finding at Screening, defined as a total University of Pennsylvania Smell Identification Test (UPSIT) score < 35 (for females) or < 34 (for males); had a current sleep apnea diagnosis; had a clinically significant ear disorder within 6 weeks; were pregnant or breastfeeding; or had a craniofacial anomaly or a disorder with decreased mucociliary clearance or higher viscosity of the mucus. Subjects were also excluded if they met any of the following criteria prior to Screening: tympanostomy tube placement (within 1 year); upper respiratory tract infection or pharyngitis, allergy or sinus condition or gastroesophageal reflux disease (within 6 weeks); tobacco/nicotine use (within 48 weeks); symptomatic herpes zoster eruptions (within 12 weeks); any malignancy (within 5 years) except for basal or squamous skin carcinomas adequately resected with no signs of metastasis for 3 years; breast cancer (within 10 years); receipt of live vaccine (within 30 days); use of medication (either topically or systemically) for ear or nose disorder (within 12 weeks); use of medication with anticholinergic side effects (within 6 weeks) or vasoconstrictive properties (within 2 weeks); or regular alcohol consumption (within 24 weeks).

Following the Screening period, eligible subjects who consented to participate were admitted to the study center for randomization and were domiciled until 1 day post-treatment (Fig. 1). Subjects had 1 follow-up visit at 5 days post-discharge before exiting the study.

Treatment

Two dose cohorts, Cohorts A and B, were enrolled. Subjects in each cohort were randomized 4:1 to receive either OP0201 or placebo. Study treatment was administered intranasally by site staff 3 times per day approximately 7 hours apart using a metered dose inhaler and included 2 (Cohort A) or 4 (Cohort B) sprays per nostril at each administration. In the OP0201 groups, subjects received a total dose of 30 mg or 60 mg per day of OP0201 in Cohort A or Cohort B, respectively. Subjects in the placebo group received the same propellant used in OP0201 without any active ingredients. During administration, OP0201 was sprayed directly backwards into each nostril by way of the anterior nostrils towards the lateral wall of the nasal cavity. After all subjects in Cohort A completed 14 days of treatment, a Safety Review Committee assessed blinded safety data to determine if treatment with OP0201 was well tolerated. The Safety Review Committee subsequently recommended escalation to Cohort B. The dose, number of sprays, and dosing interval for this study are expected to exceed those that will be tested in future studies, and thus establish a high safety threshold.

Outcome measures

Primary endpoints were adverse events and other safety and tolerability assessments made through otoscopy, tympanometry, nasal and epipharynx endoscopy, the UPSIT, audiology pure-tone hearing

testing, physical examination and measurement of vital signs, 12-lead electrocardiography, and clinical laboratory testing. Exploratory endpoints included baseline-adjusted maximum serum concentration (C_{max}) of DPPC and CP on Day 14 and time to maximum concentration (t_{max}) of DPPC and CP on Day 14.

Safety and tolerability assessments

Treatment-emergent adverse events (TEAEs) were defined as AEs that first occurred or worsened in severity after administration of study drug. The relationship of the TEAE to the study medication was evaluated by the Investigator.

Otoscopy, tympanometry, nasal and epipharynx endoscopy, olfactory testing, audiology pure-tone hearing testing, physical examination, measurement of vital signs, electrocardiography, and clinical laboratory testing were performed at various time points throughout the study. Otoscopy was performed to assess the appearance of the tympanic membrane for abnormalities in contour, color, fluid, or translucency. The overall otoscopy assessment was reported as normal or abnormal. Tympanometry was used to evaluate tympanic membrane mobility, Eustachian tube function, and middle ear function. Type A tympanograms were classified as normal; Types B and C were classified as abnormal.[12,13] Nasal and epipharynx appearance was assessed via endoscopy and reported as normal or abnormal. The length of the nasal cavity, defined as the distance from the tip of the nose to the entry point of the Eustachian tube, was included in the endoscopic assessments at baseline. The UPSIT was performed to identify potentially clinically significant conditions that could impact participation in the study. The UPSIT consists of 4 booklets, each containing 10 microencapsulated crystal odorants with accompanying multiple-choice smell identification questions.[14,15] UPSIT scores less than 35 or 34 were considered abnormal for females and males, respectively. Change from baseline in UPSIT score was captured as a TEAE. An audiology pure-tone hearing test was used to identify clinically significant abnormal hearing. Pure-tone hearing loss was evaluated at 4 frequencies (500, 1000, 2000, and 4000 Hz) with a fail criterion of > 20 dB hearing level at 1 or more frequencies in either ear. Vital signs recorded included sitting systolic and diastolic blood pressure, heart rate, respiration rate, and temperature. Electrocardiograms (ECGs) were collected to ensure that subjects did not have any condition that might present an unacceptable safety risk. Single 12-lead ECGs were collected from subjects in Cohort A; triplicate 12-lead ECGs were collected from subjects in Cohort B using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals. With the triplicate 12-lead ECGs, 3 individual ECG tracings were obtained within 4 minutes. Central laboratory assessments included hematology; clinical chemistry; coagulation; viral serology for HIV I and II, HBsAg, and Hepatitis C; and urinalysis.

Pharmacokinetic assessments

Blood samples for drug concentration and pharmacokinetic (PK) assessments were taken on Day 1 at 30 and 60 minutes prior to the first dose and Day 14 at 30 minutes prior to and 5, 20, 35, and 50 minutes after the last dose from subjects in Cohort B. Baseline samples collected from subjects were analyzed to establish the endogenous DPPC and CP concentrations, irrespective of treatment allocation.

Statistical methods

The sample size was considered adequate to characterize the distribution of the planned endpoints and was not based on statistical considerations. The entered analysis set was defined as all screened subjects who provided informed consent, including subjects who failed screening. The safety analysis set included all subjects who were assigned to a study treatment arm and received at least 1 dose of either OP0201 or placebo. The PK analysis set consisted of all subjects in Cohort B who received at least 1 dose of OP0201 and had at least 1 quantifiable serum DPPC or CP concentration collected post-dose without important protocol deviations/violations or events thought to significantly affect the pharmacokinetics.

No statistical comparisons were conducted between the treatment groups using the safety data. Baseline-corrected DPPC and CP serum levels for each subject were derived by subtracting the observed levels at sample time on Day 14 from the subject's mean baseline on Day 1 pre-dose. If the resulting value was negative, the estimated baseline-corrected level was set to zero for purposes of reporting and subsequent analysis. The C_{max} and t_{max} were estimated for serum DPPC by noncompartmental methods using actual elapsed time from dosing. PK parameters were summarized by treatment using descriptive statistics, and were derived with Phoenix® WinNonlin® Version 8.0 (Certata, L.P., Princeton, NJ, USA) and/or SAS® Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Subjects

A total of 101 subjects were screened, and 30 subjects were randomized (15 into each cohort; Fig. 2) between November 27, 2018, and March 20, 2019. All randomized subjects completed the study except for 1 subject in the placebo group of Cohort B, who withdrew on study Day 7 due to a family emergency. This subject completed all 3 doses of Day 1 treatment only and did not report any TEAEs at the time of withdrawal.

Subject demographics and baseline characteristics are shown in Table 1. The study population included more male (60%) than female (40%) subjects; however, this difference was only apparent in Cohort B. Similar numbers of black or African American (16 [53.3%]) and white (14 [46.7%]) subjects were included in the study. The mean age of subjects was 33.5 years. Overall compliance was 100% in the OP0201 treatment group and 85% in the placebo group due to 1 subject who withdrew from the trial.

Table 1

Subject Demographics and Characteristics (Safety Analysis Set)

Demographic/Characteristic	Cohort A OP0201 30 mg n = 12	Cohort B OP0201 60 mg n = 12	Placebo n = 6	Overall N = 30
Sex, n (%) Male Female	6 (50.0) 6 (50.0)	10 (83.3) 2 (16.7)	2 (33.3) 4 (66.7)	18 (60.0) 12 (40.0)
Race, n (%) White Black or African American	7 (58.3) 5 (41.7)	4 (33.3) 8 (66.7)	3 (50.0) 3 (50.0)	14 (46.7) 16 (53.3)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	1 (8.3) 11 (91.7)	0 (0) 12 (100.0)	0 (0) 6 (100.0)	1 (3.3) 29 (96.7)
Age, Mean (Range), years	33.9 (20, 49)	32.2 (25, 45)	35.3 (20, 49)	33.5 (20, 49)

Safety and tolerability

Escalation to Cohort B was approved following review of blinded safety data by a Safety Review Committee after completion of the Day 14 visit for all subjects in Cohort A. No deaths, serious AEs (SAEs), or TEAEs leading to study discontinuation were reported. Overall, 18 subjects (60.0%) reported TEAEs (Table 2); 33.3% of the low-dose treatment group; 66.7% of the high-dose treatment group; and 66.7% of the placebo group. All TEAEs were mild or moderate in severity and most resolved by study exit. (Table 3).

Table 2

Overview of Incidence of TEAEs (Safety Analysis Set)

	Cohort A OP0201 30 mg n (%)	Cohort B OP0201 60 mg n (%)	All OP0201 Treated n (%)	All Placebo n (%)	Total n (%)
	(N = 12)	(N = 12)	(N = 24)	(N = 6)	(N = 30)
Any TEAE	5 (41.7)	9 (75.0)	14 (58.3)	4 (66.7)	18 (60.0)
Treatment-related TEAE(s)	4 (33.3)	8 (66.7)	12 (50.0)	4 (66.7)	16 (53.3)
Serious TEAE(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe TEAE(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE(s) resulting in study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE(s) resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE = treatment-emergent adverse event.

Table 3

Incidence of Study Drug-Related TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class/ Preferred Term[a]	Cohort A OP0201 30 mg n (%)	Cohort B OP0201 60 mg n (%)	All OP0201 Treated n (%)	All Placebo n (%)	Total n (%)
	(N = 12)	(N = 12)	(N = 24)	(N = 6)	(N = 30)
Ear and labyrinth disorders	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (3.3)
Tinnitus	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (3.3)
Gastrointestinal disorders Toothache	1 (8.3) 1 (8.3)	0 (0) 0 (0)	1 (4.2) 1 (4.2)	0 (0) 0 (0)	1 (3.3) 1 (3.3)
General disorders and administration site conditions	0 (0)	1 (8.3)	1 (4.2)	0 (0)	1 (3.3)
Feeling cold	0 (0)	1 (8.3)	1 (4.2)	0 (0)	1 (3.3)
Infections and infestations	1 (8.3)	1 (8.3)	2 (8.3)	0 (0)	2 (6.7)
Nasopharyngitis Upper respiratory tract infection	1 (8.3) 0 (0)	0 (0) 1 (8.3)	1 (4.2) 1 (4.2)	0 (0) 0 (0)	1 (3.3) 1 (3.3)
Investigations	0 (0)	4 (33.3)	4 (16.7)	2 (33.3)	6 (20.0)
Olfactory test abnormal	0 (0)	4 (33.3)	4 (16.7)	2 (33.3)	6 (20.0)
Musculoskeletal and connective tissue disorders Pain in extremity	1 (8.3) 1 (8.3)	0 (0) 0 (0)	1 (4.2) 1 (4.2)	0 (0) 0 (0)	1 (3.3) 1 (3.3)

[a]The number of subjects in each column cannot be added because a subject may have had more than 1 adverse event. A subject experiencing multiple occurrences of an adverse event was counted, at most, once per System Organ Class and Preferred Term.

TEAE = treatment-emergent adverse event.

System Organ Class/ Preferred Term[a]	Cohort A OP0201 30 mg n (%)	Cohort B OP0201 60 mg n (%)	All OP0201 Treated n (%)	All Placebo n (%)	Total n (%)
	(N = 12)	(N = 12)	(N = 24)	(N = 6)	(N = 30)
Nervous system disorders	3 (25.0)	1 (8.3)	4 (16.7)	1 (16.7)	5 (16.7)
Headache	3 (25.0)	0 (0)	3 (12.5)	1 (16.7)	4 (13.3)
Paresthesia Somnolence	0 (0) 1 (8.3)	1 (8.3) 0 (0)	1 (4.2) 1 (4.2)	0 (0) 0 (0)	1 (3.3) 1 (3.3)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	2 (16.7)	4 (16.7)	2 (33.3)	6 (20.0)
Nasal discomfort	1 (8.3)	2 (16.7)	3 (12.5)	1 (16.7)	4 (13.3)
Epistaxis	0 (0)	1 (8.3)	1 (4.2)	0 (0)	1 (3.3)
Nasal dryness	1 (8.3)	0 (0)	1 (4.2)	0 (0)	1 (3.3)
Sneezing	0 (0)	1 (8.3)	1 (4.2)	0 (0)	1 (3.3)
Throat irritation	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (3.3)

[a]The number of subjects in each column cannot be added because a subject may have had more than 1 adverse event. A subject experiencing multiple occurrences of an adverse event was counted, at most, once per System Organ Class and Preferred Term.

TEAE = treatment-emergent adverse event.

There were no clinically significant changes from baseline in vital signs, serum chemistry or hematology parameters, ECGs, otoscopy, tympanometry, nasal and epipharynx endoscopy, UPSIT, or audiology pure-tone hearing test.

Pharmacokinetics

Serum concentrations of DPPC were quantifiable (above the lower limit of quantification [LLOQ] of 0.5 µg/mL) in all subjects at all sample collection times. The mean (SD) baseline DPPC serum

concentration for all subjects irrespective of treatment (N = 14) was 9.98 (2.50) µg/mL. Mean (SD) baseline serum DPPC concentrations on Day 1 and Day 14 were similar for subjects in the OP0201 group (10.05 [2.585] and 10.18 [2.703] µg/mL, respectively) but numerically different for subjects in the placebo group (9.53 [2.652] and 12.86 [6.145] µg/mL, respectively). Mean observed DPPC concentrations on Day 14 were similar pre- and post-dose in both treatment groups (Fig. 3). DPPC concentrations for 1 subject in the placebo group were higher on Day 14 than at baseline on Day 1. For the other subject in the placebo group, baseline and Day 14 DPPC concentrations were similar to those from subjects in the OP0201 group.

Mean baseline-corrected DPPC concentrations on Day 14 ranged from 0.30 to 0.87 µg/mL in the OP0201 group, and from 3.28 to 4.51 µg/mL in the placebo group (Fig. 4). Serum concentrations of CP were quantifiable (above the LLOQ of 0.5 µM) in all subjects at all sample collection times. The mean (SD) baseline CP serum concentration for all subjects irrespective of treatment (N = 14) was 299.36 (66.91) µM. The mean (SD) observed Day 1 baseline serum CP concentrations (OP0201: 299.50 [62.000] µM; placebo: 298.52 [126.157] µM) were similar to Day 14 pre-dose values in the OP0201 group (290.10 [35.979] µM), but numerically different from Day 14 pre-dose values in the placebo group (363.53 [178.784] µM). In both groups, CP concentrations pre-dose and post-dose on Day 14 were comparable (Fig. 5). CP concentrations for 1 subject in the placebo group were higher on Day 14 than at baseline on Day 1. For the other subject in the placebo group, baseline and Day 14 CP concentrations were similar to those from subjects in the OP0201 group.

Mean (SD) baseline-corrected CP concentrations on Day 14 ranged from 5.70 (10.410) to 15.63 (18.781) µM in the OP0201 group and 64.96 (39.617) to 89.43 (74.426) µM in the placebo group (Fig. 6). DPPC PK parameters based on baseline-corrected concentrations on Day 14 are shown in Table 4. Median t_{max} for both groups was 0.05 hours post-dose. Mean baseline-corrected DPPC C_{max} for the placebo group was numerically higher than that for the OP0201 group (4.51 vs 0.81 µg/mL, respectively). One placebo subject had a DPPC C_{max} of 7.80 µg/mL, which was more than a 3-fold increase compared with the next highest C_{max} in either treatment group. The value for the other placebo subject (1.21 µg/mL) was within the range of values of the OP0201 group (range, 0 to 2.23 µg/mL).

Table 4

Descriptive Statistics of DPPC PK Parameters on Day 14 (PK Analysis Set)

Parameter[a]	Statistic	OP0201 60 mg (N = 12)	Placebo (N = 2)
C_{max} (µg/mL)	Mean (SD)	0.82 (0.794)	4.51 (4.660)
	CV%	97.5	103.4
t_{max} (h)	Median	0.05	0.05
	(Min, Max)	0.00, 0.83	0.05, 0.05

[a]Based on baseline-corrected concentrations

C_{max}=maximum serum concentration; CV%=coefficient of variation expressed as a percentage; DPPC = dipalmitoylphosphatidylcholine; PK = pharmacokinetic; SD = standard deviation; t_{max}=time to maximum concentration.

CP PK parameters based on baseline-corrected concentrations on Day 14 are shown in Table 5. Median t_{max} for the OP0201 group was 0.05 hours post-dose (range, 0.00 to 0.35 hours). A t_{max} of 0.05 and 0.38 hours was observed for each of the 2 subjects in the placebo group. Mean (SD) C_{max} was numerically higher in the placebo group (89.50 [± 74.324] µM) relative to the OP0201 group (14.89 [± 18.328] µM). One placebo subject had a CP C_{max} of 142.05 µM, which was higher than the next highest C_{max} of 45.81 µM in either treatment group. The C_{max} for the other placebo subject (36.94 µM) was within the range of C_{max} values of the OP0201 group (range, 0.00 to 45.81 µM). In the OP0201 group, 5 subjects had CP concentrations on Day 14 that were all less than their Day 1 baseline concentration, which resulted in baseline-corrected C_{max} values of 0.00 µM.

Table 5
Descriptive Statistics of CP PK Parameters on Day 14 (PK Analysis Set)

Parameter[a]	Statistic	OP0201 60 mg (N = 12)	Placebo (N = 2)
C_{max} (µM)	Mean (SD)	14.89 (18.328)	89.50 (74.324)
	CV%	123.1	83.0
t_{max} (h)	Median	0.05	0.22
	(Min, Max)	0.00, 0.35	0.05, 0.38
[a]Based on baseline-corrected concentrations			
C_{max}=maximum serum concentration; CP = cholesteryl palmitate; CV%=coefficient of variation expressed as a percentage; PK = pharmacokinetic; SD = standard deviation; t_{max}=time to maximum concentration.			

Discussion

In this phase 1 study, intranasal OP0201 30 mg and 60 mg per day was safe and well tolerated in healthy adult volunteers. The overall incidences of TEAEs were generally similar between the OP0201 and placebo treatment groups. The majority of TEAEs were reported as mild or moderate in severity and were resolved by study exit. No deaths occurred during the study. No SAEs or AEs leading to study discontinuation were reported. There were no clinically significant changes from baseline in vital signs, serum chemistry or hematology parameters, ECGs, otoscopy, tympanometry, nasal and epipharynx endoscopy, UPSIT, or audiology pure-tone hearing test.

Serum DPPC and CP concentrations on Day 14 were generally comparable to endogenous baseline DPPC and CP serum concentrations, indicating that no supraphysiologic systemic concentrations of the active substances occurred after local intranasal administration of a high OP0201 dose (60 mg/day). The mean baseline DPPC and CP serum concentrations for the overall study population (9.98 µg/mL and 299.36 µM, respectively) are estimates of the endogenous levels of DPPC and CP in healthy adults. To the best of our knowledge, endogenous serum DPPC and CP concentrations have not previously been reported.

The study was limited in evaluating safety and tolerability of OP0201 in healthy adults; further studies are needed to evaluate the safety and tolerability in pediatric, adolescent and adult patients with otitis media. The concentration of the current OP0201 formulation (2.5 mg per spray) limited the maximum daily dose that could be practically evaluated in this study (60 mg/day as four sprays to each nostril given three times a day). A maximum tolerated dose was not yet determined. Future development studies are planned to confirm safety findings and evaluate OP0201 for the prevention and treatment of acute

and chronic otitis media. If OP0201 is successful as a mechanism to facilitate clearing middle ear fluid, it may help to reduce the need for repeated and extended courses of antibiotics, which are commonly used to treat acute otitis media and have contributed to the development of antibiotic-resistant pathogens. Additionally, OP0201 may also help to reduce the need for surgical insertion of tympanostomy tubes and its attendant complications in patients with chronic otitis media.

Conclusions

OP0201 was safe and well tolerated in healthy adult volunteers without indication of supraphysiologic systemic concentrations of the active substances at the 60 mg/day dose.

Abbreviations

C_{max}
maximum serum concentration; CP = cholesteryl palmitate; CV%=coefficient of variation expressed as a percentage; DPPC = dipalmitoylphosphatidylcholine; ECG = electrocardiogram; GCP = Good Clinical Practice; HFA 134a = hydrofluoroalkane-134a; ICH = International Conference on Harmonisation; PK = pharmacokinetic; SD = standard deviation; TEAE = treatment-emergent adverse event; t_{max}=time to maximum concentration; UPSIT = University of Pennsylvania Smell Identification Test.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the MidLands Independent Review Board. All participants provided written informed consent before participating in the study.

Consent for publication

Not applicable.

Competing interests

MDS, JAP, and CCT are employed by Novus Therapeutics. MK and BDV have received fees from Novus Therapeutics.

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Authors' contributions

MDS and CCT conceived and designed the study. MDS, JAP, and CCT contributed to data analysis and interpretation. MK and BDV conducted the study and contributed to data acquisition and analysis. All authors critically reviewed, revised, and approved the final manuscript.

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Availability of Data and Materials

Participant-level data are available upon reasonable request.

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Figures

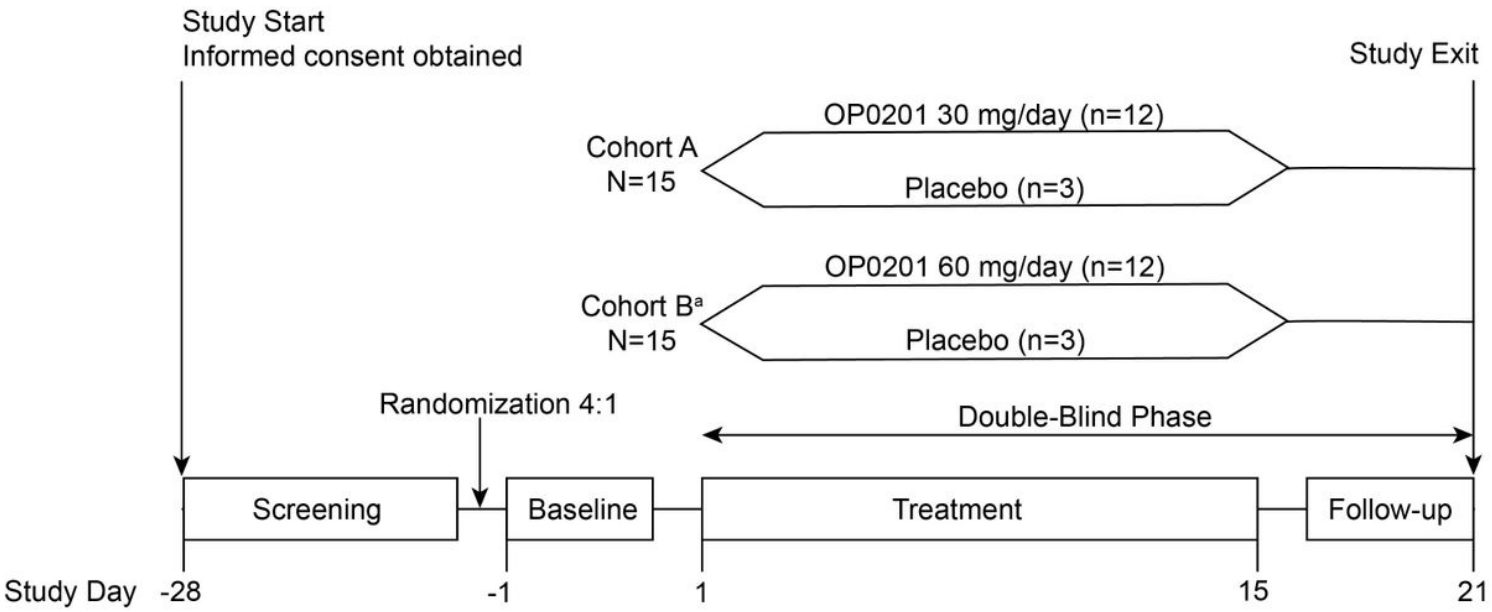

Figure 1

Study Design. aCohort B commenced after all subjects in Cohort A completed 14 days of treatment and a Safety Review Committee recommended dose escalation.

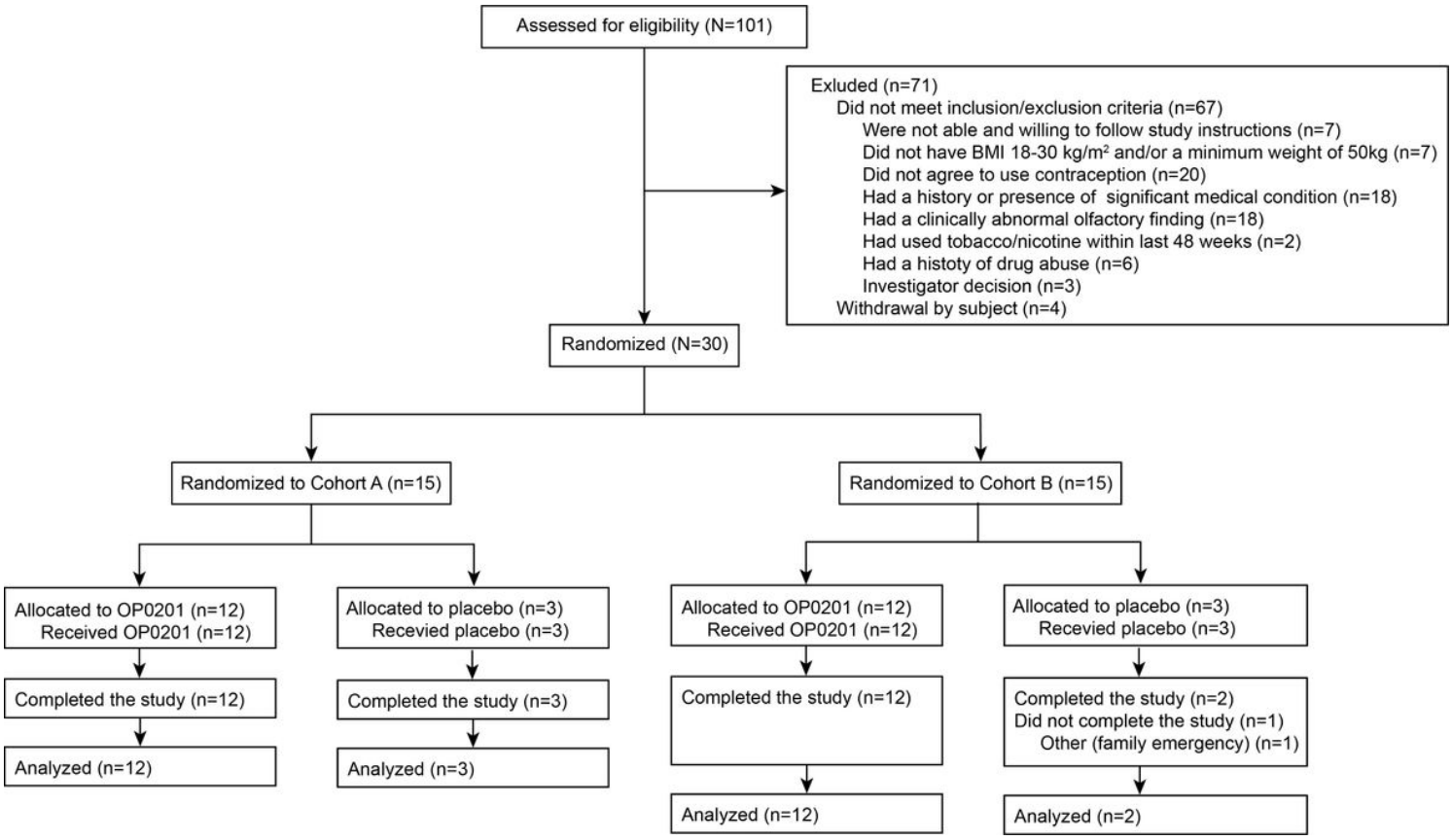

Figure 2

Subject Disposition

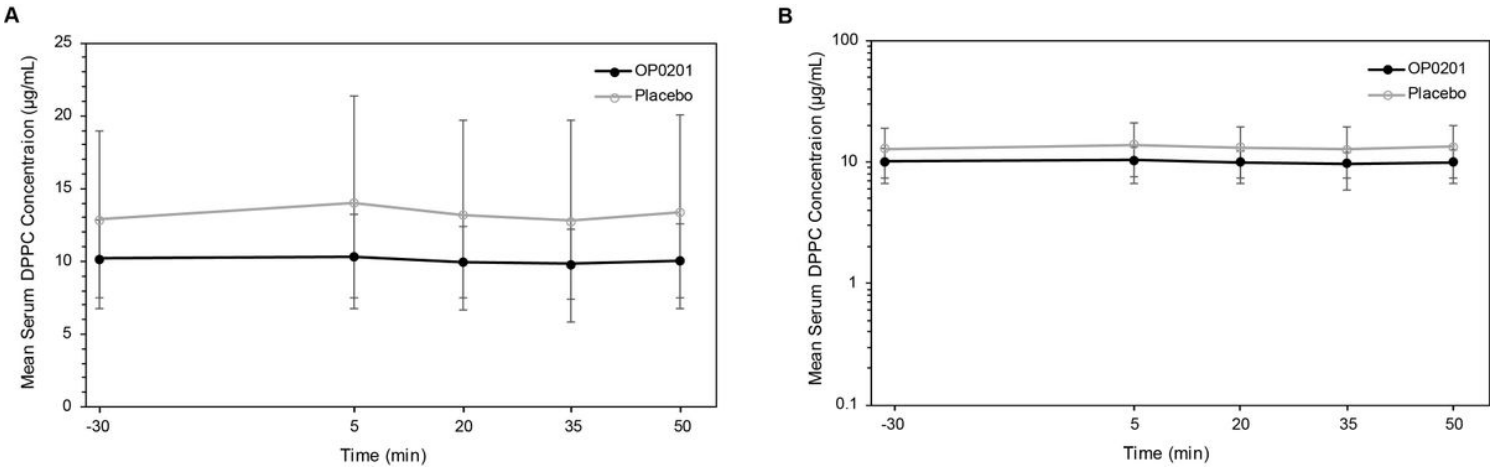

Figure 3

Day 14 Mean (±SD) Observed DPPC Serum Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scales (PK Analysis Set) DPPC=dipalmitoylphosphatidylcholine; PK=pharmacokinetic; SD=standard deviation.

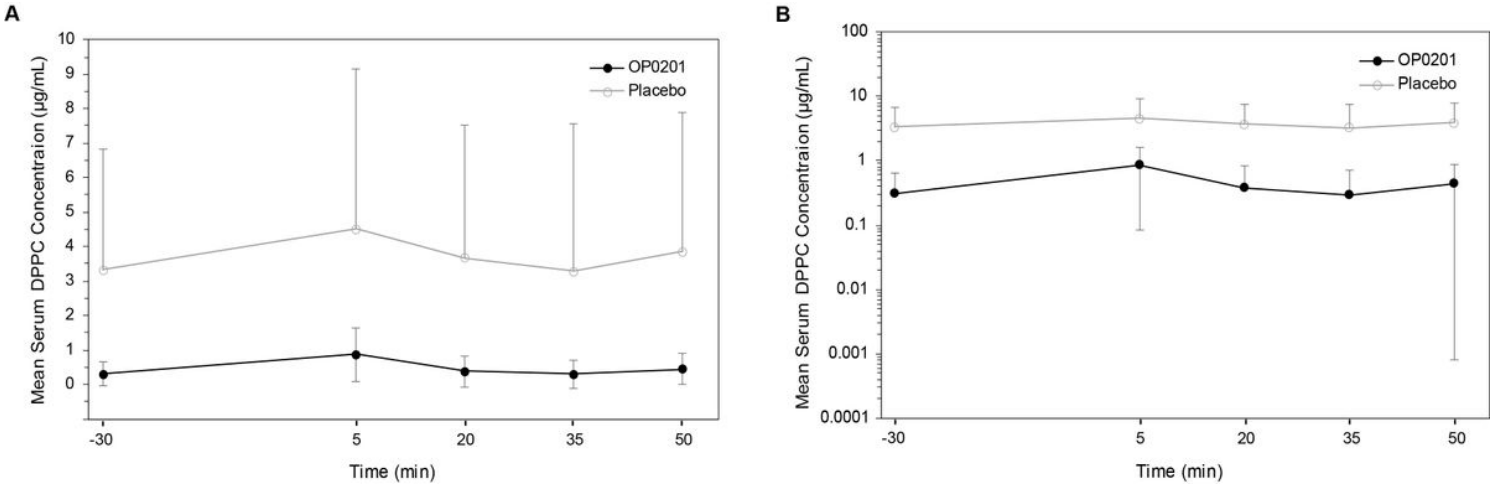

Figure 4

Mean (±SD) Baseline-Corrected DPPC Serum Concentration-Time Profiles (Day 14) on Linear (A) and Semi-logarithmic (B) Scales (PK Analysis Set) DPPC=dipalmitoylphosphatidylcholine; PK=pharmacokinetic; SD=standard deviation.

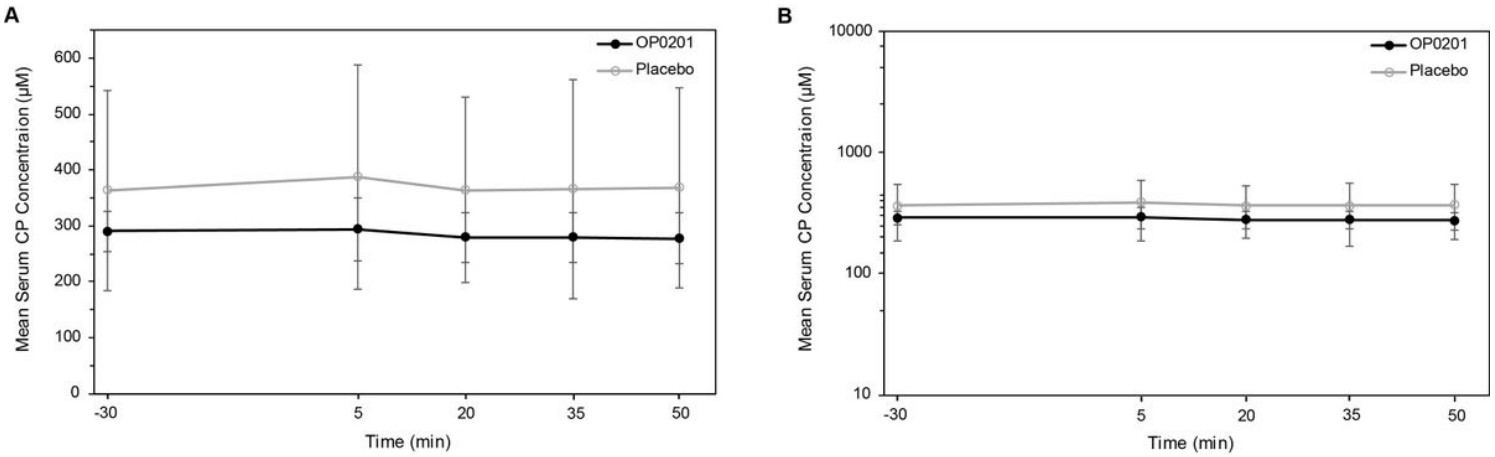

Figure 5

Mean (±SD) Observed CP Serum Concentration-Time Profiles (Day 14) on Linear (A) and Semi-logarithmic (B) Scales (PK Analysis Set) CP=cholesteryl palmitate; PK=pharmacokinetic; SD=standard deviation.

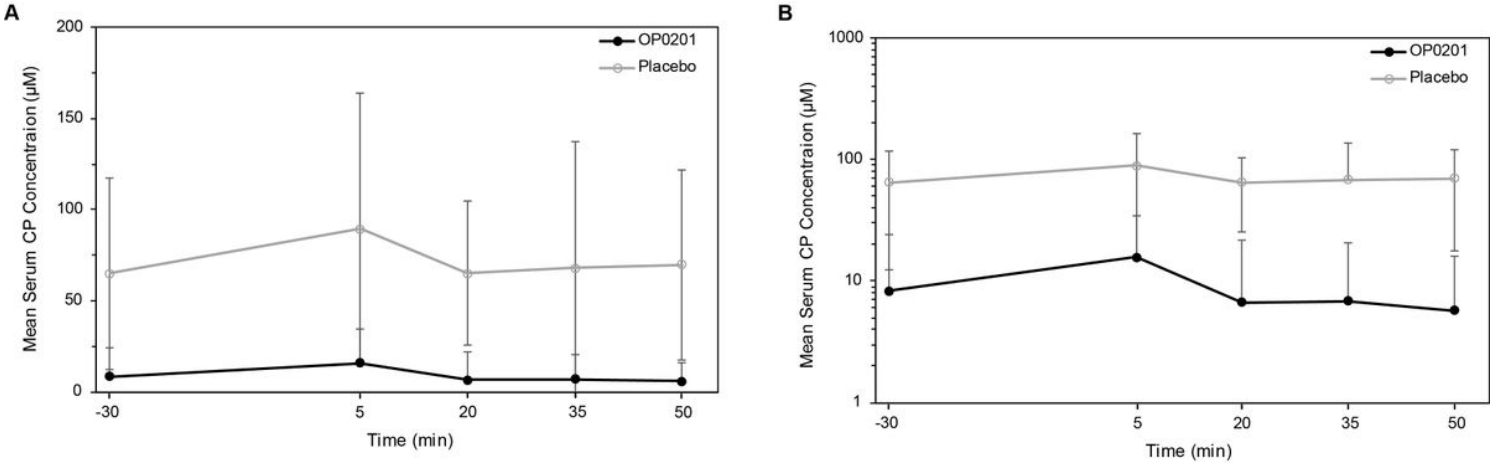

Figure 6

Mean (±SD) Baseline-Corrected CP Serum Concentration-Time Profiles (Day 14) on Linear (A) and Semi-logarithmic (B) Scales (PK Analysis Set) CP=cholesteryl palmitate; PK=pharmacokinetic; SD=standard deviation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- C002Fig6CPBLCorr.ai
- C002Fig2CONSORTDiagram.ai
- C002Fig3DPPCobs.ai
- C002Fig4DPPCBLcorrv2.ai

- C002Fig5CPobs.ai
- CONSORT2010ChecklistNovusC002.docx
- C002Fig1StudyDesign.ai