SANDOZ

Small Molecules Clinical Development

Clinical Study Report Synopsis (SAN-0791)

Mometasone + Azelastine, 50 µg/140 µg, Nasal Spray

Study Title:	An Open-label, Single-Dose, Three-way Crossover Study to Compare the Pharmacokinetics of Fixed-Dose Combination of Mometasone + Azelastine Nasal Spray to Mometasone and Azelastine Nasal Sprays in Adolescents (12 to 17 years of age) and Young Adults (18 to 24 years of age) with Seasonal Allergic Rhinitis
Test Product (Treatment A):	Mometasone furoate + Azelastine hydrochloride 50 µg + 140 µg/dose nasal spray, Lot No.: 32206107 (Lek Pharmaceuticals d.d., Slovenia)
Reference Product 1 (Treatment B):	Mometasone furoate 50 µg/dose nasal spray, Lot No.: 32205983 (Lek Pharmaceuticals d.d., Slovenia)
Reference Product 2 (Treatment C):	Azelastine hydrochloride 140 µg/dose nasal spray, Lot No.: 32206797 (Lek Pharmaceuticals d.d., Slovenia)
Dose	Mometasone furoate: 200 µg (2 actuations in each nostril); Azelastine hydrochloride: 560 µg (2 actuations in each nostril)
Description:	A comparison of the pharmacokinetics (PK) of Mometasone furoate + Azelastine hydrochloride nasal spray *versus* Mometasone Furoate nasal spray and Azelastine Hydrochloride nasal spray, after a single dose in adolescents (12 to 17 years of age; Cohort 1) and young adults (18 to 24 years of age; Cohort 2) with seasonal allergic rhinitis (SAR) and an evaluation of the safety and tolerability of the study treatments.
Name of Sponsor:	Lek Pharmaceuticals d.d. Verovškova ulica 57 SI-1526 Ljubljana Slovenia
Study code	SAN-0791
EudraCT number	2023-000362-34
Protocol No.:	2023-5437 Version: 1.1 (IRB-approved July 03, 2023)
Principal Investigator:	Mark L. Freedman, MD, FRCPC
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Study Centres:

Clinical Facility:	Pharma Medica Research Inc. 4770 Sheppard Avenue East Toronto, Ontario, Canada, M1S 3V6
Clinical Laboratory Facility:	Alpha Laboratories Incorporated 1262 Don Mills Road Toronto, Ontario, Canada, M3B 2W7
Bioanalytical, Pharmacokinetic, Statistical, and Report Issuing Facility:	Pharma Medica Research Inc. 6100 Belgrave Road Mississauga, Ontario, Canada, L5R 0B7

Good Clinical Practice Compliance:	This study was performed in compliance with the most current International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including, but not limited to, the associated Integrated Addendum and described Quality Management System therein, which encompasses a Quality Risk Management process that manages quality throughout all stages of the clinical trial process, and archiving of essential documents.
Phase of Development:	Phase I (Pharmacokinetic)
Study Initiation (First Adolescent Assent Form signature)	June 08, 2023
Date of Early Study Termination	September 06, 2023
Study Completion (Last Subject Visit)	September 29, 2023
Last Pharmacokinetic (PK) Blood Sample (Cohort-1):	August 07, 2023
Last Pharmacokinetic (PK) Blood Sample (Cohort-2):	August 23, 2023

Objectives:

The primary objective of this study was to compare the pharmacokinetics (PK) of Mometasone furoate + Azelastine hydrochloride, 50 µg + 140 µg (per actuation) liquid, nasal spray from Lek Pharmaceuticals d.d., Slovenia, versus Mometasone Furoate, 50 µg (per actuation) nasal spray from Lek Pharmaceuticals d.d., Slovenia, and Azelastine Hydrochloride 140 µg (per actuation) nasal spray from Lek Pharmaceuticals d.d., Slovenia, after a single dose, which included 4 actuations (2 actuations in each nostril), in adolescents (12 to 17 years of age; Cohort 1) and young adults (18 to 24 years of age; Cohort 2) with seasonal allergic rhinitis (SAR). The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.

Methodology:

This was an open-label, single-dose, randomized, three-period, three-treatment, three-sequence, two-cohort, crossover study, designed to compare the PK of Mometasone furoate + Azelastine hydrochloride, 50 µg + 140 µg (per actuation) liquid, nasal spray versus Mometasone Furoate 50 µg (per actuation) nasal spray and Azelastine Hydrochloride 140 µg (per actuation) nasal spray in adolescents (12 to 17 years of age; Cohort 1), and young adults (18 to 24 years of age; Cohort 2), with SAR, after a single dose of 2 actuations in each nostril.

In each study period, subjects received one of the three treatments. Pharmacokinetic blood samples for the determination of mometasone furoate and/or azelastine plasma concentrations were collected over a 48-hour interval post-dose for Cohort 1 and over a 72-hour interval post-dose for Cohort 2. The PK parameters were estimated using a non-compartmental approach. An assessment of safety was based primarily on the incidence, frequency, and severity of adverse events (AEs).

Duration of Treatment:

A single, nasal dose (two actuations in each nostril) in each of the three periods, with a 14-day washout between drug administrations.

Number of Subjects:

Sixty (60) subjects were to be enrolled into this two-cohort study, including twelve (12) adolescent subjects aged 12 to 17 years (Cohort 1) and forty-eight (48) young adult subjects aged 18 to 24 years (Cohort 2). The sample size was aligned with the European Medicines Agency decisions on the agreement of a pediatric investigation plan (including the acceptance of a modification of an agreed pediatric investigation plan).

The study was discontinued prematurely by Sponsor (reasons not related to safety).

Cohort 1

- Planned for inclusion: 12,
- Enrolled into the study: 12,

- Completed the study: 11 subjects.

Cohort 2

- Planned for inclusion: 48,
- Enrolled into the study: 26,
- Completed the study: 12 subjects.
    - Fourteen (14) subjects discontinued due to study termination by the Sponsor. Of these 14 subjects, 9 subjects were dosed in Periods 1 and 2, only, and 5 subjects were dosed in Period 1, only.

Main Criteria for Inclusion:

The study population included non-smoking, male and female subjects with SAR, who were adolescent (12 to 17 years of age; Cohort 1), or young adults (18 to 24 years of age; Cohort 2). Eligible subjects were not smokers, using drugs, or alcohol. Female subjects were not pregnant.

Statistical Methods:

Descriptive statistics of the mometasone furoate and azelastine PK parameters were calculated.

Pharmacokinetic Results, Pooled Cohorts:

Table 1. Mometasone Furoate. Descriptive Statistics for Plasma Mometasone Furoate Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*CV%*	*N*
AUC_t	**A**	74.675	38.11	31
*(hr*pg/mL)*	**B**	106.523	67.36	30
AUC_{inf}	**A**	88.151	33.46	28
*(hr*pg/mL)*	**B**	125.090	73.14	29
C_{max}	**A**	6.146	31.46	31
(pg/mL)	**B**	11.471	80.12	30
T_{max}	**A**	1.17	289.35	31
(hr)	**B**	1.17	34.34	30
T_{half}	**A**	22.03	40.07	28
(hr)	**B**	20.39	35.31	29
K_{el}	**A**	0.0315	28.66	28
(1/hr)	**B**	0.0340	40.38	29

Table 2. Azelastine. Descriptive Statistics for Plasma Azelastine Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*CV%*	*N*
AUC_t	**A**	4080.39	45.45	31
*(hr*pg/mL)*	**C**	3885.21	40.10	29
AUC_{inf}	**A**	4711.40	59.39	30
*(hr*pg/mL)*	**C**	4405.72	47.55	28
C_{max}	**A**	192.57	48.33	31
(pg/mL)	**C**	185.83	40.74	29
T_{max}	**A**	2.22	85.09	31
(hr)	**C**	2.71	108.54	29
T_{half}	**A**	21.40	38.52	30
(hr)	**C**	19.30	28.04	28
K_{el}	**A**	0.0324	32.76	30
(1/hr)	**C**	0.0359	27.97	28

Treatment A: Mometasone furoate + Azelastine hydrochloride, 50 µg + 140 µg/dose nasal spray
Treatment B: Mometasone furoate 50 µg/dose nasal spray
Treatment C: Azelastine hydrochloride 140 µg/dose nasal spray

Safety Results:

Cohort 1: Five (5) subjects (41.7% of subjects dosed) experienced 8 AEs during this study. Four (4) AEs affecting 3 subjects (25.0%) occurred after administration of Treatment A (Test Product), 2 AEs affecting 2 subjects (18.2%) occurred after administration of Treatment B (Reference Product 1), and 2 AEs affecting one subject (9.1%) occurred after administration of Treatment C (Reference Product 2). Two (2) AEs affecting 2 subjects (16.7%) were assessed as drug-related (suspected in relationship to the IMP). The two drug related AEs occurred following administration of Treatment B. Two (2) AEs (vessel puncture site reaction) affecting 2 subjects (16.7%) were assessed as having a causal relationship to the study-procedures. No investigational device-related AEs were reported during this study and none of the subjects in Cohort 1 discontinued from the study due to AEs.

Cohort 2: Nine (9) subjects (34.6% of subjects dosed) experienced 15 AEs during this study. Five (5) AEs affecting 3 subjects (14.3%) occurred after administration of Treatment A (Test Product), 8 AEs affecting 6 subjects (31.6%) occurred after administration of Treatment B (Reference Product 1), and 2 AEs affecting one subject (5.3%) occurred after administration of Treatment C (Reference Product 2). None of the AEs reported in Cohort 2 were assessed as having a suspected relationship to the IMP, or as having a causal, possible, or probable relationship to the investigational device. Four (4) AEs (vessel puncture site reaction [2], catheter site related reaction, and presyncope) were assessed as having a causal relationship to study procedures. None of the subjects in Cohort 2 discontinued from the study due to AEs.

Overall, the administration of the study drugs was, generally, well-tolerated by the subjects participating in this study. No serious adverse events (SAEs) were reported during the conduct of this study and none of the AEs compromised subject safety or had an impact on the integrity of the study results.

Conclusions, pooled cohorts:

Mometasone Furoate

The Test Product (Treatment A), Mometasone furoate + Azelastine hydrochloride, 50 µg + 140 µg (per actuation) liquid, nasal spray (Lek Pharmaceuticals d.d., Slovenia), did not exceed total and peak exposure for mometasone furoate compared to Reference Product 1 (Treatment B), Mometasone Furoate 50 µg (per actuation) nasal spray (Lek Pharmaceuticals d.d., Slovenia).

Azelastine

The Test Product (Treatment A), Mometasone furoate + Azelastine hydrochloride, 50 µg + 140 µg (per actuation) liquid, nasal spray (Lek Pharmaceuticals d.d., Slovenia), exhibited similar total and peak exposure for azelastine compared to Reference Product 2 (Treatment C), Azelastine Hydrochloride 140 µg (per actuation) nasal spray (Lek Pharmaceuticals d.d., Slovenia).

Overall, the study medications were well tolerated by the subjects that participated in this study.

Date of Final Clinical Study Report: January 05, 2024