

A Long-Term, Open-Label Study Assessing the Safety and Tolerability of LEVADEX® Orally Inhaled Dihydroergotamine in Adult Migraineurs

D. Kellerman, J. Chang, A. Reppine, S. Kori

MAP Pharmaceuticals, Inc., Mountain View, CA

RATIONALE

This was an open-label, long-term extension of a previously reported Phase 3 clinical trial (FREEDOM-301).

This open-label study was conducted to evaluate the clinical safety of long-term exposure (up to 52 weeks of exposure) to LEVADEX (MAP0004 1.0 mg nominal dose) in adult migraineurs.

About LEVADEX

- An orally inhaled, self-administered therapy intended for the treatment of migraines.
- Utilizes a breath-actuated metered dose inhaler (TEMPO® inhaler) to deliver a novel formulation of dihydroergotamine mesylate (DHE).
- One dose is two inhalations providing a 1.0 mg nominal dose (0.6 mg emitted).

METHODS

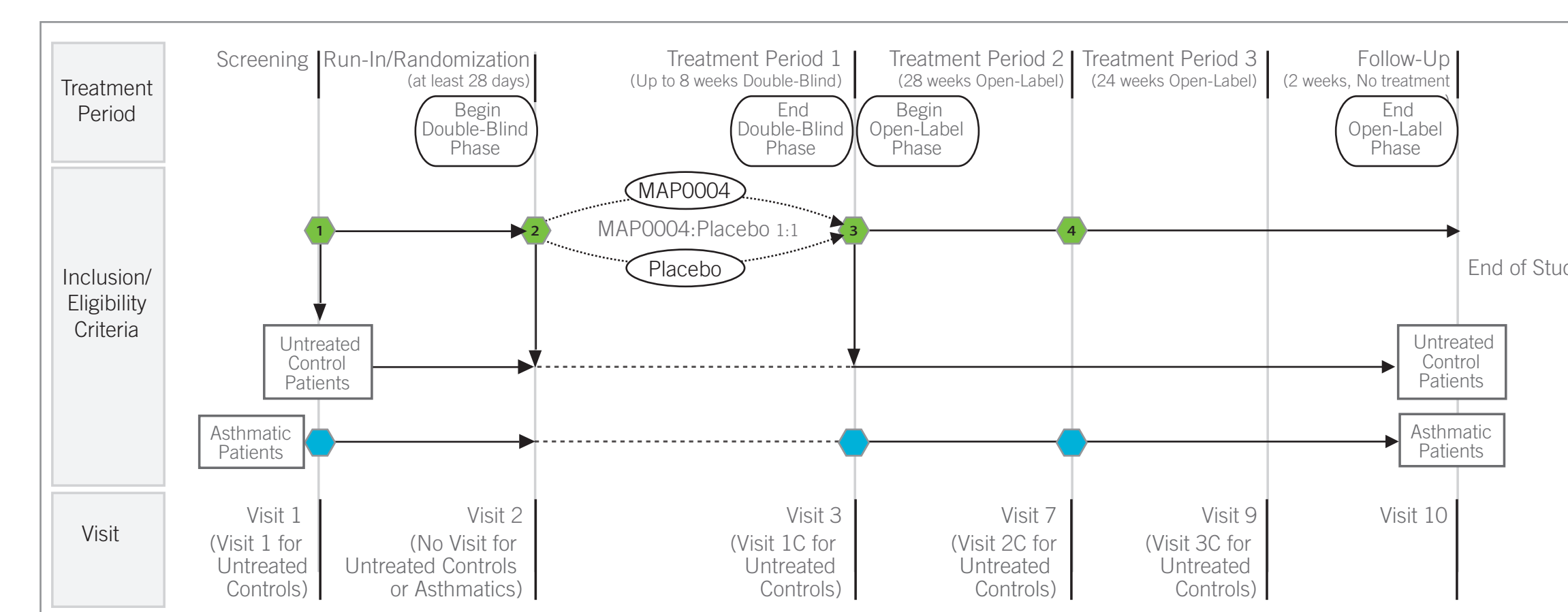
675 subjects enrolled to receive LEVADEX 1.0 mg.

160 asthmatics included to evaluate the pulmonary safety of the inhaled delivery system in subjects with asthma.

217 subjects participated in an untreated control arm to assess underlying variability in selected safety endpoints.

Adverse events, concomitant medications, vital signs, lung function testing, cardiovascular testing and clinical laboratory data were collected at various intervals for up to 52 weeks.

FIGURE 1. Study Schema: Double-Blind and Open-Label Phases



RESULTS

TABLE 1. Subject Disposition (All Enrolled)

Subjects	Untreated Control Arm	LEVADEX 1.0 mg			
		Non Asthmatics	Asthmatics	Asthmatics w/Controller Meds	Combined
Enrolled Open-label	217	515	160	104	675
Completed 1 st 6-month Period	206	360	125	84	485
Entered 2 nd 6-month Period	206	203	92	70	295*
Completed Open-label	195	178	85	64	263

*136 subjects who initially met the inclusion criteria of 2 to 8 migraine episodes per month and completed the 1st 6-month period were excluded from entering the 2nd 6-month period due to no longer meeting the minimum migraine frequency inclusion criteria of at least an average of 2 migraine episodes per month

- In addition to migraineurs, asthmatics were included in this study in order to evaluate the pulmonary safety of LEVADEX 1.0 mg in patients with potentially compromised lung function.
- A untreated control arm was included to assess underlying variability in the safety endpoints of spirometry (FEV₁), lung diffusion capacity test (DLco), echocardiography (ECHO) and chest X-ray (CXR).

TABLE 2. Demographic and Baseline Characteristics

Variable	Untreated Control (N=217)	LEVADEX 1.0 mg (N=638)*
Age, years (Mean ± SD)	37.1 ± 11.15	40.4 ± 11.52
Sex, Female (%)	86.6%	90.6%
Race, White (%)	90.8%	88.9%
Weight, kg (Mean ± SD)	76.6 ± 19.07	77.6 ± 19.31
Height, cm (Mean ± SD)	166.7 ± 7.49	165.2 ± 8.36
% Predicted FEV ₁ (Mean ± SD)	92.0 ± 12.37	91.3 ± 12.21
Years since Migraine Diagnosis (Mean ± SD)	15.7 ± 9.98	15.8 ± 10.73
Asthma History, Yes (%)	9.2%	24.5%

*Safety population is defined as those subjects who at least treated 1 migraine using study medication during the study

- The baseline characteristics (weight, height, % predicted FEV₁, migraine and asthma history) were similar between the LEVADEX 1.0 mg and the untreated control arms.

TABLE 3. Exposure to LEVADEX

Dosing	LEVADEX 1.0 mg			
	Non Asthmatics (N=482)	Asthmatics (n=156)	Asthmatics w/Controller Meds (N=102)	Combined (N=638)
Study Duration* (weeks) Mean ± SD	38.0 ± 15.25	41.8 ± 14.27	43.7 ± 13.93	38.9 ± 15.09
Study Duration* (weeks) Range	2.1 - 70.9	6.0 - 67.3	6.0 - 67.3	2.1 - 70.9
Subject with Average ≥ 2 Doses per Month	123 (25.5%)	36 (23.1%)	26 (25.5%)	159 (24.9%)

* Study duration is defined as the time of start date to the date of last visit

- Mean study duration was 38.9 weeks (range 2.1-70.9 weeks).
- 159 subjects took an average of 2 or more doses of LEVADEX 1.0 mg per month.

TABLE 4. Overview of Adverse Events

Adverse Events	LEVADEX 1.0 mg			
	Non Asthmatics (N=482)	Asthmatics (n=156)	Asthmatics w/Controller Meds (N=102)	Combined (N=638)
Subjects with Any AE	350 (72.6%)	137 (87.8%)	86 (84.3%)	487 (76.3%)
Related Adverse Events ^a	123 (25.5%)	45 (28.8%)	27 (26.5%)	168 (26.3%)
Adverse Events that Led to Withdrawal	30 (6.2%)	13 (8.3%)	8 (7.8%)	43 (6.7%)
Serious Adverse Events ^b	11 (2.3%)	3 (1.9%)	3 (2.9%)	14 (2.2%)
Related Serious Adverse Events	0	0	0	0
Deaths ^b	1 (0.2%)	0	0	1 (0.2%)

a. Related AEs include those with a definite, probable, possible, and unknown relationship to study drug
b. Not related to study medication

RESULTS

TABLE 5. All Adverse Events Reported in ≥2%

Adverse Events	LEVADEX (N=638)	
	All AEs	AEs
Upper respiratory tract infection	93 (14.6%)	<1%
Nausea	78 (12.2%)	53 (8.3%)
Nasopharyngitis	67 (10.5%)	<1%
Sinusitis	65 (10.2%)	<1%
Medication aftertaste	51 (8.0%)	51 (8.0%)
Influenza	35 (5.5%)	<1%
Vomiting	33 (5.2%)	21 (3.3%)
Cough	32 (5.0%)	<1%
Procedural pain	28 (4.4%)	0
Diarrhoea	26 (4.1%)	<1%
Back pain	25 (3.9%)	<1%
Bronchitis	24 (3.8%)	0
Dizziness	21 (3.3%)	16 (2.5%)
Urinary tract infection	20 (3.1%)	0
Migraine	18 (2.8%)	12 (1.9%)
Gastroenteritis viral	16 (2.5%)	0
Arthralgia	15 (2.4%)	<1%
Toothache	14 (2.2%)	<1%
Pyrexia	14 (2.2%)	0
Myalgia	13 (2.0%)	<1%

- AEs reported were those generally expected in a long-term trial (e.g., common nasopharyngitis and respiratory tract infection) or with the use of DHE (e.g. nausea, vomiting and medication aftertaste).

TABLE 6. Categorical Long-term Lung Function Analysis in Subjects with ≥20% Decrease from Baseline

Incidence (N/total N)	Untreated Control (N=217)	LEVADEX 1.0 mg			
		Non Asthmatics (N = 482)	Asthmatics (N = 156)	Asthmatics w/Controller Meds (N = 102)	Combined (N=638)
≥20% decline in FEV ₁ from baseline					
Week 28	2/187 (1.1%)	3/323 (0.9%)	2/124 (1.6%)	2/79 (2.5%)	5/447 (1.1%)
Week 52	2/177 (1.1%)	3/192 (1.6%)	0/89 (0%)	0/68 (0%)	3/281 (1.1%)
Last Observation*	2/199 (1.0%)	5/470 (1.1%)	1/151 (0.7%)	1/99 (1.0%)	6/621 (1.0%)
≥20% decline in DLco from baseline					
Last Observation*	4/198 (2.0%)	8/404 (2.0%)	6/141 (4.3%)	3/92 (3.3%)	14/545 (2.6%)

* Last observation was the data collected at the last visit even if it occurred earlier than Week 52

- The incidence of pre-defined significant decreases (≥20%) in either FEV₁ or DLco was less than 5% and similar to the untreated control arm.
- No subject had ≥20% decreases in both FEV₁ and DLco.
- Subjects who had abnormal tests did not have accompanying symptoms consistent with decline in pulmonary status.

CONCLUSIONS

In this study, LEVADEX was well-tolerated for the acute treatment of migraine, and not associated with any unique safety risk from the inhaled mode of administration.

AEs reported were those generally expected in a long-term trial or with the use of DHE.

There were no unique or unexpected adverse events related to pulmonary administration of DHE.

No serious drug related AEs were reported.

No clinically significant drug related cardiovascular or respiratory sequelae were observed.