Developing Instructions for Use for a Metered Dose Inhaler: Methodology and Results with the TEMPO® inhaler

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Summary

MAP0004 is an investigational orally inhaled formulation of dihydroergotamine mesylate (DHE) and a blend of hydrofluoroalkane (HFA) propellants delivered using the proprietary, breath-actuated TEMPO® inhaler and is designed to be an easy-to-use and non-invasive at-home therapy intended for the acute treatment of migraine. In a Phase 3 clinical trial, MAP0004 was well tolerated and provided both fast onset of action and sustained pain relief, as well as relief of other migraine symptoms.

The goal of this study was to develop instructions for use (IFU) for the TEMPO inhaler in MAP0004 and to test the IFU by qualitatively and quantitatively assessing subject comprehension of the IFU. The study was divided into the preliminary and confirmatory arms. The preliminary arm was conducted as an iterative evaluation in which changes were made to the IFU content between study parts. An optimal IFU design was defined at the end of the preliminary arm and this final version of the IFU was evaluated in the confirmatory arm.

An iterative process incorporating subject observations and feedback is a critical step in the development of effective instructions for the proper use of inhalers. In the confirmatory arm, 96% of subjects used the TEMPO inhaler correctly the first time without external aid, and 100% of subjects used TEMPO inhaler correctly after simple verbal instruction from a healthcare professional.

Introduction

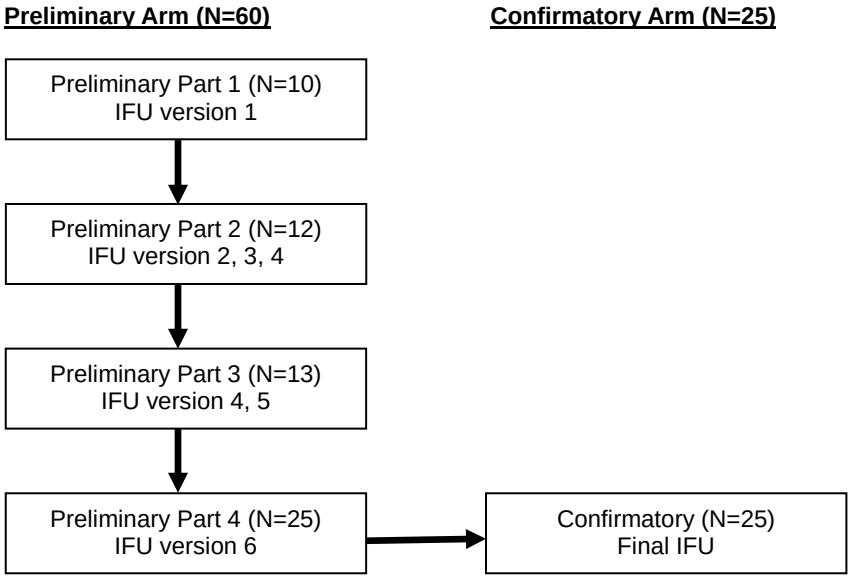
MAP Pharmaceuticals, Inc. is developing MAP0004, an investigational orally inhaled, self-administered therapy intended for the acute treatment of migraine. MAP0004 utilizes a breath-actuated metered dose inhaler (TEMPO inhaler, Figure 1) to deliver a novel, preservative-free formulation of dihydroergotamine mesylate. In a Phase 3 clinical trial (1, 2), MAP0004 was effective and well tolerated for the acute treatment of migraine and has the potential to provide both fast onset of action and sustained pain relief, as well as relief of other migraine symptoms. (3). A MAP0004 dose is two inhalations providing a 1.0 mg nominal dose (0.6 mg emitted) with an audible “click” indicating delivery of each inhalation. The purpose of this report is to outline the methodology used for developing and testing the instructions for use (IFU) and to detail the results of the testing. The process described demonstrates that the TEMPO inhaler can be correctly used with appropriate instructions.

Methods

This was an observational study conducted in 85 subjects. The study was divided into 2 sequential arms: the preliminary arm and the confirmatory arm (Figure 2). The preliminary arm was conducted with 60 subjects divided into 6 IFU cohorts in 4 different parts. Between cohorts, iterative revisions were made to improve a draft version of the IFU by assessing the readability, clarity, and ease-of-use results observed in the earlier cohort. Six versions of the IFU were evaluated using qualitative and quantitative questions. The confirmatory arm was conducted with 25 subjects to confirm understanding of the final IFU version developed using inputs from the preliminary arm.

Figure 1: TEMPO Inhaler

Figure 2: Study Schema



Study Procedure: The study was conducted at multiple geographical locations in the U.S. and was monitored by a Research Study Monitor (RSM). All subjects were given an Instruction Card (IC), the IFU and an unused TEMPO inhaler which contained no drug or propellant. Subjects were instructed to read the IC and IFU and then perform the steps to administer a simulated dose consisting of two successive inhaler actuations. If the subject failed to actuate the inhaler, the RSM provided the subject with verbal or physical demonstration assistance and assessed if the subject could then successfully actuate the inhaler. Study results were recorded on an Observation Checklist. When it was determined that the subject had finished the task, the RSM proceeded to complete the Study Questionnaire with the subject verbally. The subjects were asked to provide feedback on the IFU and ease-of-use of the inhaler.

Study Analysis: The preferred method for measuring IFU comprehension and successful study outcomes was a binomial result, such as pass/fail or yes/no for reporting domains and correct/incorrect or yes/no for individual measures.

Result and Discussion

The preliminary and confirmatory arms had similar demographic distributions (Table 1). A specific effort was made to enroll subjects with a varying distribution of education and literacy levels, as it was hypothesized that literacy might impact IFU understanding and execution. Both arms had approximately 20% of subjects who had a high school level of education or below. In addition, the recruitment plan was focused on enrollment of subjects with a history of migraine to mirror the potential MAP0004 user. No specific guidance for enrollment was given as to previous inhalation product use.

Table 1: Study Demography

Demography		**Preliminary Arm (N=60)**	**Confirmatory Arm (N=25)**
Gender	Female	73%	68%
	Male	27%	32%
Education	High School or below	20%	16%
	Some College or Graduate	73%	64%
	Post Graduate	7%	20%
Age	18-29	27%	16%
	30-49	70%	80%
	50-59	3%	4%
Race/Ethnicity	Caucasian	60%	72%
	Asian	10%	8%
	African American	12%	12%
	Hispanic	15%	8%
	Other	3%	0%

According to the results from the multiple phases of the preliminary arm (Table 2), successful inhaler use following instruction from the various drafts of the IFU was high, with nearly 90% correct performance for all critical steps. Lower scores for the ability to achieve an inhaler "click " on the first attempt reflect some difficulties experienced in actuating the inhaler and a natural learning curve. In general, there was a trend for improved outcomes for the Preliminary Phase 4. Issues with shaking the inhaler observed in the Preliminary Phase 1 were mostly resolved with subsequent IFU revisions.

In the 2nd inhalation attempt, 10 subjects did not perform the 2nd inhalation. Of these, 8 subjects did not attempt 2nd inhalation due to inability to actuate the inhaler during the 1st inhalation. Two subjects did not perform the 2nd inhalation due to lack of attention to the IFU.

Table 2: Summary Results from Preliminary Arm

1st Inhalation						
Study Phases	Began by reading instruction	Shook inhaler	Inhaler correct side up	Able to have a "click" on 1st attempt	Kept breathing through click	Held breath for 5 seconds
Phase 1 (N=10)	100%	70%	100%	60%	90%	80%
Phase 2 (N=12)	92%	92%	100%	67%	75%	83%
Phase 3 (N=13)	100%	92%	100%	62%	77%	77%
Phase 4 (N=25)	96%	100%	100%	32%	96%	96%
2nd Inhalation						
	Closed and opened the inhaler	Shook inhaler	Inhaler correct side up	Able to have a "click" on 1st attempt	Kept breathing through click	Held breath for 5 seconds
Phase 1 (N=8)	100%	75%	100%	100%	89%	88%
Phase 2 (N=9)	89%	67%	100%	78%	89%	100%
Phase 3 (N=10)	90%	80%	90%	100%	100%	100%
Phase 4 (N=23)	100%	96%	100%	78%	100%	100%

Based on the combined observations during the preliminary arm, a revised IFU was developed with modifications made to address the observed instructional limitations with each cohort of subjects. The major changes made from the first draft to the final IFU were:

1. Inclusion of all 6 steps in picture form

2. Modification of font color (to blue) and use of upper case in the text regarding performance of Steps 1-6
3. Rewording of the subtitle to “SHAKE, OPEN, INHALE, CLOSE to Use Product X” from “To use product X follow these 4 steps: Shake, Open, Inhale, Close”
4. Modification of the font color (to red) of the box “READ THESE INSTRUCTIONS BEFORE YOU BEGIN”

After implementing the above modifications, the rate of subjects successfully actuating the inhaler on the first attempt without any external input increased from 70% (42/ 60) in the preliminary arm to 96% (24/ 25) in confirmatory arm. A single subject in the confirmatory arm who initially failed to actuate the inhaler was able to actuate it successfully after receiving verbal instruction. In the confirmatory arm, 96% of subjects correctly delivered a full simulated dose (2 clicks) from the TEMPO inhaler (Table 3).

Table 3: Success Rate of Subjects Administering a Dose from the inhaler

Study Arms	1st Inhalation	2nd Inhalation	Full dose
Preliminary arm	75%	88%	70%
Confirmatory arm	96%	100%	96%

No apparent difference in the Opinion Rating of the IFU and inhaler was observed between preliminary and confirmatory (Table 4) arms. Overall, more than 80% of the subjects agreed or strongly agreed (ratings ≥4 on a 5 point scale) that both instructions in the draft IFU (preliminary arm) and the final IFU (confirmatory arm) were clear and easy to follow. Similarly high ratings were given from subjects in the confirmatory arm using the final IFU for the ease of actuating the inhaler (reflected by the subjects obtaining an inhaler “click”).

Table 4: Opinion Ratings of the IFU and TEMPO Inhaler Use (Rating 5=Very, 1=Not at all)

Questionnaire	Arm	5	4	3	2	1
How easy was it to get the inhaler to click?	Preliminary	47%	22%	12%	5%	15%
	Confirmatory	84%	16%	0%	0%	0%
Were instructions clear?	Preliminary	52%	28%	15%	5%	0%
	Confirmatory	56%	32%	12%	0%	0%
Were instructions easy to follow?	Preliminary	63%	27%	8%	2%	0%
	Confirmatory	68%	12%	20%	0%	0%

Conclusion

An iterative process incorporating subject observations and feedback is a critical step in the development of effective instructions for the proper use of metered dose inhalers. Incorporation of subjects’ feedback proved useful in improving unaided appropriate use results with the TEMPO inhaler .This study affirmed the utility of pretesting instructions for use with drug-delivery platform medications intended for self-administration by patients in order to ensure a high probability of appropriate use. In the confirmatory arm of the study, 96% of subjects were able to use the TEMPO inhaler correctly the first time without any external aid, and 100% of subjects were able to use the TEMPO inhaler correctly after simple verbal instruction from a healthcare professional.

Reference

1. MAP0004, Orally Inhaled DHE: A Randomized, Controlled Study in the Acute Treatment of Migraine. Headache 2011, 51:4:507-517

2. A long-term open-label study assessing the safety and tolerability of LEVADEX® orally inhaled Dihydroergotamine in adult migraineurs. As presented at the 53rd Annual Scientific Meeting of the American Headache Society (AHS), June 2011

3. Assessment of the consistency of pharmacokinetic parameters of LEVADEX® (MAP0004, orally inhaled DHE) in healthy volunteers-results from three clinical studies. As presented at the As presented at the 15th Congress of the International Headache Society (IHC), June 2011