AXS-07 (MoSEIC™ Meloxicam/Rizatriptan): Novel Oral Therapeutic in Clinical Development for the Acute Treatment of Migraine

Cedric O'Gorman[3], Amanda Jones[3], Karen TenHuisen[3], Mark Jacobson[3], Richard B. Lipton[1], Stewart J. Tepper[2], Herriot Tabuteau[3]

[1]Albert Einstein College of Medicine, New York, NY, USA; [2]Geisel School of Medicine at Dartmouth, Hanover, NH, USA; [3]Axsome Therapeutics Inc. New York, NY, USA

AXSOME THERAPEUTICS

200 Broadway, 3rd Floor, New York, NY 10038 USA

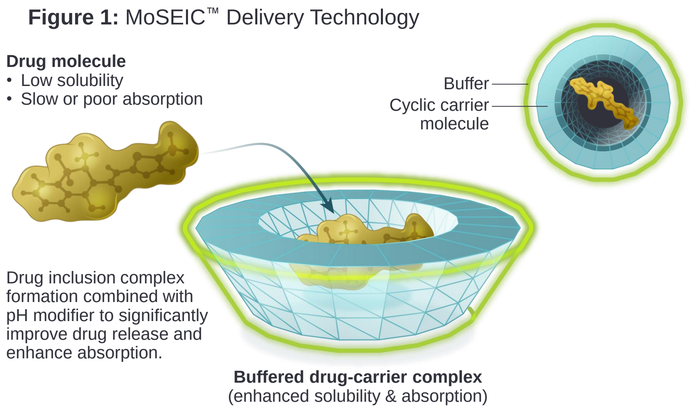
For more information, please contact Cedric O'Gorman at **cogorman@axsome.com**

Introduction

- Migraine is a disabling neurological disorder characterized by recurrent attacks of pulsating head pain accompanied by nausea and sensitivity to light and sound. These symptoms are often severe and incapacitating, requiring bed rest.
- Current treatments are suboptimal, with more than 70% of sufferers reporting dissatisfaction with existing acute treatments. The most commonly reported reasons for patient dissatisfaction are slow onset of pain relief, inconsistent pain relief, and recurrence of pain during the same day.[1,2]
- Suboptimal acute treatment is associated with a significantly increased risk of new-onset chronic migraine, which may be prevented by improving acute treatment outcomes.[3]
- AXS-07 is a novel, oral, investigational medicine, with distinct dual mechanisms of action, under development for the acute treatment of migraine. AXS-07 consists of MoSEIC™ meloxicam and rizatriptan. Meloxicam is a potent, COX-2 preferential NSAID which is limited by slow absorption. Rizatriptan is a potent 5-HT$1_{B/D}$ agonist with known efficacy in migraine.
- AXS-07 utilizes proprietary MoSEIC™ (Molecular Solubility Enhanced Inclusion Complex) delivery technology (**Figure 1**) to substantially increase the solubility and speed of absorption of meloxicam after oral administration, while maintaining its extended plasma half-life.

1. Smelt AF et al. *PLoS One*. 2014 Jun 16;9(6):e98933.
2. Lipton RB, Stewart WF. *Headache*. 1999;39(suppl 2):S20-S26.
3. Lipton RB et al. *Neurology*. 2015 Feb 17;84(7):688-95.

Figure 1: MoSEIC™ Delivery Technology



Objectives

- To determine the pharmacokinetics (PK) of AXS-07 (MoSEIC™ meloxicam and rizatriptan) after oral administration.
- To compare the PK of the MoSEIC™ meloxicam and rizatriptan components of AXS-07 to standard meloxicam and rizatriptan, respectively.
- To describe the design of an ongoing Phase 3 trial of AXS-07 in the acute treatment of migraine, as well as the patient population being studied in that trial.

Methods

Phase 1 Pharmacokinetic Trial

- A Phase 1, randomized, single-dose, parallel-group study was conducted to evaluate the PK, safety and tolerability of AXS-07 (MoSEIC™ meloxicam and rizatriptan), and Maxalt® (rizatriptan), in healthy human volunteers after oral administration under fasted conditions.
- A total of 20 healthy, adult male or female volunteers were randomized in a 1:1 ratio to receive a single dose of AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan), or Maxalt® (10 mg rizatriptan).
- Blood samples for PK analysis were collected pre dose and at multiple time points post dose.
- The pre-specified primary endpoint was T_{thera}, the time to reach a therapeutic plasma concentration of meloxicam, defined as the C_{avg} of meloxicam after administration of the highest approved dose (15 mg) of standard meloxicam.
- PK results for the rizatriptan component of AXS-07 were compared to those for Maxalt® (rizatriptan).
- PK results for the MoSEIC™ meloxicam (20 mg) component of AXS-07 from this trial were compared to PK results for Mobic® (15 mg meloxicam) from a similar previously completed trial in healthy volunteers after single-dose, oral administration under fasted conditions.

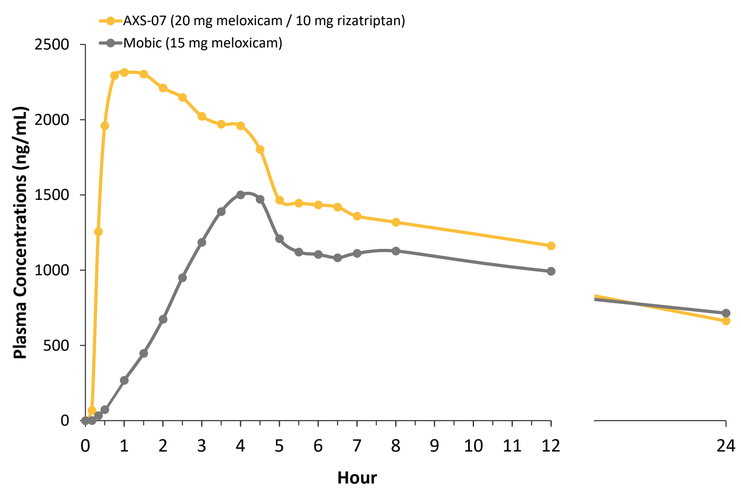
Phase 3 Efficacy Trial

- The ongoing Phase 3 MOMENTUM trial of AXS-07 in the acute treatment of migraine was examined to provide a summary of the study design, including doses being tested, to describe the instrument used for patient selection, and the resulting migraine population being studied in that trial.

Phase 1 Results

- MoSEIC™ meloxicam was rapidly absorbed after oral administration of AXS-07 (20 mg MoSEIC™ meloxicam/10 mg rizatriptan), with a median time to therapeutic plasma concentration (T_{thera}) of 17 minutes, the primary endpoint (**Figure 2** and **Table 1**). Median T_{max} was 1 hour compared to 4.5 hours for 15 mg standard meloxicam (Mobic®).
- Mean plasma elimination half-life ($T_{1/2}$) for MoSEIC™ meloxicam was 18.2 hours after administration of AXS-07, which compares to 21.5 hours for standard meloxicam.

Figure 2: Mean Meloxicam Concentrations over Time for AXS-07 versus Standard Meloxicam[a]



[a] Meloxicam concentrations for AXS-07 (20 mg meloxicam/10 mg rizatriptan) from current study; meloxicam concentrations for 15 mg standard meloxicam (Mobic®) from separate previously completed study.

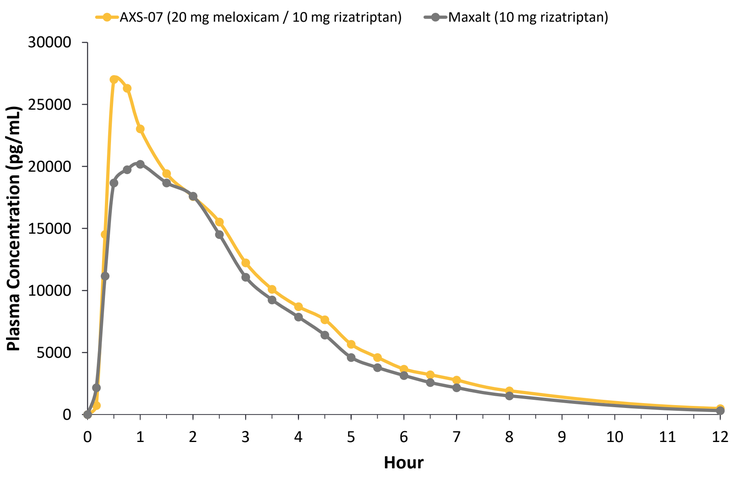
Table 1: Meloxicam Pharmacokinetic Parameters for AXS-07

	Statistic	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$T_{1/2\ el}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)[a]	T_{thera} (hr)[a]
AXS-07 (20 mg meloxicam, 10 mg rizatriptan)	N	10	10	10	10	10
	Geometric Mean	46,865	17.5	2,532	1.0	0.29
	SD	11,965	5.25	607	0.5 - 2.5	0.20 - 0.61

[a] T_{max} and T_{thera} presented as median and range.

- Rizatriptan was rapidly absorbed after oral administration of AXS-07, with a T_{max} of 0.64 hour, which compares to 0.88 hour for the same dose of standard rizatriptan (Maxalt®) (**Figure 3** and **Table 2**).
- Systemic exposure, measured using C_{max} and AUC were also numerically greater for rizatriptan after administration of AXS-07 versus standard rizatriptan.

Figure 3: Rizatriptan Concentrations over Time for AXS-07 versus Standard Rizatriptan[a]



[a] Rizatriptan concentrations for AXS-07 and standard rizatriptan (Maxalt®) from current study.

Table 2: Rizatriptan Pharmacokinetic Parameters for AXS-07 and Standard Rizatriptan

	Statistic	$AUC_{0\text{-}inf}$ (pg*hr/mL)	$T_{1/2\ el}$ (hr)	C_{max} (pg/mL)	T_{max} (hr)[a]
AXS-07 (20 mg meloxicam, 10 mg rizatriptan)	N	10	10	10	10
	Geometric Mean	83,800	1.98	29,991	0.64
	SD	22,787	0.28	11,041	0.5 - 2.5
Maxalt® (10 mg rizatriptan)	N	10	10	10	10
	Geometric Mean	71,811	1.81	23,236	0.88
	SD	24,287	0.11	9,476	0.5 - 2

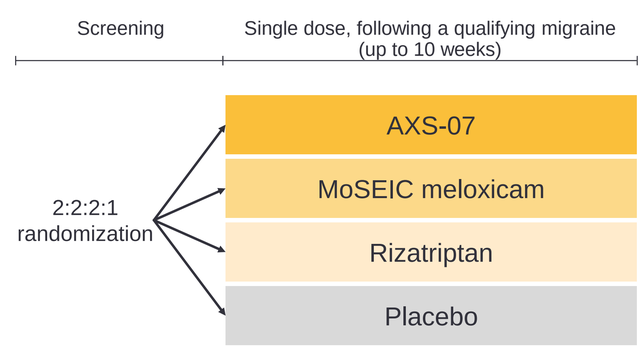
[a] T_{max} presented as median and range.

- AXS-07 was well tolerated with no relevant differences in safety profile between the two treatment arms. There were no serious adverse events in the study.

MOMENTUM Phase 3 Trial of AXS-07 in Patients with History of Inadequate Response

MOMENTUM STUDY

A Phase 3 trial of AXS-07 for the acute treatment of migraine in adults with a history of inadequate response



- MOMENTUM (Maximizing Outcomes in Treating Acute Migraine) is a Phase 3, randomized, double-blind, multicenter, active- and placebo-controlled trial to assess the efficacy and safety of AXS-07 in the acute treatment of moderate and severe migraine, in patients with a history of inadequate response to prior acute migraine treatments.
- Eligible patients are randomized in a 2:2:2:1 ratio to treatment with AXS-07 (20 mg MoSEIC™ meloxicam/10 rizatriptan), rizatriptan (10 mg), MoSEIC™ meloxicam (20 mg), or placebo.
- Co-primary endpoints are freedom from headache pain, and freedom from the most bothersome migraine-associated symptom (nausea, photophobia, or phonophobia), two hours after dosing, for AXS-07 as compared to placebo.
- Superiority of AXS-07 to the rizatriptan and MoSEIC™ meloxicam arms (component contribution) will be established based on sustained freedom from headache pain from two to 24 hours after dosing (key secondary endpoint).
- The trial is ongoing and is being conducted pursuant to an FDA Special Protocol Assessment (SPA).

Patient Population in MOMENTUM Phase 3 Trial

- Eligible patients must have a history of inadequate response to prior acute migraine treatments, assessed using the Migraine Treatment Optimization Questionnaire (mTOQ-4).
- The mTOQ-4 is a validated questionnaire that assesses efficacy response to prior acute treatments based on four aspects (two-hour pain freedom, efficacy for at least 24 hours with one dose, ability to plan daily activities, and disruption of daily activities).[1]
- The majority of patients randomized to date in the MOMENTUM trial also report allodynia with their migraine attacks. Allodynia, which is pain from normally non-painful stimuli (such as brushing hair, wearing glasses, taking a shower, etc.), has been shown to be strongly associated with worse outcomes for pain freedom and pain relief after treatment with triptan medications.[2,3]

1. Lipton RB et al. *Neurology*. 2015 Feb 17;84(7):688-95.
2. Lipton RB et al. *Headache*. 2017 Jul;57(7):1026-1040.
3. Lipton RB et al. *Headache*. 2016 Nov;56(10):1635-1648.

Conclusions

- AXS-07 was rapidly absorbed, resulting in therapeutic plasma concentrations of MoSEIC™ meloxicam in 17 minutes and maximum concentrations of rizatriptan in 38 minutes after oral administration, suggesting the potential for rapid onset of action with AXS-07.
- The long elimination half-life of MoSEIC™ meloxicam (18.2 hours) after oral administration of AXS-07 suggests the potential for AXS-07 to reduce migraine pain recurrence.
- The MOMENTUM Phase 3 trial of AXS-07 is enrolling only patients with a history of inadequate response to prior acute migraine treatments, assessed using the mTOQ-4, and the majority of patients randomized to date also report associated allodynia, reflecting a population with difficult-to-treat migraine pain.
- The rapid absorption and distinct dual mechanisms of action of AXS-07 provide a scientific rationale for potential success in providing relief for this more treatment-resistant population.

Disclosure:
COG, AJ, KT, MJ & HT are employees of Axsome Therapeutics.