Effectiveness Of Qtrypta™ (Zolmitriptan Intracutaneous System) Before and After the Initiation of CGRP Antibody Therapy in Subjects With Migraine – A Preliminary Assessment

Nada Hindiyeh MD, Pete Schmidt MD, MSc, Jean Engels MS, Whitney Halladay, Donald Kellerman PharmD

Introduction and Objectives

- The advent of anti-CGRP antibody therapies represents a significant advance in the prevention of migraine.
- Despite their demonstrated ability to reduce monthly migraine days, breakthrough migraine attacks in patients treated with these agents are not uncommon.[1,2,3]
- Consequently abortive therapies should be investigated in the context of prior prophylactic treatment.
- Adhesive Dermally-Applied Microarray (ADAM) is an investigational system that provides intracutaneous drug administration.
- ADAM zolmitriptan 2 X 1.9 mg (Qtrypta™) uses ADAM to administer zolmitriptan for the acute treatment of migraine,
- In a pivotal phase 2b/3 randomized, double-blind, placebo-controlled study (ZOTRIP), ADAM zolmitriptan 2 X 1.9 mg met both co-primary endpoints (which were selected based on 2018 FDA Guidance Document for Clinical Trials Evaluating Drugs for Acute Migraine Treatment[4]) of pain freedom and freedom from patients' usual other most bothersome symptom (MBS) two hours post-dose (**Figure 1**).[5]
- A long-term safety study of ADAM zolmitriptan 2 X 1.9 mg was recently completed (see Nahas et al. Long-term Safety of Qtrypta™ for the Acute Treatment of Migraine – 1-year Safety Results of Nearly 6,000 Treated Attacks; present at this meeting).
- The objective of this retrospective analysis was to examine the effectiveness of ADAM zolmitriptan in the small subset of subjects enrolled in this trial who also received treatment with anti-CGRP antibodies.

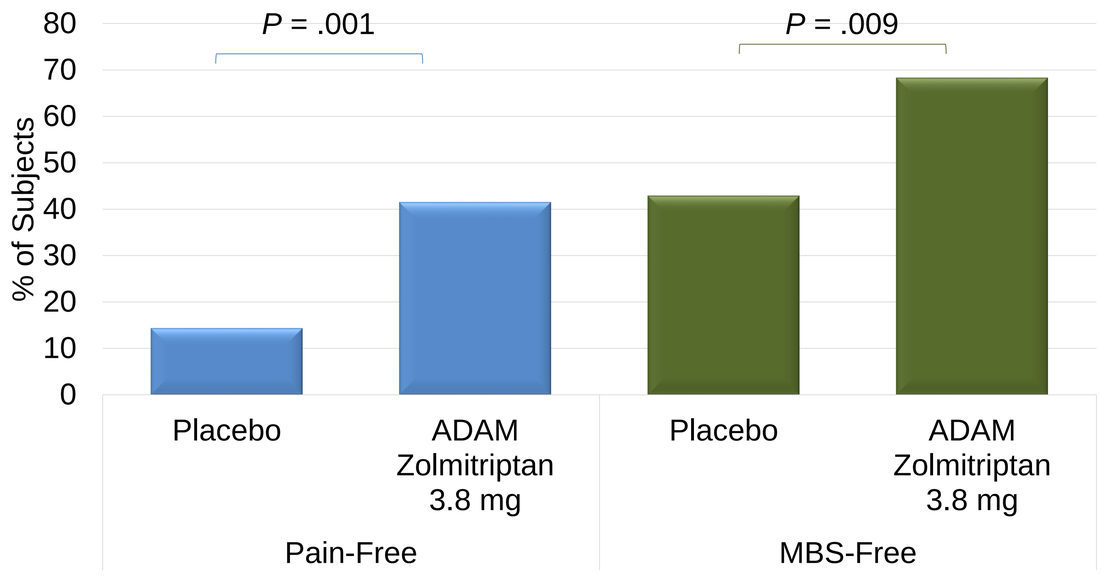

Figure 1. Percentages of Subjects who were Pain-Free and/or MBS-Free at Two Hours After Dosing in the Pivotal ZOTRIP Trial

MBS: most bothersome symptom

mITT population; LOCF for missing data; Pain-free defined as a value of 0 (no pain) on a scale of 0-3.

Study Design And Methods

- This was an open-label, 12-month, long-term safety study of ADAM zolmitriptan (M207) for the acute treatment of migraine (NCT03282227).
- Adults were eligible to participate if:
  - They had a ≥1 year history of episodic migraine diagnosed according to IHS ICHD-3 beta criteria
  - In the last 6 months they experienced 2 to 8 migraines per month with no more than 15 headache days per month
- There was a screening period followed by a run-in period (14 to 21 days) to determine treatment eligibility (migraine diagnosis and attack frequency of at least 2 per month).
- Subjects self-administered ADAM zolmitriptan 2 X 1.9 mg to treat a qualifying migraine. Subjects could treat multiple migraine attacks.
- Subjects used a daily eDiary to record migraine symptoms and application site observations.
- The primary outcome measure was long-term safety as measured by incidence of adverse events over a 12 month period.
- Secondary outcome measures included efficacy measures including pain freedom and freedom from most bothersome other headache-related symptom at 2 hours post-dose.
- Several subjects in the trial requested to also be treated with an injectable anti-CGRP antibody. As there were no safety concerns, the sponsor granted permission for the subjects to receive this treatment and continue to participate in the long-term safety trial.
- Data are evaluated here from subject-recorded eDiary symptom scores for all migraine attacks treated prior to and after CGRP antibody therapy initiation.
- Data are included only for subjects who had migraine attacks both pre and post anti-CGRP antibody initiation.

Results

- Nine subjects initiated erenumab and 1 initiated galcanezumab during the trial.
- Six subjects treated migraine attacks with ADAM zolmitriptan 2 X 1.9 mg after initiating anti-CGRP treatment.
- Seventy-two attacks were treated prior to initiating anti-CGRP treatment and 37 attacks post initiation. Results for pain and most bothersome symptom freedom at 2 hours post dose are shown for all treated attacks in **Table 1**.

Table 1. ADAM zolmitriptan Efficacy in Six Subjects who Received CGRP Antibodies

Treatment Status	Pain Freedom at 2 hours n (%)	MBS Freedom at 2 hours n (%)
Pre CGRP Ab Initiation (72 Attacks)	45 (63%)	48 (74%)
Post CGRP Ab Initiation (37 Attacks)	28/37 (76%)	30/34 (88%)

MBS: Most Bothersome Symptom

Response is defined as a pain level of none or absence of the MBS without the use of rescue medications. For MBS freedom, a subject's MBS must have been present pre-dose to be included in the analysis.

Conclusions and Discussion

- While data were only available on a limited number of subjects, it appears ADAM zolmitriptan remained highly effective in relieving acute migraine symptoms in subjects receiving prophylactic treatment with CGRP antibodies.
- Further studies are needed, but these data suggest that attacks may be more successfully treated with rapidly absorbed triptans when subjects are being treated prophylactically with a CGRP antibody

References

1. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, Klatt J Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet (London, England)*. 2018; 392:2280-2287.
2. Forderreuther S, Zhang Q, Stauffer VL, Aurora SK, Lainez MJA Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. *The journal of headache and pain*. 2018; 19:121.
3. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. *Jama*. 2018; 319:1999-2008
4. Migraine: Developing Drugs for Acute Treatment Guidance for Industry . https://www.fda.gov/downloads/drugs/guidances/ucm419465.pdf
5. Spierings EL, Brandes JL, Kudrow DB, Weintraub J, Schmidt PC, Kellerman DJ, et al. Randomized, double-blind, placebo-controlled, parallel-group, multi-center study of the safety and efficacy of ADAM zolmitriptan for the acute treatment of migraine. Cephalalgia : an international journal of headache. 2017:333102417737765.

Acknowledgements and Disclosures

- NAH serves on speaker's bureaus for Amgen, Eli Lilly, and Electrocore, and serves on advisory boards for Eli Lilly, and Zosano Pharma.
- PS, JE, WH and DK are emplyess of Zosano Pharma.
- Medical writing support provided by Pam Foreman, PhD, funded by Zosano Pharma