Rapid systemic delivery of zolmitriptan using an adhesive dermally applied microarray

Donald J Kellerman^{*,1}, Mahmoud Ameri¹ & Stewart J Tepper²

¹Zosano Pharma, 34790 Ardentech Court, Fremont, CA 94555, USA

²Neurology Department, Geisel School of Medicine at Dartmouth & Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA

* Author for correspondence: dkellerman@zosanopharma.com

Adhesive Dermally-Applied Microarray (ADAM) is a device for intracutaneous drug administration consisting of a 3 cm² disposable array of drug-coated titanium microprojections on an adhesive backing. It is applied using a low cost, reusable, handheld applicator. Microprojections penetrate the stratum corneum, delivering drug proximal to capillaries with limited likelihood of pain. The pharmacokinetics of zolmitriptan delivery using ADAM was evaluated in 20 healthy volunteers. Median $t_{\max}$ was <20 min, comparable to subcutaneous sumatriptan. Absorption was faster than for oral zolmitriptan, with higher exposure in the first 2 h. Most adverse events were consistent with those seen in previous triptan trials. Application site reactions were generally mild and resolved within 24 h. ADAM zolmitriptan shows a promising pharmacokinetic profile for migraine treatment.

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Migraine is a common cause of disability, and despite the availability of multiple treatment options, considerable unmet need persists [1]. For moderate-to-severe migraine, treatment guidelines recommend the first-line use of triptans [2–4]. Optimal migraine treatment provides rapid pain relief with good palatability; currently available formulations and routes of administration for migraine medications do not fully meet these criteria.

Although orally administered medications are user-friendly, they have some drawbacks [5]. Drug absorption is typically not rapid and may be further hindered by gastrointestinal dysmotility, resulting in inconsistent treatment effects. Moreover, as many patients experience nausea and vomiting in association with migraine, they may experience difficulty in swallowing or retaining oral formulations. Delayed gastric emptying in migraine may be further exacerbated by triptans, which can prolong gastric emptying time by activating 5-HT₁ receptors on gastric myenteric neurons [6–8]. Therefore, in many patients, rapidly acting nonoral formulations may be preferable.

Available nonoral migraine medications include injectable and intranasal formulations of sumatriptan and zolmitriptan nasal spray. Among these, subcutaneously injected sumatriptan is most rapidly absorbed with a time to maximum concentration ($t_{\max}$) of 10–12 min [9]. For sumatriptan nasal powder and nasal spray, the average $t_{\max}$ are 45 min [10] and approximately 2 h [11], respectively. The $t_{\max}$ for zolmitriptan nasal spray is 1.5–2.5 h [12]. While providing more rapid absorption than orally administered triptans, these formulations have limitations that include needle aversion and poor palatability of nasal formulations. Here we describe an investigational device that circumvents these limitations by providing intracutaneous delivery of zolmitriptan.

The Adhesive Dermally-Applied Microarray

The Adhesive Dermally-Applied Microarray (ADAM) is an investigational product for intracutaneous drug delivery allowing rapid absorption into the bloodstream. It consists of a disposable adhesive backing, with an array of drug (zolmitriptan)-coated titanium microprojections mounted on the skin-facing surface (Figure 1); and a ready to use low-cost reusable handheld applicator that ensures that each microprojection array is applied to the skin with a defined application force, ensuring consistent delivery at the site of administration (Figure 2).

Figure 1. Adhesive Dermally-Applied Microarray with zolmitriptan-coated titanium microprojections. Left panel depicts the assembled ADAM. Right shows a scanning electron micrograph of the zolmitriptan-coated microprojections.

The microprojection array is 3 cm² in diameter and consists of 1987 titanium microprojections, each 340 μm in length. The microprojections are coated with drug formulation applied as a solution, which is then dried. The array is attached to a 5 cm² adhesive backing (Figure 1). The microprojection array is mounted inside a polycarbonate plastic ring with a co-molded desiccant (Figure 3). The complete patch in ring assembly is packaged in a nitrogen-purged foil cup, which is stored at room temperature.

The user prepares the ADAM for application by simply pressing the handheld reusable applicator onto the ring assembly (Figure 3). The applicator is unlocked by a quick twist of the cap from the #1 position to #2 position (Figure 3). The user then applies the ADAM by just pressing the applicator/ring assembly onto the skin site. The applicator releases its piston when sufficient mild force is applied. The piston detaches the ADAM from the ring and easily applies it to the skin. The applicator is designed to ensure that the same energy is applied across multiple uses and is user independent.

Following application, the microprojections penetrate the stratum corneum proximal to the microcapillaries in skin. The shallow depth of penetration and the minuteness of the size of the microprojections limit the likelihood of stimulating sensory nerve endings (Figure 4). The zolmitriptan coating is rapidly reconstituted from the microprojections by the interstitial fluid in the skin and is available for absorption. The ADAM is removed after 30 min and is disposed.

Pharmacokinetic evaluation of zolmitriptan delivery using ADAM

Methods

The pharmacokinetics (PK) of zolmitriptan delivery using ADAM was evaluated in a single center, open-label, ascending dose and tolerability Phase I study in healthy volunteers, aged 18–60 years (n = 20). The study was reviewed and approved by The Alfred Hospital Ethics Committee and all participants provided informed consent.

The study was a five-way crossover study with treatments administered in a randomized order using a randomization table (Figure 5). The study treatments are outlined in Table 1. In treatment groups A, B, C and F varying doses of zolmitriptan were administered using the 5 cm² (3 cm² microarray) ADAM system and a 0.26 J applicator. In treatment groups B and F, two ADAMs of identical zolmitriptan dose (0.48 and 1.9 mg, respectively) were administered simultaneously. In treatment group G, the 3.8 mg dose was administered using 10 cm² ADAM and a 0.52 J applicator. Treatment D consisted of a single zolmitriptan tablet, and treatment E consisted of a subcutaneous injection of sumatriptan.

No concomitant prescription medications were allowed other than hormone replacement therapy, proton pump inhibitors, antihistamines or intermittently used NSAIDs.

Participants were required to stay in the clinic overnight in a fasting state, taking only liquids after 8:00 PM. Fasting was continued until 2 h after dosing. The ADAMs were removed 30 min after application. PK sampling occurred at 0, 2, 5, 10, 15, 20, 30, 60 min and 2, 4, 8, 12 and 24 h after dosing.

Figure 2. Adhesive Dermally-Applied Microarray (ADAM) application.

Table 1. Study treatments.

Part 1	
Treatment A	ADAM zolmitriptan 0.48 mg
Treatment B	2 × ADAM zolmitriptan 0.48 mg (total = 0.96 mg)
Treatment C	ADAM zolmitriptan 1.9 mg
Treatment D	Zolmitriptan tablet 2.5 mg
Treatment E	Sumatriptan succinate 6.0 mg/0.5 ml for subcutaneous injection
Part 2	
Treatment F	2 × ADAM zolmitriptan 1.9 mg (total = 3.8 mg)
Part 3	
Treatment G	ADAM zolmitriptan 3.8 mg
ADAM: Adhesive dermally applied microarray.

Figure 3. Adhesive Dermally-Applied Microarray (ADAM) patch ring assembly.

Figure 4. Schematic of drug delivery using the Adhesive Dermally-Applied Microarray.

Figure 5. Pharmacokinetic study schema.

Plasma concentrations of zolmitriptan and its active metabolite, N-desmethyl zolmitriptan, a 5-HT_{1B/1D} receptor agonist that is two- to five-times more potent than zolmitriptan in animal models [13], were determined by HPLC electrospray ionization-tandem mass spectrometry. All PK calculations and descriptive and inferential

Table 2. Participant demographics and baseline characteristics.

	Study (n = 20)
Gender Female, n	10
Mean (SD) age, years	29 (10)
Race, n (%)	
Caucasian	18 (90)
Hispanic/latino	2 (10)
Mean (SD) BMI, kg/m ²	24 (4)
SD: Standard deviation.	

statistical analyses were performed using EXCEL and SPSS v22.0 software. Pairwise comparisons of AUC_{2hr} were performed using ANOVA paired t-tests (SAS v9). The relative exposure and relative C_{max} of ADAM zolmitriptan were compared with zolmitriptan tablets using the following formula:

$$F_{rel} = \frac{AUC_{inf}(\text{ADAM zolmitriptan}) \times \text{Dose}(\text{zolmitriptan tablet})}{AUC_{inf}(\text{zolmitriptan tablet}) \times \text{Dose}(\text{ADAM zolmitriptan})}$$

Adverse events (AEs) were collected until post-study procedures for the seventh treatment were completed or until early withdrawal. All AEs considered treatment-related were followed until the event or its sequelae resolved or stabilized. Visual assessments of the application sites were made at 30 min and 24 h after removal of the ADAM. Erythema, edema, patch-related superficial punctate bruising and bleeding were scored according to severity on a scale of 0 to 3, with 0 indicating no findings and 3 indicating a severe finding.

All datasets on which the conclusions of the report rely are available on request.

Results

A total of 44 participants were screened and 20 were enrolled. Treatment was completed in 19, 20, 20, 19, 20, 20 and 20 participants in groups A, B, C, D, E, F and G, respectively. Participant demographics and baseline characteristics are provided in Table 2.

The zolmitriptan (groups A, B, C, D, F, G) and sumatriptan (group E) concentration–time curves are shown in Figure 6. The median (range) t_{max} for group E was 10 (5–20) min. Absorption in the ADAM zolmitriptan groups was rapid at all doses; t_{max} was comparable to sumatriptan subcutaneous injection, with peak median plasma concentration occurring within 20 min of application (Table 3). For the ADAM zolmitriptan 1.9 mg and above groups, C_{max} and exposure at 2 h (AUC_{2hrs}) were considerably higher than for zolmitriptan 2.5 mg oral tablets. However, overall exposure (AUC_{inf}) was lower in all ADAM zolmitriptan groups. Pairwise comparisons of AUC_{2hrs} are presented in Table 4. The AUC_{2hrs} were significantly different among all groups except groups B and D. The mean exposure was proportional to the dose for single ADAM administration. There was less conversion and less exposure to the N-desmethyl zolmitriptan metabolite for ADAM zolmitriptan compared with zolmitriptan tablets.

Overall, 95% (19/20) of participants experienced a total of 77 AEs during the study; 87% were considered mild, and none was severe. Among these, 87% (67/77) of AEs were considered possibly or probably related to treatment. No serious AEs occurred during the conduct of the study. Table 5 details adverse events that occurred in more than one participant.

Evaluation of application site(s) 30 min after application showed mostly mild-to-moderate symptoms. Mild erythema remained 24 h after patch application for all groups. By 24 h after administration, edema and bleeding returned to near baseline levels for all groups. Superficial punctate bruising returned to baseline for all groups except group C (Table 6). One patient in group F reported pain at the application site.

Conclusion & discussion

Optimal migraine treatment provides rapid pain relief with good tolerability. Triptans are the first-line acute migraine treatment in patients with disabling migraines and no vascular contraindications.

Orally administered triptans may be difficult to swallow or retain in patients with nausea. They can be slowly absorbed, which may be exacerbated by gastrointestinal dysmotility in migraine, resulting in inconsistent delivery. To circumvent these issues, intranasal and subcutaneously administered formulations have been developed. While

Figure 6. Concentration–time curves following administration of zolmitriptan with the Adhesive Dermally-Applied Microarray or subcutaneous sumatriptan. (A) Zolmitriptan groups A, B, C, D, F, G, zero to 24 h (B) Zolmitriptan groups A, B, C, D, F, G, zero to 2 h (C) Sumatriptan group E, zero to 24 h (D) Sumatriptan group E, zero to 2 h.

Table 3. Plasma pharmacokinetic parameters.									
Treatment group	t _{max} (min) median (range)	t _{1/2} (H) mean (SD)	C _{max} (ng/ml) mean (SD)	AUC _{inf} (ng.H/ml) mean (SD)	AUC _{2hrs} (ng.H/ml) mean (SD)	AUC _{0–30 min} (ng.H/ml) mean (SD)	AUC _{0–15 min} (ng.H/ml) mean (SD)	F _{rel} AUC _{inf}	F _{rel} C _{max}
Zolmitriptan									
A	20 (2–30) [†]	1.15 (0.3) [†]	1.84 (0.5) [†]	3.81 (1.5) [†]	2.11 (0.7) [†]	0.7 (0.23) [†]	0.3 (0.12) [†]	0.73	2.60
B	20 (2–30)	1.29 (0.3)	3.70 (1.0)	7.71 (2.0)	4.15 (1.0)	1.4 (0.39)	0.6 (0.21)	0.77	2.65
C	20 (2–30)	1.46 (0.3)	6.76 (2.8)	14.14 (4.5)	7.36 (2.5)	2.4 (1.02)	1.1 (0.52)	0.70	2.35
D	60 (30–240)	3.27 (0.8) [‡]	3.77 (1.5) [†]	27.19 (11.3) [‡]	4.72 (2.2) [†]	5.6 (1.87)	2.5 (0.76)	–	–
F	18 (2–30)	1.53 (0.3)	14.61 (4.5)	30.12 (10.1)	16.44 (5.3)	0.33 (0.34)	0.04 (0.11)	0.74	2.63
G	15 (2–30)	1.52 (0.3)	22.56 (14.0)	33.81 (8.0)	19.33 (5.4)	0.7 (0.23)	0.3 (0.12)	0.86	3.73
N-desmethyl zolmitriptan metabolite									
A	60 (30–120) [‡]	3.31 (1.6) [§]	0.22 (0.1) [‡]	1.38 (0.5) [‡]	0.31 (0) [‡]	ND	ND	0.46	0.52
B	60 (15–90)	3.28 (1.8)	0.42 (0.1)	2.43 (0.8)	0.62 (0.2)	ND	ND	0.43	0.52
C	60 (30–90)	3.05 (1.0)	0.74 (0.3)	3.65 (1.2)	1.07 (0)	ND	ND	0.32	0.43
D	120 (60–240) [†]	3.22 (1.1) [†]	2.08 (0.5) [†]	14.55 (3.1) [†]	2.31 (0.9) [†]	ND	ND	–	–
F	60 (30–90)	2.82 (0.5)	1.41 (0.5)	7.21 (2.3)	2.15 (0.7)	ND	ND	0.32	0.43
G	60 (20–90)	2.70 (0.5)	1.77 (0.6)	8.17 (2.0)	2.66 (0.8)	ND	ND	0.36	0.52

^{†‡§}n = 19; n = 18; n = 16.
AUC: Area under the concentration–time curve; C_{max}: Peak plasma concentration; ND: Not determined; SD: Standard deviation; t_{1/2}: Half life; t_{max}: Time to reach C_{max}.

administering the drugs via these routes of administrations may result in faster absorption, intranasal formulations suffer from poor palatability, and many patients are averse to the use of needles.

Here we have described an ADAM system for intracutaneous administration of zolmitriptan. ADAM is a needle-free device that is applied to the skin where microprojections penetrate the stratum corneum delivering drug proximal to the capillaries, with limited likelihood of stimulating sensory nerve endings.

Table 4. Intergroup pairwise comparisons of AUC_{2h}.

Treatment group	B	C	D	F	G
A	p < 0.0001	p < 0.0001	p = 0.0003	p < 0.0001	p < 0.0001
B		p < 0.0001	p = 0.4196	p < 0.0001	p < 0.0001
C			p = 0.0015	p < 0.0001	p < 0.0001
D				p < 0.0001	p = 0.0001
F					p = 0.0334

Table 5. Adverse events with incidence ≥ 1 .

Number of adverse events n (%)	Treatment group						
	A (n = 19)	B (n = 20)	C (n = 20)	D (n = 19)	E (n = 20)	F (n = 20)	G (n = 20)
Paresthesia	–	2 (10)	3 (5)	–	6 (30)	10 (50)	8 (40)
Headache	3 (16)	2 (10)	4 (20)	–	–	4 (20)	4 (20)
Throat and jaw tightness, heaviness, ache	–	–	1 (5)	–	–	2 (10)	2 (10)
Hot flushes	–	–	–	–	–	2 (10)	2 (10)
Lightheadedness and vasovagal response	1 (5)	–	–	–	1 (5)	–	1 (5)
Nausea	1 (5)	–	–	–	–	1 (5)	–
Neck tightness and stiffness	–	–	–	–	1 (5)	1 (5)	–
Upper respiratory tract infection	–	–	–	–	–	2 (10)	–

Table 6. Application site assessments at 30 min and 24 h after removal of the Adhesive Dermally-Applied Microarray.

Group mean score	Time postapplication							
	Erythema		Edema		Punctate bruising		Bleeding	
	30 min	24 h	30 min	24 h	30 min	24 h	30 min	24 h
A [†]	1.11	0.74	0.47	0.05	0.11	0.00	0.79	0.00
B	1.10	0.78	0.50	0.23	0.15	0.05	0.85	0.03
C	1.30	0.95	0.85	0.10	0.55	1.20	1.35	0.00
F	1.20	0.90	1.05	0.00	1.10	0.30	1.20	0.00
G	1.35	1.00	1.50	0.00	0.50	0.00	1.85	0.00

[†]n = 19.

Erythema: 0 = None, 1 = Mild redness, 2 = Well-defined redness, 3 = Beet redness.

Edema: 0 = None, 1 = Slight edema, 2 = Moderate edema, 3 = Severe edema.

Punctate bruising: 0 = None, 1 = $\leq 25\%$ application site(s) has punctate bruising spots, 2 = ≥ 26 to $\leq 50\%$ application site(s) has punctate bruising spots, 3 = $> 50\%$ application site(s) has punctate bruising spots.

Bleeding: 0 = None, 1 = Color on swab, 2 = Visible blood drop, 3 = Active bleeding.

In this Phase I trial, zolmitriptan delivery with ADAM provided rapid and reproducible zolmitriptan delivery. The $t_{\max}$ was less than 20 min and was comparable to subcutaneously administered sumatriptan. Absorption was substantially faster than for orally administered zolmitriptan, with less measurable N-desmethyl zolmitriptan metabolite, presumably due to a lack of first pass metabolism. PK parameters for subcutaneous sumatriptan and oral zolmitriptan in this study were similar to those previously reported [14,15].

Most AEs (88%) were consistent with those commonly seen in previous trials with triptans [16]. It should be noted that headache is the most frequently reported adverse event in clinical trials in healthy volunteers, and the incidence reported here is in keeping with these findings [17–19]. ADAM was well tolerated, with only one participant in one

treatment group reporting any pain at the application site. Where application site reactions were observed, they were generally mild and resolved after 24 h.

These initial data indicate that ADAM zolmitriptan is a promising approach for rapid and tolerable delivery of zolmitriptan. Results from a recently concluded Phase II/III trial will further elucidate safety and efficacy in migraine treatment. A generally painless, easy to use, skin delivery system for zolmitriptan, with PK comparable to injectable sumatriptan, is likely to be very useful clinically as a nonoral alternative for acute migraine treatment.

The flexibility of the ADAM system with respect to drug formulation makes it amenable to multiple additional indications, particularly when rapid needle-free delivery is warranted.

Executive summary

Migraine treatment

- Despite the availability of multiple treatment options, considerable unmet need persists in the treatment of migraine.
- Triptans are the first-line acute migraine treatment in patients with disabling migraines and no vascular contraindications.
- Optimal migraine treatment provides rapid pain relief with good palatability; currently available formulations and routes of administration for migraine medications do not fully meet these criteria.

Adhesive dermally applied microarray

- The Adhesive Dermally Applied-Microarray (ADAM) is a device for intracutaneous drug administration. It consists of a disposable adhesive backing, with an array of drug (zolmitriptan) coated titanium microprojections mounted on the skin-facing surface. The ADAM microprojection array measures 3 cm² in diameter with 1987 titanium microprojections, each 340 µm in length.
- It is applied to the skin using a low cost, reusable, handheld applicator. Following application, the microprojections penetrate the stratum corneum proximal to the microcapillaries in skin. The shallow depth of penetration and the minuteness of the size of the microprojections limit the likelihood of stimulating sensory nerve endings.
- The ADAM is removed after 30 min and is disposed of.
- Each ADAM is individually packaged and stored at room temperature.

Pharmacokinetic evaluation of zolmitriptan delivery using ADAM

- The pharmacokinetics of zolmitriptan delivery using ADAM was evaluated in a Phase I, single center, open-label, ascending dose, tolerability Phase I study in healthy volunteers, aged 18–60 years (n = 20).
- The time to maximum concentration was less than 20 min and was comparable to subcutaneously administered sumatriptan.
- Absorption was substantially faster than for orally administered zolmitriptan with less N-desmethyl zolmitriptan metabolite, presumably due to a lack of first pass metabolism.

Tolerability of ADAM

- In the Phase I study, most adverse events were consistent with those commonly seen in previous trials with triptans.
- The most commonly reported adverse events (≥10% in any group) were paresthesia; headache; throat and jaw tightness, heaviness or ache; hot flushes; and upper respiratory tract infection.
- ADAM was well tolerated, with only one participant in one of five ADAM treatment groups reporting any pain at the application site.
- Where application site reactions were observed, they were generally mild and resolved after 24 h.

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Informed consent disclosure

The study was reviewed and approved by The Alfred Hospital Ethics Committee and all participants provided informed consent.

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