Pharmacokinetics and Tolerability of a New Intracutaneous Microneedle System of Zolmitriptan (ZP-Zolmitriptan)

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ABSTRACT

Background

Zolmitriptan has been used extensively for the treatment of migraine. Zosano Pharma has developed an intracutaneous microneedle system (patch) of zolmitriptan that in preclinical studies achieved maximum absorption in 5-30 minutes following administration to mini-pigs. This Phase 1 study was designed to evaluate the pharmacokineticis and tolerability of ZP-Zolmitriptan at various doses in healthy volunteers. Oral zolmitriptan 2.5 mg and subcutaneous sumatriptan 6.0 mg were included as comparators.

Methods

The study was a 5-way randomized crossover of ZP-Zolmitriptan 0.48 mg, 0.96 mg, 1.9 mg, oral zolmitriptan 2.5 mg, and SC sumatriptan 6.0 mg in 10 male and 10 female healthy volunteers. Following completion of this portion, subjects received ZP-Zolmitriptan 3.8 mg, initially as 2 x 1.9 mg, and then as a single larger 3.8 mg patch. All patches were applied with proprietary applicators.

Results

All subjects completed the study. ZP-Zolmitriptan administration resulted in rapid absorption of zolmitriptan, with maximum plasma concentrations (Cmax) achieved on average at approximately 17 minutes (range 2-30 minutes). Cmax and AUCs following ZP-Zolmitriptan were dose proportional. Cmax following 0.96 mg, 1.9 mg, and 3.8 mg of ZP-Zolmitriptan were comparable to or greater than those seen following 2.5 mg of oral zolmitriptan. ZP-Zolmitriptan was well-tolerated, reported adverse events were those typically reported for zolmitriptan (e.g. paresthesia and headache) nearly all mild in intensity, and incidence rates increased as systemic zolmitriptan exposure increased. The rate and type of adverse events seen at 3.8 mg of ZP-Zolmitriptan was similar to those seen after 6.0 mg of sumatriptan.

The ZP-Zolmitriptan system is a new formulation of zolmitriptan that rapidly delivers drug to the systemic circulation in a dose-related manner. The rapid delivery of zolmitriptan was well-tolerated. The ZP-Zolmitriptan system is a promising approach for rapid delivery of a proven drug, and larger studies in patients with migraine are planned.

OBJECTIVES

Study Objective

The objectives of this Phase 1 pharmacokinetic study in healthy volunteers were to:

1. Evaluate the pharmacokinetic parameters (AUCt, AUCinf, Cmax, Tmax, and t1/2) and tolerability of ascending single doses of ZP-Zolmitriptan intracutaneous microneedle systems;
2. Understand the extent (%) of zolmitriptan converted to the active, N-desmethylzolmitriptan metabolite;
3. Determine the relative bioavailability of ZP-Zolmitriptan (compared with a conventional release oral zolmitriptan tablet);
4. Compare the pharmacokinetic profiles of ZP-Zolmitriptan intracutaneous microneedle systems administered as a single system or multiple systems;
5. Compare the pharmacokinetic profiles of ZP-Zolmitriptan intracutaneous microneedle systems with both oral zolmitriptan (Cmax) and SC sumatriptan (Tmax).

METHODS

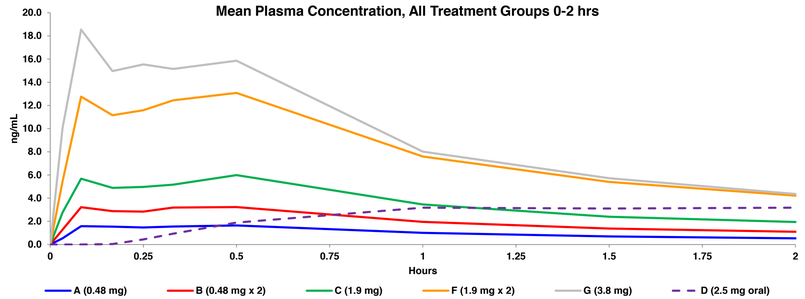
Method

Five-way crossover (Part 1) followed by dose escalation (Parts 2 and 3) in 10 females and 10 male healthy volunteers

- **Part 1 (Cross-Over Design)**
  - Treatment A: ZP-Zolmitriptan system 0.48 mg
  - Treatment B: ZP-Zolmitriptan system 0.48 mg x 2
  - Treatment C: ZP-Zolmitriptan system 1.9 mg
  - Treatment D: Zolmitriptan 2.5 mg oral
  - Treatment E: Sumatriptan 6.0 mg SC
- **Part 2**
  - Treatment F: Zolmitriptan system 1.9 mg x 2
- **Part 3**
  - Treatment G: Zolmitriptan system 3.8 mg
- Blood samples at 0, 2, 5, 10, 15, 20, 30, 60 min and 2, 4, 8, 12, 24 hr
- ECGs and Vital signs collected pre-dose and frequently post-dose
- All 20 subjects completed all 7 visits, with the exception of 1 subject not receiving Treatment A and 1 subject not receiving Treatment D
- Mean Age of the subjects was 28.9 years

PK RESULTS

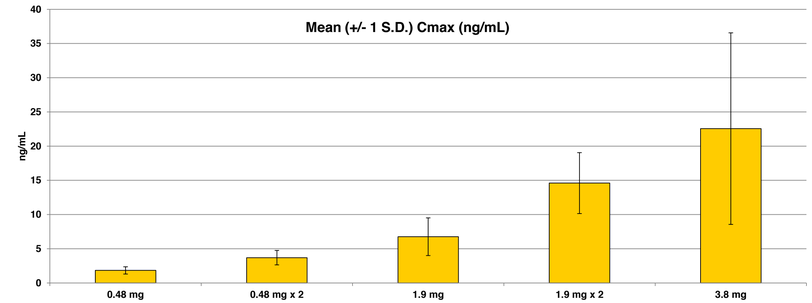
Zolmitriptan Plasma Concentrations



PK Parameters

	Dose (mg)	Mean C_{max} (SD) ng/mL	Median T_{max} (Range) Min	Mean AUC_{0-2hr} (SD) ng/mL hour	Mean AUC_{0-last} (SD) ng/mL hour	Mean AUC_{0-last} /Dose	BA v Oral
A (ZP Zolmi) (n=19)	0.48	1.8 (0.53)	20 (2-30)	2.1 (0.73)	2.8 (1.36)	5.8	67%
B (ZP Zolmi) (n=20)	0.48 x 2	3.7 (1.05)	20 (2-30)	4.2 (0.95)	6.5 (1.97)	7.5	87%
C (ZP Zolmi) (n=20)	1.9	6.8 (2.75)	20 (2-30)	7.4 (2.53)	12.3 (4.31)	6.5	76%
F (ZP Zolmi) (n=20)	1.9 x 2	14.6 (4.46)	17.5 (2-30)	16.4 (5.34)	27.8 (9.93)	7.3	85%
G (ZP Zolmi) (n=20)	3.8	22.6 (14.00)	15 (2-30)	19.3 (5.37)	31.7 (8.35)	8.3	97%
D (Oral Zolmi) (n=19)	2.5	3.8 (1.51)	60 (30-240)	4.7 (2.24)	22.2 (10.79)	8.6	100%
E (SC Suma) (n=20)	6.0	88.8 (27.56)	10 (5-20)	70.9 (14.15)	100.9 (23.29)	16.8	

Dose Linearity (Cmax)



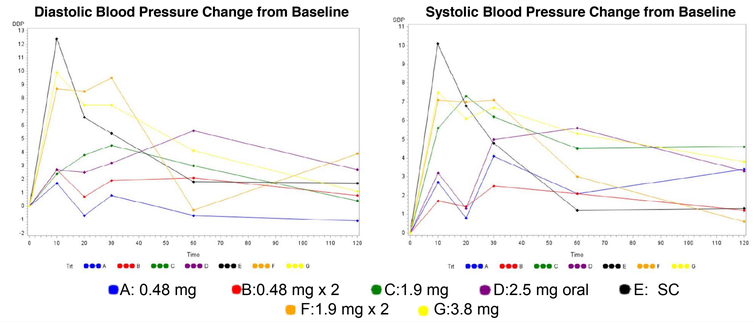
Time to Oral Cmax (3.8 ng/mL)

Proportion of Subjects Reaching Oral Cmax Plasma Concentration by Time Post Patch Administration

	By 2 min	By 5 min	By 10 min	By 15 min	By 20 min	By 30 min	By 60 min	By 90 min	By 120 min
A: 0.48 mg	5%	11%	11%	11%	11%	11%	11%	11%	11%
B: 0.48 mg x 2	20%	37%	45%	45%	45%	50%	55%	55%	55%
C: 1.9 mg	35%	63%	70%	70%	75%	85%	85%	85%	85%
F: 1.9 mg x 2	70%	100%	100%	100%	100%	100%	100%	100%	100%
G: 3.8 mg	60%	100%	100%	100%	100%	100%	100%	100%	100%

SAFETY RESULTS

Vital Signs (Blood Pressures)



Adverse Events

Most Common Adverse Events in the Phase 1 Trial

	Part 1					Part 2	Part 3	
Adverse Events	**ZP-Zolmi 0.48 mg (n=19)**	**ZP-Zolmi 0.48 mg x 2 (n=20)**	**ZP-Zolmi 1.9 mg (n=20)**	**ZP-Zolmi 2.5 mg (oral) (n=19)**	**Suma 6.0 mg SC (n=20)**	**ZP-Zolmi 1.9 mg x 2 (n=20)**	**ZP-Zolmi 3.8 mg (n=20)**	**Total**
Headache	3	2	4	0	0	4	4	17
Hot flushes	0	0	0	0	0	2	2	4
Paresthesia	0	2	3	0	6	10	8	29
Throat and jaw tightness, heaviness, ache	0	0	1	0	0	2	2	5

CONCLUSIONS

1. ZP-Zolmitriptan administration resulted in rapid peak plasma concentrations (Tmax) that occurred within 20 minutes of patch application.
2. There was excellent dose linearity observed for high and low dose for C_{max} and AUC_{inf}.
3. ZP-Zolmitriptan was well-tolerated. Adverse events were predominantly mild (87%), of a short (<24 hour) duration and the majority were consistent with events previously reported with zolmitriptan.
4. ZP-Zolmitriptan intracutaneous microneedle system offers pharmacokinetic advantages over zolmitriptan tablets that may result in a faster onset of action, comparable exposure and reduced first-pass metabolism with the lowered potential for drug interactions and adverse events.