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A Randomized, Double-blind, Vehicle-controlled Phase I Study Evaluating the Safety and Pharmacokinetic Profile of RSS0393 Ointment as a Single and Multiple Dose Ascending Local Dermal Administration in Healthy and Adult Subjects with Psoriasis

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Introduction & Objectives:

RSS0393 is a highly potent, selective PDE-4 inhibitor in development for once-daily topical treatment of chronic plaque psoriasis. This first-in-human study was objected to evaluate the safety, tolerability, pharmacokinetic parameters in healthy adults and also to evaluate the clinical response in patients with plaque psoriasis of RSS0393 ointment treatment.

Materials & Methods:

This phase 1, randomized, double-blind, vehicle-controlled, first-in-human study contained three parts (Clinicaltrials.gov, NCT 06308393). Part 1 was single-ascending dose (SAD) study in healthy subjects randomized (3:1) in 4 groups of 2 doses (0.01% and 0.03% of RSS0393) or corresponding vehicle to apply to about 2% – 20% of skin measured by the body surface area (BSA), respectively. Part 2 was a multiple ascending dose (MAD) study consecutively administrated for 10 days in healthy subjects randomized (3:1) in 3 groups of 2 doses or corresponding vehicle, respectively. Part 3 was a multiple dose groups study consecutively administrated for 28 days in psoriasis patients randomized (2:1) in 2 groups of 2 doses or corresponding vehicle (Figure 1). The primary endpoints of safety and tolerance were including treatment-emergent adverse events (TEAEs) and percent of local skin tolerance. Clinical response was measured by the percentage change in psoriasis area and severity index (PASI) score from baseline, the percentage of subjects' achieving physician's global assessment (PGA) score of 0 or 1 and which improvement ≥ 2 from baseline, and PASI75, etc.

Results:

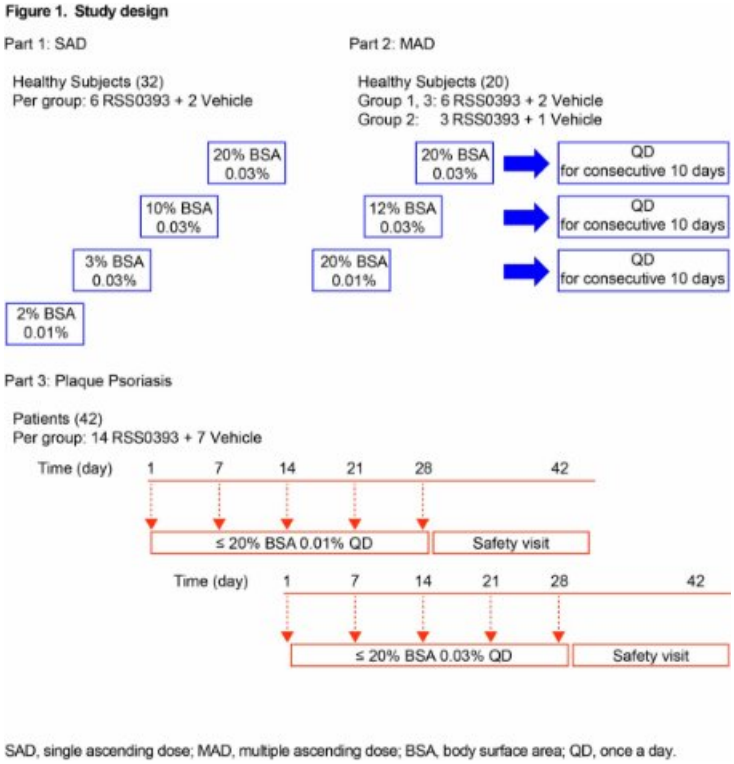
In total, 52 healthy subjects (32 of SAD and 20 of MAD) and 46 psoriasis patients were randomized. Demographics and baseline characteristics were balanced across groups. Most TEAEs in this study were mild or moderate. In healthy subjects of SAD and MAD, TEAEs occurred in 33.3% to 66.7% of RSS0393 groups while in 50% to 80% of vehicle groups. In psoriasis patients, the incidence of TEAEs in RSS0393 groups and vehicle was 71.4%, 64.7% and 33.33%, respectively. The majority of TEAEs were laboratory test abnormalities and no participants discontinued study due to TEAEs (Table 1). Additionally, the tolerability assessment of RSS0393 group

showed no skin irritation reported in healthy subjects, and several mild skin irritation cases in psoriasis patients (2 in physician's assessment and 3 in patient's assessment). As the exposure of RSS0393 through local dermal administration was low, the geometric mean of Cmax was from 47.7 to 62.0 pg/mL in SAD and from 95.9 to 109.0 pg/mL in MAD after the last dose. The mean percentage change in PASI from baseline was up to -56.8% in RSS0393 groups (vs. -25.3% in vehicle). Clinical response of PGA score of 0 or 1 and which improvement ≥ 2 from baseline and PASI 75 also outperformed in RSS0393 compared to vehicle (Table 2).

Conclusion:

Local dermal administration of RSS0393 showed acceptable safety and tolerance of in healthy subjects and potential efficacy in psoriasis patients. These results support further clinical development of RSS0393 ointment for plaque psoriasis.

Figure 1. Study design



SAD, single ascending dose; MAD, multiple ascending dose; BSA, body surface area; QD, once a day.

Table 1. Treatment-emergent adverse events

	SAD		MAD				PsO		
TEAE，n (%)	Total Vehicle (N=8)	Total RSS0393 (N=24)	Total Vehicle (N=5)	0.01% 20% BSA (N=6)	0.03% 12% BSA (N=3)	0.03% 20% BSA (N=6)	Total Vehicle (N=15)	0.01% (N=14)	0.03% (N=17)
Any TEAEs	4 (50.0)	12 (50.0)	4 (80.0)	2 (33.3)	1 (33.3)	4 (66.7)	5 (33.3)	10 (71.4)	11 (64.7)
Mild	4 (50.0)	11 (45.8)	4 (80.0)	2 (33.3)	1 (33.3)	4 (66.7)	3 (20.0)	9 (64.3)	9 (52.9)
Moderate	0	1 (4.2)	0	0	0	0	2 (13.3)	1 (7.1)	2 (11.8)
Severe	0	0	0	0	0	0	0	0	0
TEAE leading to study discontinuation	0	0	0	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0	0	0	0
TEAEs occurring in ≥ 2 participants in any groups									
Bilirubin conjugated increased	2 (25.0)	4 (16.7)	0	0	0	1 (16.7)	0	0	1 (5.9)
Blood triglycerides increased	0	2 (8.3)	3 (60.0)	1 (16.7)	1 (33.3)	0	1 (6.7)	1 (7.1)	2 (11.8)
Blood uric acid increased	0	0	2 (40.0)	0	1 (33.3)	2 (33.3)	0	0	0
Blood bilirubin unconjugated increased	0	1 (4.2)	0	0	0	2 (33.3)	0	0	0
Urinary occult blood positive	0	0	0	0	0	0	0	1 (7.1)	4 (23.5)
Blood lactate dehydrogenase increased	0	1 (4.2)	0	0	0	0	0	2 (14.3)	1 (5.9)
Hypophagia	0	0	0	0	0	4 (66.7)	0	0	0
Nausea	0	0	0	0	0	3 (50.0)	0	0	0
Abdominal discomfort	0	0	0	0	0	3 (50.0)	0	0	0
Headache	0	0	0	0	0	2 (33.3)	0	0	0
Dizziness	0	0	0	0	0	2 (33.3)	0	0	0
Hyperuricaemia	0	0	0	0	0	0	0	2 (14.3)	0
Sinus bradycardia	0	0	0	0	0	0	0	0	3 (17.6)
Ventricular extrasystoles	0	0	0	0	0	0	0	0	2 (11.8)

TEAE, Treatment-emergent adverse event; SAD, single ascending dose; MAD, multiple ascending dose; PsO, psoriatic patients.

Table 2. Demographic, baseline characteristics and clinical response of RSS0393 ointment in 4 weeks treatment

	Vehicle	RSS0393 Ointment	
		0.01%	0.03%
Baseline, n	15	14	17
Age, year (SD)	45.1 (14.1)	41.7 (11.3)	46.1 (8.8)
Male sex, n (%)	12 (80.0)	13 (92.9)	13 (76.5)
PASI, mean (SD)	7.5(2.6)	8.6 (2.1)	7.8 (3.6)
PGA score 2, n (%)	7 (46.7)	3 (21.4)	7 (41.2)
PGA score 3, n (%)	8 (53.3)	11 (78.6)	10 (58.8)
BSA, mean (SD)	7.3 (4.0)	9.8 (4.2)	7.9 (4.2)
4 Weeks, n	9	13	17
Percentage change in PASI from baseline, mean (SD)	-25.3 (17.3)	-46.3 (23.3)	-56.8 (21.3)
PGA score of 0 or 1 and which improvement ≥ 2 from baseline, n (%)	0	1 (7.1)	3 (17.6)
PASI 75, n (%)	0	0	3 (17.6)

SD, standard deviation; PASI, psoriasis area and severity index; PGA, physician's global assessment; BSA, body surface area.

PASI 75 indicates a reduction from baseline in the PASI score of at least 75%.