Evaluation of the Immunogenicity and Safety of Recombinant Human Thrombin After Subsequent Surgical Re-exposure

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INTRODUCTION

Recombinant human thrombin (rThrombin; RECOTHROM®) is an active topical hemostat that is approved by the FDA as an aid to hemostasis. The safety, immunogenicity, and efficacy of rThrombin have been assessed in clinical studies, including a randomized, double-blind Phase 3 study as well as studies of rThrombin in adult, adolescent, and pediatric burn wound excision.[1,2,3] No safety observations have been deemed clearly causally related to exposure to rThrombin in these studies, and a low rate of non-neutralizing antibody formation to rThrombin product has been consistently observed.

Because therapeutic proteins may induce an immune response, it is important to evaluate their potential for immunogenicity upon re-exposure.

- Therapeutic proteins typically have a complex production process, potential for immunogenicity, and limited data on immunogenic potential prior to commercialization.[4]
- Some therapeutic proteins have been associated with allergic reactions (e.g., streptokinase, bovine insulin, recombinant Factor VIII, bovine thrombin).[5]
- Antibodies to bovine thrombin or bovine Factor V have been associated with immune-mediated coagulopathies in some patients. This has resulted in a "boxed" warning in the labeling of the US bovine thrombin product (Thrombin-JMI®; King Pharmaceuticals®, Inc.) stating that "patients with antibodies to bovine thrombin preparations should not be re-exposed to these products."[6]
- Immunogenicity of a protein upon secondary exposure represents a key marker of drug tolerability.

To date, no published study has prospectively evaluated the safety and immunogenicity of any stand-alone thrombin product upon deliberate re-exposure during surgery.

Subjects undergoing spinal, cardiovascular, and orthopedic procedures represent an appropriate patient population for evaluating rThrombin immunogenicity because these patients often require the use of hemostatic adjuncts during surgery.

OBJECTIVE

To evaluate the immunogenicity and safety of rThrombin in subjects with prior exposure to rThrombin

METHODS

- Phase 4, open-label, single-group, multisite study
- 31 adult patients with documented prior exposure to rThrombin
- Undergoing surgical procedure in which topical rThrombin application was planned
- Received rThrombin during surgical procedure; safety follow-up 1-48 hours post-surgery; additional safety and immunogenicity follow-up at Day 29
- Immunogenicity evaluated by enzyme-linked immunosorbent assay (ELISA) at baseline and Day 29
- Adverse events (AEs) collected through Day 29
- Safety evaluations included incidence/severity of AEs, incidence/grade of clinical laboratory abnormalities

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RESULTS

- 31 subjects treated with rThrombin
- 30 subjects had both baseline and Day 29 immunogenicity data available

Table 1. Patient Characteristics

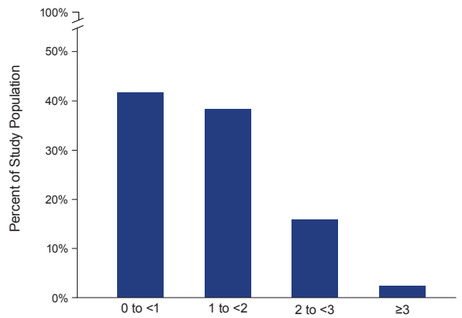
	Category/Statistic	Total (N = 31)
Age (years)	Mean (SD)	59.48 (12.30)
	Median	61.0
	Min, Max	22.0, 81.0
Gender, n (%)	Male	19 (61.3%)
	Female	12 (38.7%)
Race, n (%)	Black/Affrican-American	4 (12.9%)
	Hispanic	6 (19.4%)
	White	21 (67.7%)
Surgery Type, n (%)	Spinal	23 (74.2%)
	Arterial reconstruction/PAB	4 (12.9%)
	AV access	3 (9.7%)
	Other	1 (3.2%)
Number prior rThrombin exposures, n (%)	1	30 (96.8%)
	2	1 (3.2)

Abbreviations: AV, arteriovenous vascular; PAB, peripheral arterial bypass

Exposure to rThrombin

- Most subjects (n=30/31; 96.8%) had 1 known prior exposure to rThrombin; 1 subject had 2 known prior exposures (n=1/31; 3.2%)
- Mean interval between documented prior exposures was 464.7 d (1.27 yr); range 19-1204 d (3.29 yr)
- Mean (SD) volume of rThrombin reconstituted per subject = 19.8 mL (19.0); median 10.0 mL, range 5-60 mL
- rThrombin concentration: 1000 IU/mL

Figure 1. Time Interval Since Prior Exposure to rThrombin



Safety of rThrombin

- No subjects discontinued the study due to AEs
- One subject discontinued due to death unrelated to study-drug treatment
- 12 SAEs experienced by 6/31 (19.4%) of subjects; none identified as related to treatment with rThrombin
- No clinically meaningful changes in laboratory values

Table 2. rThrombin Antibody Status by Visit

Visit	Antibody Status	n/N	% (95% CI[a])
Baseline	Pre-existing[b]	0/30	0.0% (0.0, 11.6)
Day 29	Antibody positive[b,c]	0/30	0.0% (1.0, 11.6)
	Seroconversion[d]	0/30	0.0% (0.0, 11.6)
	> 1.0 titer change[e]	0/0	0.0%

[a] Two-sided exact binomial confidence interval
[b] Denominator includes subjects in the immunogenicity analysis set
[c] Subjects are considered antibody positive if they seroconvert or have a post-baseline increase of ≥1.0 titer unit in anti-rThrombin product antibody titer
[d] Denominator includes subjects without specific anti-rThrombin product antibodies at baseline and with post-baseline immunogenicity data
[e] Denominator includes subjects with specific anti-rThrombin product antibodies at baseline and with post-baseline immunogenicity data

Immunogenicity of rThrombin

- Immunogenicity analysis set comprised 30 subjects treated with rThrombin who had data from both baseline and Day 29 antibody assessments
- No pre-existing anti-rThrombin product antibodies were observed in any of the 30 subjects evaluated (0%; 95% CI: 0.0%, 11.6%)
- No subjects were antibody positive for anti-rThrombin product antibodies at Day 29 (0%; 95% CI: 0.0%, 11.6%)
- Study was not powered to determine exact incidence of anti-rThrombin product antibodies upon re-exposure to rThrombin

Table 3. Treatment-Emergent AEs for > 10% of Patients

Preferred Term*	Total (N = 31), n (%)
Any AE	29 (93.5%)
Procedural pain	23 (74.2%)
Constipation	8 (25.8%)
Nausea	8 (25.8%)
Anaemia postoperative	6 (19.4%)
Muscle spasms	6 (19.4%)
Tachycardia	6 (19.4%)
Incision site pain	5 (16.1%)
Insomnia	4 (12.9%)
Pruritus	4 (12.9%)

*MedDRA version 13.0

CONCLUSIONS

- rThrombin was well tolerated; AEs and clinical laboratory abnormalities were as expected for these surgical populations and consistent with previous rThrombin studies[7]
- Re-exposure to rThrombin did not lead to the development of anti-rThrombin product antibodies in any patient
- Lack of antibody development suggests that incidence upon re-exposure is not substantially increased from incidence upon first exposure
- Patients with known prior exposure to rThrombin may be safely re-exposed to the product