# Recombinant factor XIII is safe and effective for prophylaxis in young children with congenital FXIII A-subunit deficiency: results from the mentor™5 international phase 3 trial

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## Objective

- To evaluate the long-term safety and efficacy of monthly prophylaxis with recombinant FXIII (rFXIII) for the prevention of bleeding episodes in young children with congenital factor XIII (FXIII) A-subunit deficiency.

## Conclusions

- Prophylaxis with rFXIII was well tolerated, with no safety issues identified. No anti-rFXIII antibodies, no thromboembolic events and no allergic reactions were detected.
- Prophylaxis with rFXIII was effective with mean trough pre-dose FXIII activity levels well above 0.1 IU/mL (10%) and a geometric mean trough FXIII activity of 0.19 IU/mL.
- The annualized bleeding rate (ABR) was zero.
- rFXIII is safe and effective in paediatric subjects younger than six years with congenital FXIII A-subunit deficiency.

## Introduction

- Congenital FXIII deficiency is a rare and severe bleeding disorder associated with unpredictable and serious bleeds including spontaneous intracranial hemorrhage (ICH).
- FXIII prophylaxis is the standard of care for patients with severe deficiency; rFXIII was demonstrated to be safe and effective for prophylaxis in patients aged ≥6 years[1] and has recently been approved for bleeding prophylaxis in patients with congenital FXIII-A deficiency.

## Methods

### Study design

- Children <6 years who had previously completed the single-dose pharmacokinetic and safety trial mentor™4 were recruited.[2]
- 35 IU/kg rFXIII were administered intravenously every 28±2 days for a minimum of 52 weeks.
- The primary safety endpoint was defined as treatment emergent serious and non-serious adverse events; secondary safety endpoints included inhibitory and non-inhibitory antibody development, laboratory, physical examination, and laboratory or clinical abnormalities.
- The secondary efficacy endpoint included the rate of treatment-requiring bleeds and number of subjects withdrawn due to lack of efficacy.

### Assays

- Pre- and post-dose samples were assessed for FXIII activity and anti-rFXIII antibodies by the Berichrom® FXIII activity assay[1-4], and by ELISA[1], respectively, at each dose visit for 48 weeks; thereafter pre-dose samples were assessed at least every 12 weeks.



## Results

### Patient characteristics

- 3 boys and 3 girls from 5 sites were included in the trial (Israel [1], UK [3], USA [2]).
- Patient baseline characteristics are summarized in Table 1.
- The 6 patients were exposed to a mean of 35.7 (± 8.6) doses per patient over a mean of 33.1 (± 8.1) months. Total treatment duration was 1.8-3.5 years for a total of 16.6 patient-years.

**Table 1** Patient demographics and disposition at baseline.

| Parameter | | Patients (n=6) |
|---|---|---|
| Age at baseline [years] | Mean (SD) | 3.0 (1.3) |
| | Median | 3.5 |
| | Min; Max | 1; 4 |
| Race | Asian | 3 (50.0%) |
| | Black or African American | 1 (16.7%) |
| | White | 2 (33.3%) |
| Screened and exposed | | 6 |
| Withdrawals | Adverse event | 0 (0.0%) |
| | Non-compliance | 0 (0.0%) |
| | Protocol deviation | 0 (0.0%) |
| | Withdrawal criteria: w2* | 1 (16.7%) |
| | Other | 0 (0.0%) |

*w2: withdrawn after 20 months per investigator's discretion (family went abroad for time period which exceeded that between trial visits).

### Adverse events (AE)

- No thromboembolic events or systemic allergic reactions were detected in any of the patients.
  - 3 skin rashes (atopic dermatitis) were reported in 1 patient.
- The reported AEs are summarized in Table 2.
- A total of 93 mild and 7 moderate AEs were reported including:
  - 2 serious AEs occurred in 1 patient, both head injuries related to falls during play, without ICH.
  - 2 AEs were considered probably or possibly related to rFXIII: 1 patient had a viral gastroenteritis and recovered uneventfully without change in dose. 1 patient, lympho-cytopenic at baseline, continued to have fluctuating, mild lymphocytopenia during the trial.

**Table 2** Summary of adverse events

| | N | (%) | E |
|---|---|---|---|
| All AE | 6 | (100) | 100 |
| Serious AE | 1 | (17) | 2 |
| AE by severity | | | |
| Severe | 0 | (0) | 0 |
| Moderate | 3 | (50) | 7 |
| Mild | 6 | (100) | 93 |
| AE by relationship | | | |
| Probably or possibly related | 2 | (33) | 2 |
| Unlikely related | 6 | (100) | 98 |
| MESI[$] | 4 | (67) | 6 |

N: Number of subjects. %: Percentage of subjects. E: Number of AEs.
[$]MESI: Medical event of special interest: 3 incorrect administrations of rFXIII and 3 skin rashes, all judged to be unrelated to the use of rFXIII.

### Antibody assessment

- No anti-rFXIII antibodies (inhibitory or non-inhibitory) were detected in any of the patients during the trial.

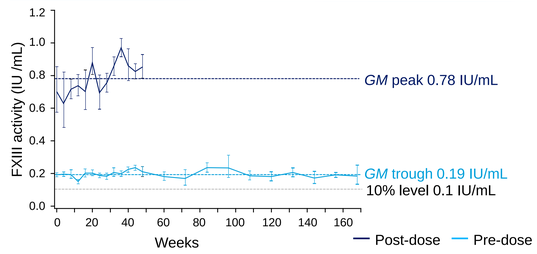
### Bleeding episodes

- No treatment-requiring bleeding episodes occurred.
  - 14 minor bleeding episodes that did not require treatment with a FXIII-containing product occurred in 5 patients.
- The **annualized bleeding rate was 0**.

### FXIII activity

- All mean trough FXIII activity levels, obtained 30 minutes before the dose, were above 0.1 IU/mL with a geometric mean (GM) FXIII activity of 0.19 IU/mL (Fig. 1). The GM peak FXIII activity, obtained one hour after the dose, was 0.78 IU/mL.

**Figure 1** FXIII activity profile (IU/ ml).




## References

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### Conflict of interest disclosure

S. Kearney has served as a consultant for Biogen Idec, and has received grant/research support from Bayer, Biogen Idec and Novo Nordisk. A. Inbal has nothing to declare. A. Will has nothing to declare. M. Williams has received financial support to attend scientific meetings from Baxter, Bayer, CSL Behring and Novo Nordisk, and has served as a consultant for Baxter, Bayer and CSL Behring. M.-L. Garly and L. Jacobsen are employees of Novo Nordisk A/S, the manufacturer of the study drug. B. Kerlin has served as a consultant for Baxalta Inc, Bayer Healthcare US and Novo Nordisk and has received research support from CSL Behring Foundation and Novo Nordisk A/S.

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