

RECORD OF TELEPHONE CONVERSATION

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Title/Product: Coagulation Factor IX (Recombinant), Albumin Fusion Protein
Sponsor/Applicant: CSL Behring Recombinant Facility AG (CSLB)
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Telecon Summary: Telecon Requested by CSLB for Clarification on PI Revisions by the FDA and FDA's re-evaluation of the 14-day dosing regimen for IDELVION

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Telecon Body:

This teleconference was requested by CSLB to discuss the package insert revision requested in an information request dated January 21, 2016. CSLB also included further discussion for the FDA's re-evaluation of the 14-day dosing regimen for IDELVION.

Prior to the meeting CSLB sent a discussion document for the scheduled teleconference late Thursday, January 21, 2016. The RPM received the document in the morning of January 22, 2016 and routed to the FDA participants.

These are the discussion points that were conveyed in the 1/21/16 document from CSLB:

FDA Comment #1:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We are providing the following comments and request for labeling revision to continue our review:

We have considered your request to allow a labeling claim for both 7-day and 14-day dosing regimens, and have concluded that:

- 1. Population and observed pharmacokinetic (PK) data do not support a claim for a 14-day dosing regimen for the general hemophilia population. These data suggest that patients would not be able to maintain FIX activity levels above 3%, which FDA considers more clinically relevant than the 1% threshold that you proposed.*

CSLB Discussion Points:

- Observed PK data from Pivotal Study 3001 following single dose of 50 IU/kg in 35 subjects yielded a mean/SD (6.10% [3.288]) and median (5.3%) Factor IX activity levels at 336 hours (Module 5.3.5.2; Table 14.3.2.1).
- Observed PK data from PK Study 2001 following a single dose of 75 IU/kg in 8 subjects yielded a mean/SD (6.65% [2.299]) and median 5.95%; all were above 3% at 336 hours (Module 5.3.3.2, Table 14.2.1.1.2).
- The lowest observed value from the Population PK dataset (Module 5.3.3.5, RA2120032 addendum) at 75 IU/kg is 2.6%, up to 360 hours (Day 15) across Studies 2001, 2004 and 3001; all other points are above 3% activity.

- **Table 1** indicates that with a repeated dose of 75 IU/kg once every 14 days for a median time of over 12 months, the trough increases, rather than decreases as FDA suggested. All eighteen patients tested have over 3% trough with a median of 12.4%, consistent with the PK model presented in the BLA with an exogenous median activity of 8% [90% PI 2.6-18.5]. (Module 5.3.3.5, RA2120032 addendum).

Table 1. Observed FIX activity trough for 75 IU/kg once every 14-days in Study 3001

Parameter	FIX activity (IU/dL)
N	18
Observations	116
Mean (SD)	13.66 (9.89)
Median	12.4
Q1, Q3	10.1, 15.1
Minimum	3.1

Source data: Listing 16.2.5.7, Study 3001.

All FIX activity values were included which were collected on Day 14 following a prophylaxis dose of 75 IU/kg for subjects on a 14-day treatment interval. PK, repeat-PK and surgery periods were excluded. If a dose for any other reason was given between two prophylaxis dose time intervals, the FIX activity value was excluded.

- During the late cycle meeting, FDA stated that there was an effort to harmonize the coagulation prescribing information. However, there was no mention of a change in FDA’s definition for standard of care which is considered to be a clinically relevant threshold for factor IX activity and associated labeling expectations. In the 21 Jan 2016 request for information, FDA stated that 3% is more clinically relevant than 1%. However, in approvals for other coagulation products it appears that the Agency has advocated that 1% is clinically relevant.

For example, in Alprolix’s Clinical Pharmacology BLA review (08 Jan 2013), the FDA reviewer rejected the every 14-day dosing “...as a dose of 100 IU/kg every 10 days more than 85% of the population was within the range of 1% to 150%. These results suggest that in a dosing regimen of 100 IU/kg every 14 days nearly 50% of the patients will not achieve therapeutic concentrations”. However, the 10-day regimen was considered to be sufficient to achieve and sustain therapeutic concentrations above 1%.

In addition, there is no restriction (dose adjustment) for children in the Alprolix prescribing information, even though the population for Alprolix mentioned above does not include children <12 years of age.

- Observed pediatric PK data (Module 5.3.5.2, Study 3002, Table 14.2.12.1) demonstrated that for the total population of 24 children receiving a single dose of 50 IU/kg at Day 10, the median was 5.3% (IQR 4.0 to 6.65%). At Day 14, children (n=15) receiving a single dose of 50 IU/kg, the median was 2.4% (IQR 2.0 to 3.2%).

Population and observed PK data do support dosage and administration of IDELVION for routine prophylaxis of 50-75IU/kg at 10 to14-day intervals.

FDA Comment #2:

2. *The clinical trial data do not support a claim for a 14-day dosing regimen for the general population because the subjects treated with the extended (10 or 14-day) regimens were a select population who were maintained on a 7-day regimen and met pre-specified switching criteria. Because of this selection bias, any observed efficacy may not be generalizable to the hemophilia population at large. To support a claim for the 14-day regimen for the general population, please submit a supplemental biologics licensing application (BLA) with safety and efficacy data for subjects maintained on a 14-day regimen only (i.e., not treated initially with a 7-day regimen). We further recommend that trough factor VIII activity should be measured at Days 7, 10 and 14. FDA understands that an additional trial may be required to obtain these data.*

CSLB Discussion Points:

As noted in the above discussion points, sufficient PK supporting FDA’s preferable clinically relevant threshold of 3%, along with robust efficacy data while applying appropriate switching criteria per protocol, supports 50-75 IU/kg body weight at both 10 and14-day dosing intervals (Section 2.1 Routine Prophylaxis USPI).

FDA Comment #3:

3. *FDA noted that following repeat dosing, FIX activity in the terminal phase (168 and 240 hours) is generally lower than the first dose. For example (Table 14.3.2.6), baseline corrected FIX activity following 50 IU/kg dose was 12.46 IU/dL and 9.71 IU/dL (168 hours after infusion) following single and repeat dose, respectively (both minimum and maximum FIX activities were lower following single and repeat dosing). A similar observation was noted at 240 hours after infusion. Since there is an overall 17% increase in AUC following repeat dosing, the lower FIX activity in the terminal phase is counterintuitive. Please explain this phenomenon.*

CSLB Discussion Points:

The Factor IX activity levels above which FDA references (Study 3001, Table 14.3.2.6) are based upon baseline corrected data. However, the patients were not completely washed out per protocol for repeat PK evaluation. Therefore, the Factor IX activity data at 168, 240 and 336 hours are artificially lower if corrected by the subject's residual Factor IX activity level prior to receiving the dose for repeat PK analysis. Therefore, baseline correction is not the preferred method for evaluating the summary statistics for the concentration over time during repeat PK evaluation.

For the analysis of a baseline corrected PK parameters (AUC), the patient's pre-dose value from initial PK was used for baseline correction for both initial and repeat PK, in order to characterize relative accumulation. However, for the baseline correction of the Factor IX activity levels in Table 14.3.2.6, the patient's pre-dose Factor IX activity level prior to repeat PK dosing was used (Study 3001, Listing 16.2.5.7).

Therefore, the noted levels from baseline corrected data in Table 14.3.2.6 are inconsistent with the noted consistent and expected increase (~17%) in multiple AUC metrics. Accumulation due to long half-life characteristics of IDELVION is anticipated, and apparent in the repeat PK evaluation for both baseline corrected and uncorrected AUC values.

The phenomenon noted by the FDA review is explained by the different approaches to baseline correction.

FDA Comment #4:

4. The clinical trial and observed PK data allow for a claim for a 10-day regimen for patients who will be treated on the 7-day regimen and meet the same switching criteria as was used in clinical trial 3001 (see proposed language in the attached draft Prescribing Information). However, there is insufficient evidence to support the 14-day regimen for this selected population. Because FIX activity trough levels may be lower after repeat dosing, FDA is concerned that patients maintained on a 14-day regimen may not be able to maintain appropriate FIX activity levels over time and therefore may pose a safety risk to patients. To support a claim for the 14-day regimen for the selected population, please submit a supplemental BLA that includes a full PK analysis to adequately address this safety risk.

CSLB Discussion Points:

CSLB believes that the data from Study 3001 provides sufficient evidence to support a 14-day dosing regimen. The 14-day regimen was shown to be non-inferior to the 7-day regimen; subjects were on 14-day regimen for a median of 12.7 months; and the Median AsBR was 0.0. [Table 1](#) provides the observed factor IX activity on repeated 75 IU/kg

dose once every 14 days; the median trough for this dose regimen was 12.4%. Subjects provided 116 observed values for the trough for this dose regimen and no subject had less than 3% Factor IX activity at Day 14.

Table 1 indicates that with repeated dose of 75 IU/kg once every 14 days the trough increases, rather than decreases as FDA suggested. In the PK model, a repeat dosing of 75 IU/kg once every 14 day predicts a trough of 8%; observed trough is higher (12.4%) with repeat dosing of IDELVION.

Therefore, CSLB confirms Factor IX activity levels can be maintained with repeat dosing at 14 day intervals over an extended period of time and poses no safety risk.

[End of discussion paper from CSLB dated 1/21/16]

The FDA conveyed to CSLB that adequate time was not provided to review the discussion paper. FDA advised that further internal discussion and consideration by FDA management was needed prior to reaching a conclusion on the suitability of a 14-day prophylaxis dosing regimen for a subset of patients treated with the product and the appropriateness of targeting a FIX concentration level of 1% versus 3%.

In response to CSLB's discussion points to FDA comment #1 and #2 (see above), FDA clarified that the minimum and maximum FIX concentration levels from the observed PK data, as opposed to the population PK data, do not support a 14-day regimen in adults. FDA stated that the dose needs to be adjusted for the pediatric population due to the increased clearance of the product by these patients.

FDA did not agree with CSLB's assertion that the baseline uncorrected data is a better representation (CSLB discussion point to FDA comment #3), but pointed out that even the baseline uncorrected data did not support the 14-day regimen. CSLB reiterated that the data do not suggest a concern for decreased exposure over time with decreased levels of the product. FDA clarified that the concern is for decrease concentration levels over time, and not decreased exposure.

CSLB clarified that based on their experiences from the pivotal and extension studies, patients prefer the 14-day regimen and the data supports a robust efficacy with the product. FDA reiterated that further consideration would be given to the points presented during the discussion and committed to providing a response in one week after discussion with management. FDA stated the following review issues would be considered: The appropriate target trough level (1% or 3%), the concern for decreased FIX levels with continued dosing, and the current summary data presented in the information discussion document submitted on Thursday night.