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Antihemophilic Factor (Xyntha)

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Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In Study 1, a pivotal phase 3 study, in which previously treated patients (PTPs) with hemophilia A received XYNTHA (antihemophilic factor) for routine prophylaxis]**Clinical Studies**and on-demand treatment, 94 subjects received at least one dose of XYNTHA (antihemophilic factor) , resulting in a total of 6775 infusions. [see

Study 2 is an on-going open-label, single-arm study of at least 25 evaluable PTPs with severe or moderately severe hemophilia A (factor VIII activity in plasma [FVIII:C] ? 2%) who require elective major surgery and are planned to receive XYNTHA (antihemophilic factor) replacement therapy for at least 6 days post-surgery.]**Clinical Studies**Twenty-two subjects received at least one dose of XYNTHA, resulting in 766 infusions. [see

In Study 1 (safety and efficacy study), the most frequently reported treatment-emergent adverse reaction was headache (24% of subjects). Other adverse reactions reported in ? 5% of subjects were: nausea (6%), diarrhea (5%), asthenia (5%) and pyrexia (5%). No subject developed anti- CHO or anti-TN8.2 antibodies.

In Study 2 (surgery study), the most frequently reported treatment-emergent adverse reaction was pyrexia (41% of subjects). Other adverse reactions reported in ? 5% of subjects were: headache (9%), nausea (9%), diarrhea (5%), vomiting (5%) and asthenia (5%). The adverse reactions reported in either study were considered mild or moderate in severity.

Immunogenicity is discussed below.

Immunogenicity

In Study 1, the incidence of FVIII inhibitors to XYNTHA (antihemophilic factor) was the primary safety endpoint. Two subjects with inhibitors were observed in 89 subjects (2.2%) who completed ? 50 exposure days. These results were consistent with the pre-specified endpoint that no more than 2 inhibitors may be observed in at least 81 subjects.

In a Bayesian statistical analysis, results from this study were used to update PTP results from a prior supporting study using XYNTHA (antihemophilic factor) and two recurrent inhibitors were observed in 110 subjects, and the experience with predecessor product (1 *de novo*manufactured at the initial facility, where one inhibitor in 113 subjects). This Bayesian analysis indicates that the population (true) inhibitor rate for XYNTHA (antihemophilic factor) , the estimate of the 95% upper limit of the true inhibitor rate, was 4.17% (see Table 1).

Table 1: Bayesian Posterior Distribution of Inhibitor Rate

Posterior Beta Distribution Characteristics				Observed Inhibitor Rate (%)	Number of Subjects Analyzed	Number of Inhibitors	FVIII Inhibitor Nijmegen Result (BU/mL)
95% Upper Limitof Inhibitor [d]Rate (%)	Posterior [c]	[b] Beta	[a] Alpha				
4.17	0.9613	197	4.5	2.25	89	2	? 0.6

[a] Prior alpha of 2.5 plus the number of observed inhibitors.
[b] Prior beta of 110 plus the number of subjects analyzed minus the number of observed inhibitors.
[c] Posterior probability is the probability that the true inhibitor rate is less than the upper acceptable limit of 4.4%. Aposterior probability greater than 0.95 is deemed acceptable.
[d] The 95% upper limit of the true inhibitor rate (the maximum rate calculated with at least 95% probability) based onthe posterior distribution. An inhibitor rate less than 4.4% is deemed acceptable.