Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	BSP AG Germany/Bayer Healthcare Pharmaceuticals	
Study Number:	11859	NCT00586521
Study Phase:	Phase 4	
Study Title:	A prospective controlled study on the effect on bleeding events and joint function in young adults with severe hemophilia A after a 6-month prophylaxis treatment compared to on-demand treatment	
Therapeutic Area:	Hemophilia A	
Name of Test Product:	Kogenate-FS/Bayer/Octocog alfa (rFVIII)	
Active Ingredient:	Antihemophilic Factor (recombinant) (rAHF)	
Dosage:	20-40 IU/kg IV, 3 times/wk (prophylactic treatment) at a stable dose per investigator's choice; continue subject's prior treatment dosage (on-demand treatment)	
Reference Therapy:	NA	
Dosage:	NA	
Placebo:	NA	
Route of Administration:	IV	
Treatment Duration:	6 months on-demand treatment followed by 7 months prophylactic treatment	
Study Period:	Date of first subjects' first visit:	03 Feb 2006
	Date of last subjects' last visit	25 Mar 2008
Methodology:	Multicenter, open, prospective study with a 1-group, 2-treatment schedules comparison of the number of joint bleeds, joint function (Gilbert score), the number of all bleeds, quality of life (QoL) and health-economics under prophylactic treatment versus on-demand treatment in adult subjects (30-45 years of age) with severe hemophilia A. After enrollment, all subjects (N=20) were evaluated clinically (Gilbert score), by the QoL questionnaire and by laboratory analyses at Baseline (Visit 1) and after 6 (Visit 3) and 13 months (Visit 5) of treatment. All subjects continued with the on-demand treatment schedule which they used before the study using Kogenate-FS/Bayer as their sole source of antihemophilic factor (AHF). After 6 months, subjects were switched to prophylactic treatment schedule for 7 months. The first month run-in prophylaxis (Month 7) was for stabilization and washout and was not included in the primary endpoint analysis. All subjects were monitored for a period of 13 months (Visits 1-5) and by subject diaries including infusion records. FVIII trough levels before recovery were measured in the hospital before the next planned injection and ≥ 3 days after last on-demand treatment (at Month 6 [Visit 3]) and 48 and 72h after the last prophylactic injection before Month 10 (Visit 4). Otherwise, FVIII trough levels were performed at end of study.	
Study Site:	The study was conducted at 9 centers from 4 countries: France (1), Great Britain (2), Italy (3), and United States (3)	
Main Inclusion Criteria:	Male subjects (30-45 years of age) with severe hemophilia A (<1% FVIII:C) and severe clinical behavior with an average of 2 relevant bleeds per month and no additional bleeding disorder, previously treated with on-demand treatment (>100 exposure days to any FVIII) and no history of inhibitor including negative inhibitor assay result at Screening.	

Study Objectives:	Overall: To lessen the physical and psychosocial disabilities of frequent joint bleeds in severe hemophilia subjects by prophylactic treatment with Kogenate-FS/Bayer Primary: To evaluate the effect of prophylactic treatment on the number of joint bleeds in severe hemophilia A subjects compared to on-demand treatment in a 1-group, 2-treatment schedule design. Secondary: To evaluate the effect of prophylactic treatment on the joint function, the number of all bleeds and on the quality of life compared to on-demand treatment. To assess health-economic data.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy endpoint was the number of joint bleeds during Months 8-13 compared to Months 1-6. Efficacy (Secondary): Secondary efficacy variables included: the number of all bleeds and joint function before and after prophylactic and on-demand treatment periods (Joint function was assessed by the physician using the physical examination score of the Gilbert scale); quality of life (Haemo-QoL A questionnaire completed by subjects); and health-economic data (days off work, visits at the general practitioner, and hospitalization days due to hemophilia). The efficacy population was all enrolled subjects. Safety The safety variables were the incidence rate of adverse events (AEs), including inhibitor development. AEs were assessed in terms of seriousness, severity, and relationship to study drug. The safety population was all subjects who received any amount of study drug. Pharmacokinetics NA
Statistical Methods:	Efficacy (Primary): The primary efficacy variable was summarized using mean, standard deviation (SD), median, quartiles, and minima/maxima by treatment and analyzed by a paired t-test and Wilcoxon test (on prophylaxis minus on-demand) at 6 months of treatment. Efficacy (Secondary): The secondary efficacy variables were summarized using mean, SD, median, quartiles, and minima/maxima by treatment; and analyzed by a paired t-test and Wilcoxon test (on prophylaxis minus on-demand) at 6 months of treatment. Safety Treatment-emergent AEs and serious AEs (SAEs) were presented in incidence tables using MedDRA, Version 9.1 glossary (all subjects receiving Kogenate-FS/Bayer as well as by treatment on-demand and on-prophylaxis). The AE onset date was compared to the infusion date of the first on-demand or prophylaxis infusion to assign the AE to the treatment. Frequency and percent of subjects with AEs necessitating removal from study were displayed, as well as subjects removed from study due to lack of efficacy and the total of all subjects who prematurely discontinued treatment. The safety analysis included any incidence of the development of antibodies with neutralizing properties (FVIII inhibitor). Pharmacokinetics NA
Number of Subjects:	20 adult men

Results Summary — Subject Disposition and Baseline

Subject disposition — 20 adult men were enrolled and participated in the study. There were no screening failures. One subject withdrew his consent during the on-demand treatment period after he had received a total of 30 injections. All other subjects completed the study as planned. Subject disposition and baseline characteristics are presented in the Table below.

Demographics and Baseline Characteristics

Subject Characteristic	On-Demand Treatment[a] (N=20)	Prophylaxis Treatment[a] (N=19)
Gender (N (%)) [b]		
Male	20 (100.0%)	19 (100.0%)
Race (N (%))		
Caucasian	19 (95.0%)	18 (94.7%)
Hispanic	1 (5.0%)	1 (5.3%)
Age (years)		
N	20	19
Mean (SD)[b]	36.4 (3.53)	36.4 (3.63)
Min, Max	30, 45	30, 45
Target Joint for bleedings (N (%))		
No	4 (20.0%)	3 (15.8%)
Yes	16 (80.0%)	16 (84.2%)

[a] The on-demand group consists of all enrolled subjects. The prophylaxis group consists of all enrolled subjects who did not discontinue prior to receiving prophylaxis treatment.

[b] N=number of subjects, SD=standard deviation Results

Results Summary — Efficacy

The reduction in actual number of joint bleeds (primary efficacy variable) shown in the Table below was not only statistically (P<0.001; paired t-teat), but also clinically significant. Notably, 16/20 subjects had target joints at the beginning of the study and 10/19 subjects who completed both treatment periods did not experience any joint bleeds during the prophylaxis period, including all subjects without target joints.

Similar results as for joint bleeds which accounted for almost 80% of bleeds, were obtained in the analysis of the actual number of all bleeds (mostly spontaneous bleeds), where the mean treatment difference was -22.3±12.6 bleeds (P<0.001 paired t-test). Irrespective of the treatment scheme, the response to treatment was excellent or good in the majority of bleeds. Most of the bleeds were successfully treated with 1 (89.9% during on-demand treatment; 85.7% during prophylactic treatment) or 2 (7.9% during on-demand treatment; 7.1% during prophylactic treatment) injections.

The mean total Gilbert score decreased after the switch by -5.5 points (P<0.001; paired t-test), which was mainly due to the reduced number of joint bleeds. Exclusion of the domains “bleed” and “pain” from the analysis resulted in a mean change by -1.3 points (P=0.067, paired t-test), indicating at least a trend toward an improvement in joint condition after 7 months of prophylaxis treatment.

The mean changes in the Haemo-QoL A questionnaire between Month 6 and Month 13 were small (<0.5 points) but mostly positive for all items and domains, pointing to minimal improvement. Health-economic data collected during the 13-month observation period did not reveal any relevant differences between the 2 treatment schedules.

Comparison of the actual number of joint bleeds (efficacy population)

Joint bleeds	On-demand Months 1-6 (N=20)	Prophylaxis Months 8-13 (N=19)
Actual number		
Mean ± SD	18.5 ± 11.6	1.5 ± 2.1
Median	15.0	0.0
(Range)	(2; 42)	(0, 6)
Mean difference		
To Months 1-6		-17.2 ± 11.3
P-value (paired t-test)		<0.001

Results Summary — Pharmacokinetics

NA

Results Summary — Safety

A total of 51 AEs were reported in 13 (65%) subjects, of which 26 AEs occurred in 9 (45%) subjects during the on-demand period and 25 occurred in 10 (53%) subjects during the prophylaxis period. With the exception of 3 AEs which were of severe intensity (femur fracture in connection with a car accident, and back pain), all other AEs were either mild (37/51) or moderate (11/51). None of the AEs led to a subjects's withdrawal from the study.

In both treatment periods, 1 subject each experienced serious adverse events (SAEs): subject no. 122020003 − excess consumption of alcohol, dehydration, and suspected carbon monoxide poisoning on 2 occasions during on-demand treatment; subject no. 225020004 − road traffic accident and femur fracture during prophylaxis treatment. None of the SAEs was drug-related and both subjects recovered. Non-SAEs assessed as durg-related occurred in 2 (10%) subjects (dysgeusia and headache). No subject developed neutralizing antibodies to FVIII (ie, FVIII inhibitor).

Forty-nine of the 51 AEs had resolved by the end of the respective treatment period. No subject died.

Conclusion(s)

FVIII secondary prophylaxis therapy provides a significant benefit to subjects with severe hemophilia without and with target joints in reducing the frequency of joint bleeds and improvement in the total Gilbert joint score even when initiated in adulthood. No safety signals arose from the higher number of injections administered for prophylactic treatment**.**

Publication(s)

NA

Updated: March 2009

Product Identification Information

Product Type	Biological Product
US Brand/Trade Name(s)	Kogenate FS
Brand/Trade Name(s) ex-US	Kogenate FS, Kogenate Bayer, Kogenate SF; Octocog alpha Bayer; Kogenate FS BioSet; Kogenate SF BioSet
Generic Name	Octocog-alfa, antihemophilic factor (recombinant)
Main Product Company Code	BAY14-2222
Other Company Code(s)	
Chemical Description	Recombinant human blood coagulation Factor VIII
Other Product Aliases	rFVIII, rhFVIII, rAHF

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