DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Final Review Memo:

TO: STN 103332/5794

SPONSOR: Bayer Healthcare Corporation

PRODUCT: Kogenate® FS, Antihemophilic Factor (Recombinant, formulated in sucrose),

FROM: Nisha Jain, M.D., Clinical Review Branch, HFM-392

SUBJECT: Final review of the BLA (STN 103332/5794)

TO: Michael Wiack, Regulatory Project Manager, HFM-380

THROUGH: Toby Silverman, M.D., Chief, Clinical Review Branch, HFM-392

CHAIRPERSON: Nisha Jain, M.D,

RECOMMENDATION:

I recommend the approval of Kogenate FS, Antihemophilic Factor, recombinant, for primary prophylactic treatment to reduce the risk of joint damage in children with Hemophilia A who do not have existing joint damage. Although the study subjects included age groups < two and a half years, study results can be extrapolated for all pediatric (0-16 years) patients with Hemophilia A with no existing joint damage.

REVIEW RESPONSIBILITIES:

Medical:	Nisha Jain, M.D.
Statistician:	Vivian Yuan
RPM:	Michael Wiack
BIMO:	Robert Wesley

Consult: Robert Smith (CDRH), M.D.
APLB: Katherine Miller

TRADE NAME:

The trade name Kogenate was approved in 1993. The trade name Kogenate was changed to Kogenate FS in June 2000 when albumin was eliminated and the product was formulated in sucrose and S/D treatment was incorporated as a viral inactivation step. Kogenate FS is indicated for "the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor FVIII. Kogenate FS provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency or elective surgery in hemophiliacs."

ORPHAN DRUG STATUS:

N/A

PREA:

Please see Appendix 1 for Pediatric page, pediatric assessment and waiver for ages >2-16 years.

PeRC meeting held on September 10, 2008. PeRC recommended that they consider the pediatric studies to be complete instead of waiver request for to 21/2 -16 years. As per PeRC the benefits of prophylactic treatment can to extended to all pediatric age groups provided the patient presents with no existing joint damage. The review division agrees the PeRC.

FINANCIAL DISCLOSURE:

Financial disclosure statements have been submitted in the application.

BIMO REPORT:

Pending

INDICATION SOUGHT:

"Kogenate FS can reduce the occurrence of spontaneous hemorrhagic episodes when used as a regular prophylactic treatment and has been demonstrated to significantly reduce the risk of joint damage compared to episodic treatment in children."

REGULATORY HISTORY:

2001: IND -(b)(4)- submitted. The study had been initiated prior to the submission of the IND

Oct 2, 2001: FDA exempted the IND but provided extensive comments to the sponsor .

April 2007: Pre BLA meeting held

Dec 2007: BLA supplement submitted

INTRODUCTION:

The study data submitted in this application was investigator sponsored and funded by Centers for Disease Control and Prevention (CDC). The principal investigator of this study was Marilyn Manco- Johnson, M.D, Director, Mountain States Regional hemophilia Center at the University of Colorado Health Sciences Center, Denver, Colorado.

Study Design:
The study was conducted as a randomized, open label (assessor blind for primary endpoint), parallel group, with comparison of prophylaxis versus enhanced episodic therapy.

Primary objective
"To determine whether prophylactic infusion of Kogenate FS given every other day is more effective in preventing joint damage than an enhanced on demand treatment."

The inclusion criteria were:

- Male subjects < 2.5 years of age diagnosed with hemophilia (< 2.5 % of circulating Factor VIII activity),
- History of < 3 joint bleeds in the same elbow, knee or ankle,
- A Pettersson score of zero in each of the 6 index joints evaluated by plain X-ray and/or no evidence of bone or cartilage damage on MRI.
- Negative Bethesda titer (c0.5 BU) was to be determined by the coordinating center laboratory within 1 month prior to study entry.

The subjects were followed for at least 5.5 years.

Subjects eligible for enrolment were randomized 1:1 to either arm.

Treatment Regimen
Prophylactic treatment consisted of 25 IU/kg administered IV every other day. For enhanced on demand treatment a dose of 40 IU/kg was given at the time of joint bleeding followed by 20 IU/kg at 24 and 72 hours after first infusion.

In the prophylaxis arm breakthrough hemorrhage was treated using a single dose of 40 IU/kg. The next day, subjects reinitiated their prophylaxis regimen to receive Factor VIII treatment qod.

Any subject who developed inhibitor of >25 BU was removed from the study. If the inhibitor titer was < 25 then the prophylaxis dose was increased to 70IU/kg qod for as long recovery and half life studies warranted it.

Efficacy Endpoints:
The primary efficacy endpoint of the study was to assess number of subjects who developed bone and /or cartilage damage in at least one index joint at any time during the study in either arm.

Secondary efficacy endpoints included the following:

- Total number of subjects
    - failing on each study arm for reasons including bone or cartilage damage
    - Life-threatening bleeding problems for which the assigned treatment arm was inadequate
    - Occurrence of inhibitors with a titer of *>25* BU at any time, persistence of inhibitors with a titer of >10 BU for more than 3 months, and parental or primary investigator's withdrawal of the subject from the study

- Number of subjects with a maximal (failing) score on any of the following physical assessment items: swelling, muscle atrophy, range of motion, gait, or strength

- Mean x-ray score for each index joint on a per subject basis

- Mean magnetic resonance imaging (MRI) score for each index joint on a per subject basis

- Mean total hemorrhages into index joints per subject by study arm

- Mean index joints with hemorrhages per subject by study arm

- Mean total hemorrhages per joint per subject by study arm

- Mean total bleeding events (joint and other) per subject by study arm

- Total number of CVADs placed by treatment arm and total associated complications

- Number of subjects who develop low- and high-titer inhibitors on each treatment arm

Safety Endpoints:

- Number and frequency of adverse events and serious adverse events by study arm

- Laboratory assessment of inhibitor titers and blood-borne viral assays

Other variables:

- Factor VIII trough (48 h k 6 h) concentrations (prophylaxis group only)

- Factor VIII gene mutation analysis

- Quality of life and psychosocial questionnaires (Maryland QOL, hemophilia-specific QOL instrument, Parenting Stress Inventory, Family Environment Scale, Parenting Styles Inventory, Uncertainty in Illness Scale, Parental Protectiveness Scale, and Parenting Locus of Control Scale)

- Cost of treatment by study arm

The criteria for study withdrawal were:
- Family or physician decision
- Death

Subjects could be withdrawn from the assigned treatment regimen but remain on study for the final assessment at age 6 years $\pm$ 3 months for:
- Treatment failure, defined as
    - bone and/or cartilage damage by x-ray and/or MRI
    - documentation of recurrent life-threatening hemorrhage, usually intracranial, for which the assigned treatment arm therapy is inadequate
    - occurrence of an inhibitor titer of *>25* BU
    - persistence of an inhibitor titer >10 BU for 3 or more months
- Family or physician decision

A subject who failed the primary endpoint of bone or cartilage damage while receiving enhanced infusion therapy, was considered a study failure and removed from the study. These subjects were offered prophylaxis as secondary therapy off study and were provided product for prophylaxis until the age of 6. In these subject's data were censored at the time of study failure but a final assessment was conducted at 6 years $\pm$3 months based upon the original treatment assignment.

Statistical methods / considerations: (as described by the sponsor)**:**
The intent-to-treat (ITT) population was used for both efficacy and safety analyses.

The primary efficacy variable was analyzed 2 ways:
1. including only those subjects who had completed MRI or x-ray exit examinations; and

2. including all randomized subjects, assuming subjects without available exit examination data to be treatment failures.

The numbers of subjects in each study arm who had achieved criteria for joint failure were compared between the two arms using Fisher's Exact test. In addition, the relative risk and 95% confidence intervals were calculated for the risk of joint damage while receiving enhanced episodic therapy compared to prophylactic therapy. The secondary outcomes were evaluated using the t-test and Mann-Whitney test. A p-value of <0.05 was considered statistically significant. Correlation analysis for overall and each index joint were performed using the Spearman correlation coefficient among average MRI score, x-ray score, joint physical exam score, and lifetime hemorrhages. Two interim efficacy analyses were conducted and presented to the Data Safety Monitoring Board (DSMB) at approximately one-third and two-thirds of the way through the follow-up period. The sponsor~investigator was not privy to the results of the interim analyses. The Lan-Demets alpha spending function procedure estimating O'Brien-Fleming boundaries *(i.e.*, a relatively small alpha such as 0.001) was used to adjust the significance levels at these interim occasions.

Results:
The study was conducted in 14 centers in US.

Table 1: Number of Subjects Enrolled per Center

Center[a]	Prophylaxis	Episodic Therapy	Total
Atlanta	3	4	7
Chicago Children's	2	2	4
Chicago Rush	3	2	5
Columbia	2	1	3
Dallas	1	1	2
Denver	12	11	23
Houston	3	4	7
Indianapolis	2	2	4
New Orleans	1	2	3
New York	1	0	1
Oakland	0	1	1
Orange County	1	1	2
Philadelphia	0	1	1
Portland	1	1	2
Total	32	33	65

a. Center where subjects were enrolled and randomized. Some subjects might have been treated at their local hospital

The site bias was eliminated because the primary endpoint was subjective and evaluated based on readings by independent readers located centrally.

Table 2: Subject Disposition

	Prophylaxis	Episodic	Total
Randomized	32	33	65

Completed study	27 (84%)	22 (67%)	49 (75%)
Early discontinuation	5 (16%)	11 (33%)	16(25%)
Reasons for discontinuation			
Joint damage	1(3%)	6 (18%)	7(11%)
Life threatening bleeding*	0	3(9%)	3(5%)
Early withdrawal	2(6%)	1(3%)	3(5%)
Inhibitor	2(6%)	0	2(3%)
Lost to follow-up	0	1(3%)	1(2%)

* Two cases of intracranial hemorrhage and one case of gastrointestinal hemorrhage

Table 3: Study Demographics

Parameter[a]	Prophylaxis	Episodic Therapy	Total
Age (years)			
N	32	33	65
Mean (SD)	1.56 (0.51)	1.59 (0.49)	1.58 (0.50)
Median	1.51	1.54	1.52
Range	0.9-2.5	0.6-2.5	0.6-2.5

97% of the subject enrolled met the eligibility requirement for a Factor VIII activity level of < 2%. The distribution of subjects with Factor VIII activity levels <I% and 1% to 2% was similar between treatment groups. 3% (2/65) of the subjects who did not have FVII activity levels below <2% are described below.

One subject (-(b)(6)-) in the episodic therapy treatment group had a higher than permissible Factor VIII activity level (3.4%) at enrollment following an eligible level (<1%) at screening. The blood sample analyzed at enrollment had been drawn 72 h following the subject's last Factor VIII infusion. All subsequent Factor VIII activity tests for this subject that were performed on blood samples collected at least 72 h after previous Factor VIII infusion were <I%.

Another subject (-(b)(6)-) in the episodic treatment group had an undetermined Factor VIII activity level at enrollment due to a poor blood sample.

Table 4: Subjects Factor VIII Activity and Inhibitor Status at Study Entry

Parameter	Prophylaxis (n=32)	Episodic Therapy (n=33)	Total (N=65)
Presence of Inhibitor			
No	31 (97%)	32 (97%)	63 (97%)
Yes	1 (3%)	0	1 (2%)
Unknown	0	1 (3%)	1 (2%)
Factor VIII Activity Level			
<1%	29 (91%)	26 (79%)	55 (85%)
1% to 2%	3 (9%)	5 (15%)	8 (12%)
>2%	0	1 (3%)	1 (2%)
Unknown	0	1 (3%)	1 (2%)

Efficacy Analysis:

Primary Efficacy Analysis:

Please see Dr. Robert Smith's (consult radiologist at CDRH) memo for analysis of the primary efficacy endpoint.

The primary efficacy endpoint of the study was to assess number of subjects who developed bone and /or cartilage damage in at least one index joint at any time during the study in either arm by x-ray or MRI. Not all patients had complete exit x-ray or MRI data, Therefore, this analysis was conducted in 2 ways for all randomized subjects (ITT population): (1) for all subjects who had both baseline and exit x-ray and/or MRI data available; and (2) for the entire randomized population assuming subjects with missing endpoint data to be treatment failures. In both cases, for subjects who prematurely discontinued study due to joint damage, the interim exam which first identified the joint damage was used.

Presented below is the sponsor's analysis of the primary endpoint.

Table 5: Subjects with Joint Damage (Subjects with Available Baseline And Endpoint Data)

Endpoint	Prophylaxis N=32		Episodic N=33		p-value
	Incidence (%)	Relative risk (95%CI)	Incidence (%)	Relative risk (95%CI)	
MRI	2*/27 (7%)	0.17 (0.04, 0.67)	13^/29(45%)	6.05 (1.50, 24.38)	0.002
X-ray	1/28 (4%)	0.19 (0.02, 1.55)	5/27 (19%)	5.19 (0.65, 41.51)	0.101
MRI or X-ray	2/30(7%)	0.16 (0.04, 0.65)	13/31(42%)	6.29 (1.55, 25.38)	0.002

*same subject also had X-ray

^ 5 subjects were also assessed by X-ray

Table 6: Subjects with Joint Damage (All Randomized Subjects): Worst Case Scenario Analysis. This analysis assumes all subjects without available endpoint data to be treatment failures.

Endpoint Assessment	Prophylaxis (n=32)		Episodic Therapy (n=33)		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	7 (22%)	0.42 (0.20, 0.88)	17 (52%)	2.35 (1.13, 4.90)	0.020
X-ray	5 (16%)	0.47 (0.18, 1.20)	11 (33%)	2.13 (0.83, 5.45)	0.150
MRI or X-ray	8 (25%)	0.43 (0.22, 0.85)	19 (58%)	2.30 (1.18, 4.49)	0.012

The incidence of joint damage was statistically significantly lower in the prophylactic group when assessed by MRI, using predefined criteria (described below) for establishing joint damage, when analyzed by both ways. When assessed by using either MRI or X-ray, the incidence of joint damage was statistically significantly lower in the prophylactic group than enhanced episodic treatment group. However, there was no statistical significant difference between the two groups when joint damage was assessed by X-ray.

Criteria used to evaluate joint damage:
MRIs were scored using scale developed by Nuss et. al, X-rays were scored using the method of Petterson et.al. Both the scales have been validated in various clinical trails and are routinely used for joint damage evaluation in hemophiliacs. Joint damage was defined as bone and or cartilage damage including subchondral cysts, erosions and cartilage loss with narrowing of joint space. This corresponded to a total MRI score of $\geq$ 7 or an X-ray score of $\geq$ 1 in any of the following categories: subchondral cysts, erosions of joint surfaces or narrowing of joint spaces. Images were read separately by two independent radiologists centrally: one bone and other pediatric radiologist. Any discrepant reading was read by an independent third bone radiologist who was not aware of the initial reading results. The concordant reading of two out of three readers was used for analysis purposes.

Joint damage was most frequently observed in ankle joints and was detected at higher rates by MRI than by x-ray. Ankles were also the index joint that demonstrated the highest frequency of .bleeding events in this study (left ankle, mean 2.7 hemorrhages; right ankle, mean 2.6 hemorrhages)

Table 7: Subjects with Joint Damage by Index Joints*

Endpoint Assessment	Prophylaxis		Episodic Therapy	
	MRI	X-ray	MRI	X-ray
Left ankle	1/31 (3%)	0/31 (0%)	6/29 (21%)	2/27 (7%)
Right ankle	1/31 (3%)	1/31 (3%)	5/29 (17%)	3/28 (11%)
Left elbow	0/29 (0%)	0/30 (0%)	2/26 (8%)	1/29 (3%)
Right elbow	0/29 (0%)	0/31 (0%)	0/26 (0%)	0/29 (0%)
Left knee	0/31 (0%)	0/29 (0%)	0/28 (0%)	0/28 (0%)
Right knee	0/30 (0%)	0/29 (0%)	1/28 (4%)	1/29 (3%)

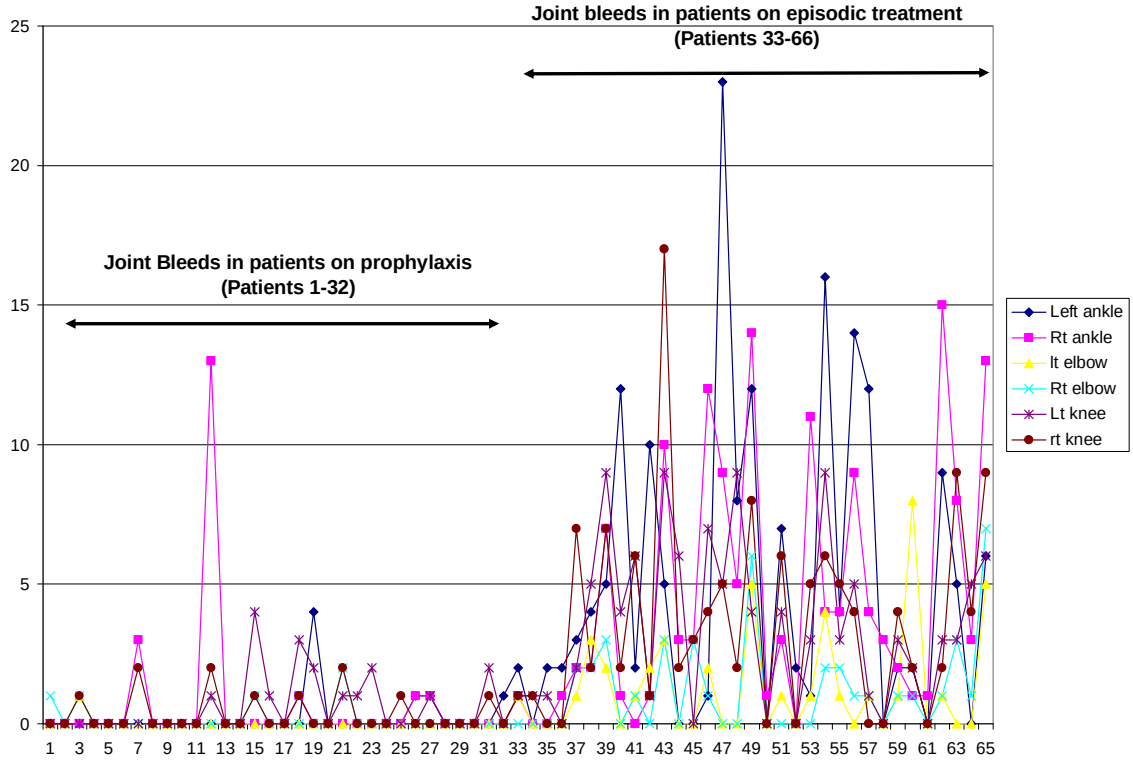
In one subject receiving episodic treatment damage was observed in two joints by MRI.

Secondary Outcomes:

Incidence of index joint bleeding and other site bleeding

The annual rate of bleeding was statistically significantly higher for subjects assigned to episodic therapy than for subjects assigned to prophylactic therapy. The mean rate of index joint hemorrhages in the episodic treatment group was 4.89 bleeds per subject per year, and 0.63 bleeds per subject per year in prophylaxis group ($p<0.001$). The mean incidence of all hemorrhages in the episodic treatment group was 17.69 bleeds per subject per year compared to 3.27 bleeds per subject per year in the prophylaxis group ($p<0.001$).

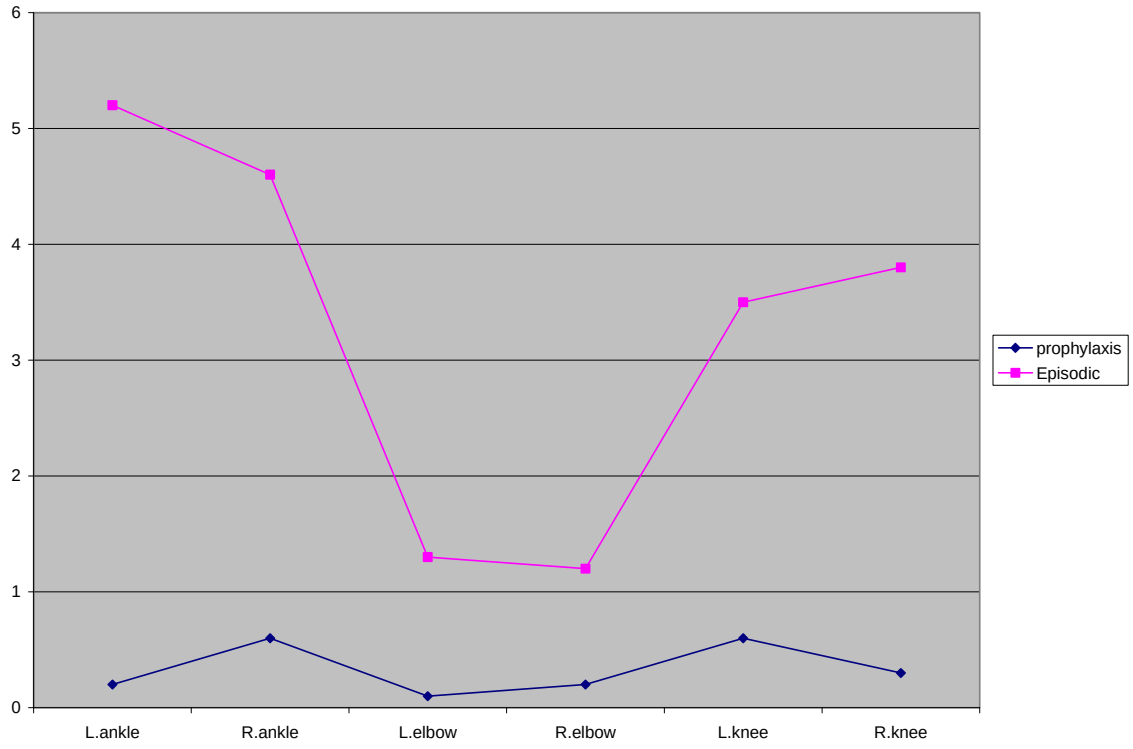
Graph 1: Target Joint Bleeds in Patients on Prophylaxis and Episodic Therapy



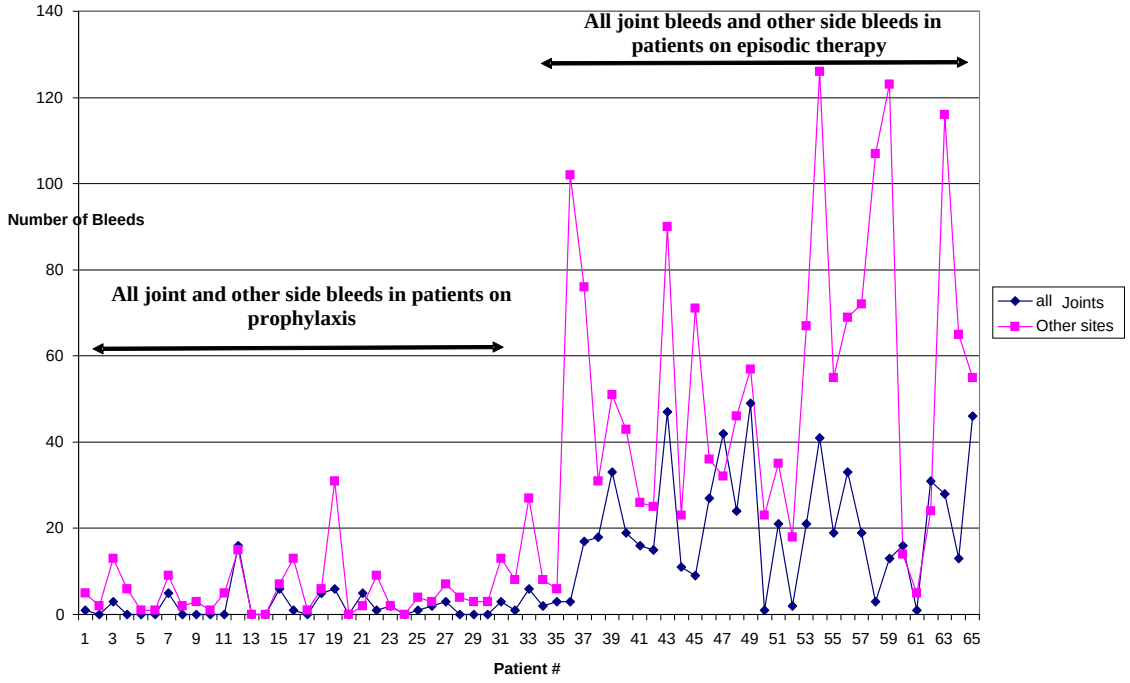
Number of index joint bleeds per subject and the number of bleeds in each joint per subject over the course of the study:

The mean number of joints with bleeds per subject in the prophylactic group was 1.0 (median 1, range 0-.3.0) and 4.4 (median 5.0, range 1.0-6.0) in the episodic group. The mean number of bleeds per joint per subject is presented below in the graph:

Graph 2: Mean Number of Bleeds Per Joint Per Subject



Graph 3: All Joint Bleeds and Other Bleeds in Patients on Prophylaxis and Episodic Therapy



Treatment failures

The incidence of treatment failures was compared by study arm. Table7 below provides a summary of subjects who failed study treatment for bone or cartilage damage, life-threatening hemorrhage, the development of inhibitor titer, or for withdrawal by physician or family decision. Of the subjects who failed treatment, the most common reason for failure was bone or cartilage damage, 25% versus 58% for subjects receiving prophylaxis versus episodic therapy, respectively. The incidence of treatment failure due to life-threatening hemorrhages (n=3, 5%) was seen in the episodic treatment group. Positive high-titer inhibitors (>25 BU peak or >10 BU or >3 months) (n=2, 3%) was seen in the prophylactic group.

Table 8: Reasons for Treatment Failure

Reason for Failure	Prophylaxis (n=32)	Episodic Therapy (n=33)	Total (n=65)
Bone or cartilage damage	2 (6%)	13 (39%)	15 (23%)
Recurrent life-threatening bleeds	0	3 (9%)	3 (5%)
Positive high-titer inhibitors[a]	2 (6%)	0	2 (3%)
Parental or physician withdrawal	2 (6%)	1 (3%)	3 (5%)
Total	6 (19%)	17 (52%)	23 (35%)

a. Subjects were discontinued for positive inhibitor titers of >25 BU at any time or >10 BU for at least 3 months.

Details of subjects with positive inhibitor:
2 subjects in the prophylactic group had measurable FVIII inhibitor titers.

Subject --(b)(6)- had a measurable titer (1.6 BU) following a negative result at screening. This subject's inhibitor titer peaked at 30 BU and the subject was removed from the study after less than 3 weeks.

Subject --(b)(6)- had negative baseline FVIII but developed high titer being only 1.6 months on study.

Joint physical assessment score:
Functional disability was measured by the incidence of maximal physical assessment scores for swelling, muscle atrophy, range of motion, gait, and strength, and compared by study arm. Subjects whose physical assessments led to a maximal score for any of these parameters were identified for further joint assessments by imaging (x-ray and MRI). Table below provides the percent of subjects in each study arm whose evaluations resulted in maximal scores for any of these joint physical assessment parameters and triggered early x-ray or MRI evaluation.

Fewer subject in the prophylaxis arm than had maximal scores for the physical parameters that would indicate early joint imaging. Among these 5 parameters, the most commonly noted maximal scores occurred for gait (n=17, 26%: 16% among subjects receiving prophylactic therapy and 36% among subjects receiving episodic therapy) and range of motion (n=4, 6%: 3% among subjects receiving prophylactic therapy and 9% among subjects receiving episodic therapy). The occurrence of maximal physical joint assessment scores did not correlate with joint damage.

Table 9: Incidence of Maximal Physical Assessment Scores

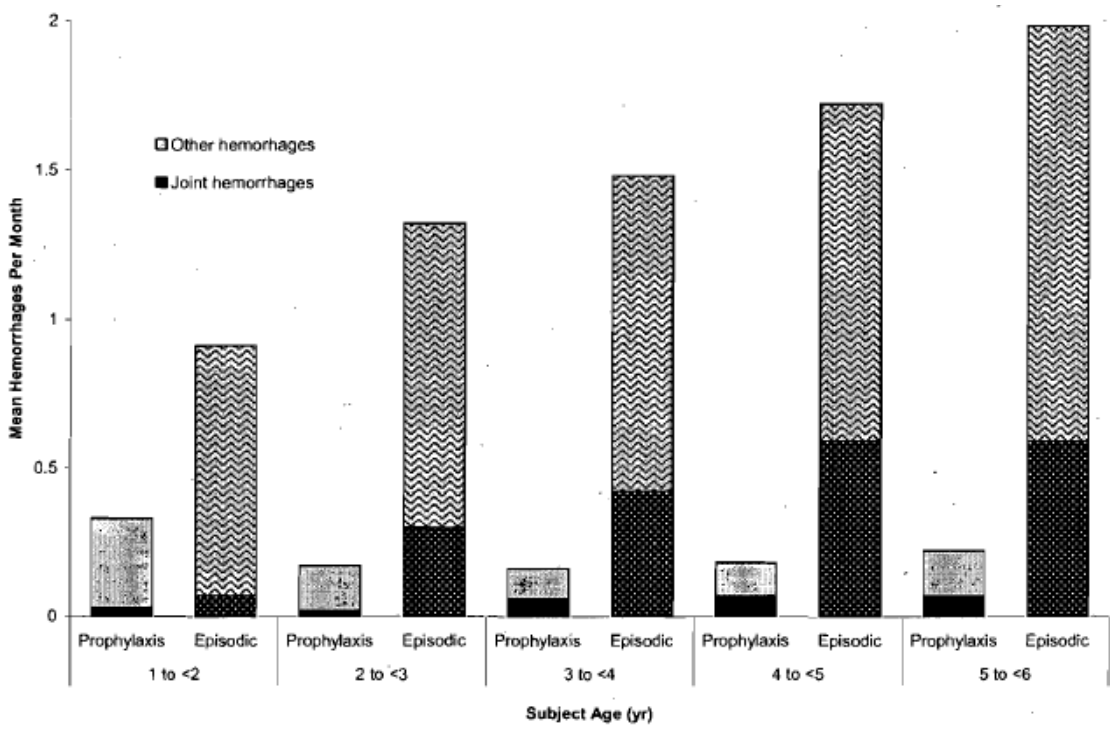
Physical Assessment Parameter	Prophylaxis (n=32)	Episodic Therapy (n=33)	Total (n=65)
Any Evaluation	14 (44%)	19 (58%)	33 (51%)
Axial deformity	13 (41%)	10 (30%)	23 (35%)
Gait[b]	5 (16%)	12 (36%)	17 (26%)
Range of motion[b]	1 (3%)	3 (9%)	4 (6%)
Splinting / Orthotics	2 (6%)	2 (6%)	4 (6%)
Flexion contracture	0	2 (6%)	2 (3%)
Pain without activity	1 (3%)	1 (3%)	2 (3%)
Pain with activity	1 (3%)	1 (3%)	2 (3%)
Swelling[b]	0	1 (3%)	1 (2%)
Muscle atrophy[b]	1 (3%)	0	1 (2%)
Strength[b]	1 (3%)	0	1 (2%)

a. Subjects who received the maximal (most abnormal) score in at least one index joint for the given evaluation. 'Any Evaluation' presents the number of subjects who received the maximal score for any of the evaluations in at least one index joint.

b. Physical assessment parameters that were specified in the protocol as triggering an early joint imaging evaluation by x-ray or MRI if a maximal score was reached.

Monthly index joint and non joint bleeds by age:
The sponsor has analyzed the monthly index joint and non joint bleeds by subject's age. The graph below shows the subject's actual age at the end of the month in which bleeding data was collected. In subjects receiving episodic therapy, the frequency of monthly index joint and non-joint bleeds increased each year as the subjects grew older. By contrast, the monthly bleeding frequency for both index joint and non-joint bleeds in subjects receiving prophylaxis is low in all age groups throughout the study. This data supports the data results on reduction in joint bleeds and other bleeds with prophylaxis treatment.

Graph 4: Monthly Index Joint and Other Hemorrhages by Subject Age



Incidence of CVADs and associated complications:
Total number of CVADs placed by treatment and total associated complications:
23 subjects (35%) had a CVAD placed before study start. Over the course of treatment, an additional 31 subjects received CVADs. The frequency of CVAD placement was similar between treatment groups both at baseline and throughout treatment. Rates of infections associated with CVAD placement or maintenance was equal between treatment groups, approximately 19% and 18% respectively (6/32 in the prophylaxis arm and 6/33 in the episodic arm).

Table 10: Subjects with CVAD and Associated Complications

Number of subjects with:	Prophylaxis (n=32)	Episodic Therapy (n=33)
CVAD[a]	29	25
CVAD infection	6	6

Incidence of hospitalization and life threatening hemorrhages:
Three subjects receiving episodic therapy and no subjects receiving prophylactic therapy experienced recurrent life-threatening hemorrhages (two had ICH and one gastro-intestinal bleed). In the prophylactic group mean hospitalizations (annualized) days are 1.70 whereas or the episodic group it was 0.47. Subject --(b)(6)- (prophylactic arm) who had two hospitalizations during 16 days he was on study had a projected annual incidence

of 45.7 hospitalizations as hospitalization data was analyzed as annualized rate. This could have accounted for higher mean rate of hospitalization in the prophylactic group.

Safety analysis:
All randomized subjects (n=65) were included in the analysis of safety. A total of 46 unique subjects experienced adverse events, 23 subjects (72%) receiving prophylactic therapy and 23 (70%) subjects receiving episodic therapy.

10 serious adverse events were reported for 6 subjects.
High-titer inhibitor formation occurred in 2 subjects (prophylactic therapy, subject ID # ---(b)(6)--, --------), and intracranial hemorrhage occurred in 2 subjects (episodic therapy, two instances each, ---(b)(6)--, --------) and gastro-intestinal hemorrhage in one subject (--(b)(6)--) receiving episodic therapy. Five subjects listed above discontinued from the study as a result of adverse events. There were no deaths reported.

Table 12: List of Subjects who Discontinued

Subject Number	Enrollment Date	Treatment Assignment	Preferred Term	Exit Date	Months on Study
(b)(6)	31 Jul 1997	Prophylaxis	Factor VIII inhibition	18 Sep 1997	1.6
(b)(6)	22 Apr 1998	Prophylaxis	Factor VIII inhibition	08 May 1998	0.5
(b)(6)	28 May 1997	Episodic	Intracranial hemorrhage (subdural hematoma)	15 Jul 1998	13.6
(b)(6)	12 May 2000	Episodic	Intracranial hemorrhage	25 Sep 2001	16.5
(b)(6)	27 Oct 1998	Episodic	Gastrointestinal hemorrhage	17 Mar 2003	52.6

The most commonly occurring adverse events in the study: central venous catherization occurred most frequently [17 subjects, 53% (prophylactic); and 14 subjects, 42% (episodic)], followed by central line infection [6 subjects, 19% (prophylactic); and 6 subjects, 19% (episodic)], and pyrexia [1 subject, 3% (prophylactic); and 4 subjects, 12% (episodic)].

Table 11: Most Commonly Occurring AEs in the Study

Adverse Events	Prophylaxis N=32	Epiosdic N=33
CVAD	17 (53%)	14 (42%)
CVAD infection	6 (19%)	6 (18%)
Catheter sepsis	1 (3%)	2 (6%)
Pyrexia	1 (3%)	4 (12%)
Infections and Infestations		
Otitis media	0	2(6%)
Gastroenteritis	1 (3%)	1 (3%)
FVII inhibitors (>0.5BU)*	2 (6%)	5 (15%)

* Two subjects in the prophylactic who developed very high inhibitor titers (>25 BU) are not included. The inhibitors developed were transient in all subjects

Table 12: List of All Subjects With Positive Factor VIII

Subject Number	Treatment Assignment	First Infusion Date	First Positive Titer (Value and Date)		Peak Positive Titer (Value and Date)		Final Positive Titer (Value and Date)	
(b)(6)	Prophylaxis	07 Jun 1999	1.8	23 Sep 1999	10.0	21 Jan 2000	10.0	21 Jan 2000
(b)(6)	Prophylaxis	01 Aug 1997	18.0	28 Aug 1997	100.0	18 Sep 1997	100.0	18 Sep 1997
(b)(6)	Prophylaxis	16 Sep 1997	1.0	16 Dec 1997	1.0	16 Dec 1997	1.0	26 Nov 2002
(b)(6)	Prophylaxis	23 Apr 1998	1.6	22 Apr 1998	30.0	07 May 1998	30.0	07 May 1998
(b)(6)	Episodic	06 Jan 1997	0.5	15 Jul 1997	0.5	15 Jul 1997	0.0	09 Nov 2001
(b)(6)	Episodic	27 Jan 1999	0.5	07 Apr 1999	0.5	07 Apr 1999	0.2	02 Feb 2004
(b)(6)	Episodic	28 Aug 1997	0.5	20 Jan 1999	0.5	20 Jan 1999	0.0	30 May 2002
(b)(6)	Episodic	21 May 2000	3.5	11 Dec 2000	3.5	11 Dec 2000	0.25	22 Aug 2001
(b)(6)	Episodic	01 Nov 1996	0.8	14 Jun 2000	1.5	11 Dec 2001	1.5	11 Dec 2001

CONCLUSION:

The study met its primary endpoint and the results show that prophylactic treatment in children with no existing joint damage reduces statistically significantly the risk of joint damage when compared to children who receive episodic treatment. Prophylactic treatment also statistically significantly reduces target joint bleeding and bleeding at other sites when compared to episodic treatment. The incidence of inhibitor formation was as expected in this population. No other safety concerns were identified from the study.

APPENDIX 1
PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 103332 | Supplement Number: 5794 | NDA Supplement Type (e.g. SE5): _____

Division Name: Division of hematology | PDUFA Goal Date: 10, Oct 2008 | Stamp Date: Dec 11, 2007

Proprietary Name: Kogenate FS

Established/Generic Name: Anti hemophilic factor, recombinant, sucrose formulated

Dosage Form: Intravenous

Applicant/Sponsor: Bayer healthcare LLC

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Control and prevention of bleeding episodes in patients with hemophilia A
(2) Perioperative management in patients with hemophilia A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):one
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Primary Prophylactic treatment to prevent joint damage in children with hemophilia A.

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue

No X☐ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____
PMC/PMR #:_____

Does the division agree that this is a complete response to the PMC/PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); X☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

X☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

X☐ Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

X☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulat failed[4]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Children	yr. mo.	yr. __ mo.	☐		☐	☐
☐	Adolescent	yr. __ mo.	yr. __ mo.	☐		☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

X Product does not represent a meaningful therapeutic benefit* over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applica Certifica** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Receiv
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. 6__ mo.	__ wk. __2.5 mo.	Yes X☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; x☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
X ☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	X☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; X☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; X☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

Nisha Jain, M.D.

_____

Medical reviewer

Dear Review Division:

In order review the Pediatric Assessments, the Pediatric Review Committee will evaluate the key terms of the proposed study. The Division must be able to answer specific questions with respect to a sponsor's submission and the elements of the proposed study. The template that follows, which includes a table, has been created to facilitate the Division's presentation to the Pediatric Review Committee.

We will need:

Approval letter
Pediatric Page
Proposed Labeling
Please fill out template below, or provide Medical Officer Review

PeRC Pediatric Assessment Template

*Note: This table contains instructions to assist the division when completing this form (italicized text**). Please remove the italicized text prior to sending the completed table to the PeRC. .***

When completing the table, each section is intended to reflect elements considered important by the PeRC. When filling out the section, please insert what the Sponsor is proposing. Some elements may not be applicable, or there may be other important issues that the Division wishes to discuss. Please add items that you believe are necessary. If an element is not applicable, please write "NA" rather than deleting the element.

Application # 103332/5794

Drug Name Kogenate FS (anti hemophilic factor, recombinant, sucrose formulated0

Approved Indications:
(1) Control and prevention of bleeding episodes in patients with hemophilia A
(2) Perioperative management in patients with hemophilia A
(3) Primary Prophylactic treatment to reduce the risks of joint damage in children.
This assessment is only applicable to indication # 3

Date Submitted: December 11, 2007

PDUFA DUE DATE: October 10, 2008

PREA Commitment No

Was Plan Reviewed by PeRC? No
If yes, did sponsor follow plan? N?A

Indication(s) to be studied:
Primary Prophylactic treatment to reduce the risks of joint damage in children.

Drug information:

- **Route of administration:** Intravenous
- **Formulation:** lyophilized powder for injection
- **Dosage:** 250IU, 500IU, 1000IU, 2000IU
- **Regimen:** 25IU/kg of body weight every other day

Types of studies/ Study Design:

The study was conducted as a randomized, open label (assessor blind for primary endpoint), parallel group, w
prophylaxis versus enhanced episodic therapy.

Age group and population in which study will be performed:
Male hemophiliacs <2.5 years
In the prophylaxis arm, the mean age was 1.56, median age was 1.51 and range was 0.9-2.5 years.
In the enhanced episodic therapy arm the mean age was 1.59, median was 1.54, and range was 0.6-2.5

Number of patients to be studied or power of study to be achieved:
65 patients randomized in 1:1 ratio to prophylactic dosing arm and enhanced episodic treatment arm

Entry criteria:
The inclusion criteria were:

- male subjects < 2.5 years of age diagnosed with hemophilia (< 2.5 % of circulating Factor VIII activi
- history of < 3 joint bleeds in the same elbow, knee or ankle,
- a Pettersson score of zero in each of the 6 index joints evaluated by plain X-ray and
- no evidence of bone or cartilage damage on MRI.

Clinical endpoints:

The primary efficacy endpoint of the study to determine the number of subjects who developed bone and/or c least one index joint as determined by Pettersson criteria of >1 only for subchondral cyst and/or erosion and/o plain x-ray; OR evidence of bone damage by a --(b)(4)-- magnetic resonance imaging (MRI) score > 7

The safety endpoint included incidence of inhibitor development

Timing of assessments:

MRI and X-ray done at baseline and semi-annually if evaluation of joint swelling, muscle atrophy, muscle s joint motion and gait were abnormal and at study conclusion: subject age 6 years ± 3 months.

Statistical information (statistical analyses of the data to be performed):
The primary efficacy variable was analyzed 2 ways: (I) including only those subjects who had completed MR examinations; and (2) including all randomized subjects, assuming subjects without available exit examinatio failures.

The numbers of subjects in each study arm who had achieved criteria for joint failure were compared betwee Fisher's Exact test. In addition, the relative risk and 95% confidence intervals were calculated for the risk of j receiving enhanced episodic therapy compared to prophylactic therapy. The secondary outcomes were evalua Mann-Whitney test. A p-value of <0.05 was considered statistically significant. Correlation analysis for overa were performed using the Spearman correlation coefficient among average MRI score, x-ray score, joint phys lifetime hemorrhages.

Overall conclusions; the study met its primary efficacy endpoint and no safety concerns present.

Pediatric Research and Equity Act Waivers

Product name and active ingredient/ dosage form:

BLA #: 103332 Supplement Type: Efficacy Supplement Number: 5794

HFM: 392

Sponsor: Bayer Healthcare

Indications(s): Primary Prophylactic treatment to reduce the risks of joint damage in children.

1. Pediatric age group(s) to be waived: >2.5- 16 years

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

    b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. Suggested language includes, "FDA has not required pediatric studies in ages ___ to ___ because (state the safety or effectiveness reason)."

    c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

Children with very few joint bleeds are expected to have no joint damage. Hemophiliac males with history of < 3 joint bleeds in the same elbow, knee or ankle, a Pettersson score of zero in each of the 6 index joints evaluated by plain X-ray and no evidence of bone or cartilage damage on MRI when given prophylactic infusions was effective in preventing joint damage by reducing eth number of joint bleeds. In older children (>2.5-16years) due to recurrent bleeding in joints, joint damage

occurs and prophylactic treatment is not effective in reversing /preventing joint damage.

d. Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders

Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine