

**CENTER FOR DRUG EVALUATION AND
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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drugs Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

CLINICAL PHARMACOLOGY REVIEW

Date: May 17, 2005

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Through: Marc Walton, M.D., Director, Division of Therapeutic Biological Internal Medicine Products, ODE VI

Subject: Clinical Pharmacology Review of Biologic License Application STN 125117 for Biomarin Pharmaceutical Inc.'s Galsulfase (NAGLAZYME™)

To: Center / Division / Office -- CDER / ODE VI / DTBIMP
Primary Reviewer -- Ilan Irony, M.D.

Please see the attached review.

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INTRODUCTION

Galsulfase is a polymorphic variant of the human enzyme, N-acetylgalactosamine 4-sulfatase (Arylsulfatase B or ASB) that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. N-acetylgalactosamine 4-sulfatase is a lysosomal hydrolase that cleaves the sulfate ester from N-acetylgalactosamine 4-sulfate residues at the end of the glycosaminoglycans (GAGs), chondroitin 4-sulfate and dermatan sulfate. The enzyme is a single polypeptide chain of molecular mass 55.9 kiloDaltons (from translated cDNA sequence). rhASB contains six asparagine-linked glycosylation sites, four of which carry the bis-mannose-6-phosphate oligomannose7 oligosaccharide that binds the target cell surface receptor.

Galsulfase or recombinant human N-acetylgalactosamine 4-sulfatase (rhASB) is an enzyme replacement therapy (ERT) for patients with the Mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy Syndrome. MPS VI is a rare genetic lysosomal storage disorder caused by a deficiency in N-acetylgalactosamine 4-sulfatase (Arylsulfatase B or ASB). Reduced or absent ASB activity results in the accumulation of the GAG substrates throughout the body and leads to widespread cellular, tissue, and organ dysfunction. MPS VI is a serious, progressive and ultimately fatal disease. The diagnosis of MPS VI is usually made from 6-24 months of age when children show progressive deceleration of growth, enlarged liver and spleen, skeletal deformities, coarse facial features, upper airway obstruction, and joint deformities. Progressive clouding of the cornea, communicating hydrocephalus, or heart disease may also develop in MPS VI children.

Galsulfase treatment replaces the lysosomal enzyme that is absent or deficient in MPS VI patients, thereby halting or reversing some aspects of disease progression. The rationale for galsulfase therapy is to provide exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAGs. Galsulfase uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of galsulfase to specific mannose-6-phosphate receptors.

The proposed indication for galsulfase is patients with a confirmed diagnosis of Mucopolysaccharidosis VI. The proposed dosing regimen of galsulfase is 1.0 mg/kg administered once weekly as an intravenous infusion over a 4-hour period.

The pharmacokinetics of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) have been characterized in 31 patients with MPS VI (Maroteaux-Lamy syndrome) in three clinical studies of safety and efficacy. In Study ASB-00-01 (Phase 1/2), rhASB was administered at doses of 0.2 or 1.0 mg/kg/week. In Study ASB-01-04 (Phase 2) and Study ASB-03-05 (Phase 3), rhASB was administered at a dose of 1.0 mg/kg/week. All three clinical studies included pharmacokinetic assessments at various intervals through 24 weeks of double-blind treatment. In addition, pharmacokinetic assessments were done through 188 weeks (\approx 3.6 years) in open-label extensions of the Phase 1/2 and 117 weeks (\approx 2.25 years) in the Phase 2 study.

In Study ASB-XO-001, comparisons of clinical process material rhASB (Lot No. AV60304-A, produced using a 30-day cell culture duration) and commercial process material rhASB (Lot No. V60401-B, produced using a 60-day cell culture duration) were done using data from Study ASB-00-01 and Study ASB-01-04.

In Study ASB-53-APK, a pharmacokinetic study in male beagle dogs, comparisons were made of a lot of rhASB material harvested from Day 1–30 (Lot No. AV60307) of a production campaign and a lot of rhASB material harvested from Day 60-100 (Lot No. P60406) of the same campaign.

Comparisons and analyses of results across clinical studies were done to examine the effects of duration of treatment, age, and gender on rhASB pharmacokinetics.

Summary of Clinical Studies/Analyses

A summary of the three clinical studies is shown below:

Study	Phase	Process	Dose (mg/kg)	No. of Weekly Doses	Total No. Subjects Receiving rhASB	No. Subjects with PK Assessments
Study ASB-00-01	1 / 2	Clinical ^{a,b}	0.2 or 1.0 mg/kg/wk	144	7 ^c	7 ^c
Study ASB-01-04	2	Clinical ^d	1.0 mg/kg/wk	72	10	10
Study ASB-03-05	3	Clinical	1.0 mg/kg/wk	24	19 ^e	14 ^e

- Patients were transitioned from batch cell culture to perfusion-based cell culture process that included Polysorbate 80 after Week 83.
- Open-label extension of Study ASB-00-01-PK used commercial process rhASB after 179 to 188 weeks. Open-label extension of Study ASB-01-04-PK used commercial process rhASB.
- 4 subjects received 0.2 mg/kg/wk rhASB dose; of these 4 subjects, 1 subject received only 3 infusions. 3 subjects received 1.0 mg/kg/wk rhASB dose.
- 19 subjects received rhASB; 20 subjects received placebo.
- At Week 1, N=13 for AUC_{0-t}, N=11 for AUC_∞, CL, Vz, and t_{1/2}, N=14 for C_{max} and T_{max}; at Week 24, N=13 for C_{max}, T_{max}, AUC_{0-t}, AUC_∞, CL, Vz, and t_{1/2}.

A summary of the analyses that used clinical data from the three studies is shown below:

Study	Process	Dose (mg/kg)	Studies Data Taken From	Total No. Subjects Receiving rhASB
Study ASB-XO-001	Clinical and Commercial	1.0 mg/kg/wk	ASB-00-01 ASB-01-04	14 ^a
<u>Comparison and Analyses of Results Across Studies</u>	Clinical And Commercial	1.0 mg/kg/wk	ASB-00-01 ASB-01-04 ASB-03-05	23 ^b

- After 179 to 188 weeks of rhASB treatment, the 4 patients in the Phase 1/2 study (Study ASB-00-01-PK) were transitioned to the commercial process rhASB. Similarly, the 10 patients in the Phase 2 study (Study ASB-01-04-PK) were transitioned to commercial process rhASB between Weeks 98 and 117 of treatment.
- 23 patients had values available for AUC_∞, CL, Vz, and t_{1/2} at Week 24, the end of double-blind treatment in the three studies

SYNOPSIS**Study ASB-00-01-PK**

A Phase 1/2 Randomized, Double Blind, Two Dose Group Study of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) Enzyme Replacement Therapy in Patients with Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)

Methods

This was a double-blind, randomized, two dose level (0.2 mg/kg and 1.0 mg/kg) study.

rhASB was administered once weekly for 24 weeks to two groups of MPS VI patients. Four patients received 0.2 mg/kg/week. Three patients received 1.0 mg/kg/week. Study drug was administered intravenously over approximately a 4-hour period.

An interim analysis of unblinded safety and efficacy data of treatment for each patient was performed after the sixth patient that was enrolled had completed 24 weeks of treatment. After results of the interim analysis were available and reviewed, all patients randomized to 0.2 mg/kg/week were transitioned to 1.0 mg/kg/week for the remainder of the study. Patients originally randomized to the 1.0 mg/kg/week dosage level remained at that level.

For both groups, a switch to a drug product produced by a different process and formulation was made at Week 84. Patients were transitioned from — process that included — Polysorbate 80.

Plasma concentrations of ASB were measured at BioMarin Pharmaceuticals, Inc. using an ELISA method. Limit of detection of the assay (LOQ) was — ng/mL.

Blood samples for measurement of ASB were collected as follows for the infusions administered during Weeks 1, 2, 12, and 24 of double-blind therapy and 83, 84, and 96 of the open-label extension.

- During the infusion: 0, 15, 30, 60, 90, and 180 minutes
 - End of infusion: 240 minutes
 - Post Infusion: 5, 10, 15, 30, 45, 60, 90, 120, and 240 minutes
- (Note: If the duration of the infusion was >240 minutes, then an additional blood sample was collected at the end of the infusion.)

Pharmacokinetic Analysis:

Only those plasma ASB concentrations that were equal to or greater than the qualified limit of detection of the assay (LOQ: — ng/mL) were used in the pharmacokinetic analyses. Concentrations < LOQ prior to C_{max} were set equal to 0 and those after C_{max} were set to missing. Actual blood sampling times were used for all pharmacokinetic calculations. All pharmacokinetic calculations were done using SAS Version 9.0 under Windows 2000. Pharmacokinetic parameters for ASB were calculated using non-compartmental methods. Due to the short t_{1/2} of < 45 minutes observed in this study relative to the dosing frequency of once every week, each infusion was treated as a single dose for pharmacokinetic analysis.

Results

rhASB was administered once weekly for 24 weeks in a double-blind fashion to two groups of MPS VI patients at doses of 0.2 mg/kg/wk (n = 4 patients) and 1.0 mg/kg/wk (n = 3 patients), respectively. One patient in the 0.2 mg/kg/week group (Patient 40) dropped out of the study after receiving a total of 3 infusions. Another patient in the low dose group dropped out of the study at Week 32. The remaining two subjects in the low dose (0.2 mg/kg/week) group completed the 96 weeks of treatment after having been switched to the high dose (1.0 mg/kg/week) at Weeks 59 and 69, respectively. The three patients in the high dose (1.0 mg/kg/week) group continued at this dose through Week 96.

Pharmacokinetics Results:

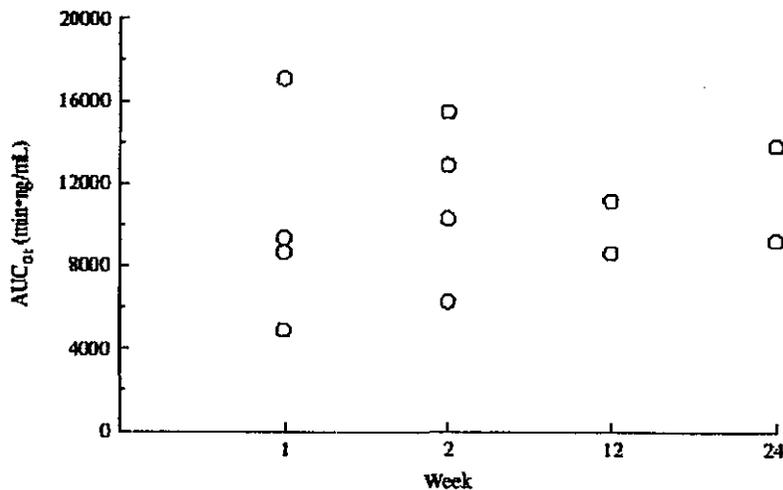
0.2 mg/kg/week dose:

PK Parameters for rhASB in Patients with MPS VI (ASB-00-01-PK)								
Mean (\pm SD)								
Dose [mg/kg/wk]	Wk	N	C _{max} [ng/mL]	AUC _{0-t} [min*ng/mL]	AUC _∞ [min*ng/mL]	CL [mL/min/kg]	V _z [mL/kg]	t _{1/2} [min]
0.2	1	4	75 \pm 29	10009 \pm 5107	--	--	--	--
	2	4	88 \pm 26	11232 \pm 3914	--	--	--	--
	12	2*	87; 67	13812; 9230	--	--	--	--
	24	2*	94; 75	13812; 9230	--	--	--	--

* N=2 at Weeks 12 and 24 because one patient (#40) dropped out after Week 3, and one patient (#41) had plasma concentrations that were below the LOQ at Weeks 12 and 24.
 Values for AUC_∞, CL, V_z, and t_{1/2} could not be calculated in the 0.2 mg/kg/week group because λ_z could not be calculated.
 (Values in the table above were taken from page 11 of the ASB-00-01 PK Study Report.)

Individual Patient AUC_{0-t} values versus week of treatment are shown in the figure below.

Individual Patient AUC_{0-t} after rhASB 0.2 mg/kg/week (ASB-00-01-PK)



(The above diagram was taken from page 12 of the ASB-00-01 PK Study Report.)

For patients administered 0.2 mg/kg/week, the mean values for AUC_{0-t} were relatively consistent from Week 1 through Week 24 (see table above and figure above).

1.0 mg/kg/week dose:

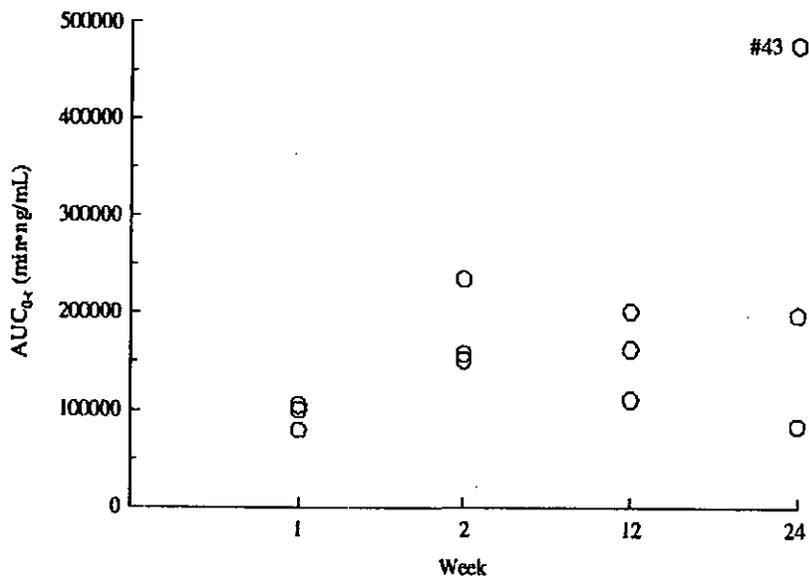
PK Parameters for rhASB in Patients with MPS VI (ASB-00-01-PK)								
Mean (\pm SD)								
Dose [mg/kg/wk]	Wk	N*	C _{max} [ng/mL]	AUC _{0-t} [min*ng/mL]	AUC _∞ [min*ng/mL]	CL [mL/min/kg]	V _z [mL/kg]	t _{1/2} [min]
1.0	1	3;1	572 \pm 60	94476 \pm 13785	100280	10	62	4
	2	3;2	2072 \pm 2017	180909 \pm 46377	157720; 152514	6; 7	64; 57	7; 6
	12	3	1001 \pm 307	157890 \pm 45386	158670 \pm 45789	7 \pm 2	54 \pm 4	6 \pm 2
	24	3	1651 \pm 1423	251907 \pm 201747	255847 \pm 207600	6 \pm 5	71 \pm 25	15 \pm 16
	83	5	1143 \pm 284	172423 \pm 49495	173570 \pm 49969	6 \pm 2	68 \pm 22	8 \pm 5
	84	5	1367 \pm 262	213713 \pm 45794	215383 \pm 47018	5 \pm 1	122 \pm 60	19 \pm 13
	96	4	1341 \pm 523	200116 \pm 76506	201517 \pm 77243	6 \pm 2	123 \pm 17	17 \pm 8

* At Week 1: N=3 for C_{max} and AUC_{0-t}; N=1 for AUC_{0-∞}, CL, V_z, t_{1/2}
 At Week 2: N=3 for C_{max} and AUC_{0-t}; N=2 for AUC_{0-∞}, CL, V_z, t_{1/2}
 (Values in the table above were taken from page 4 of the Clinical Pharmacology Summary and page 11 of the ASB-00-01 PK Study Report.)

Comparison of the mean values for AUC_{0-t} or AUC_∞ between the 0.2 and 1.0 mg/kg/week cohorts shows an increase much higher than the 5-fold increase in dose, indicating that the pharmacokinetics of rhASB are not linear over this dose range (see tables above).

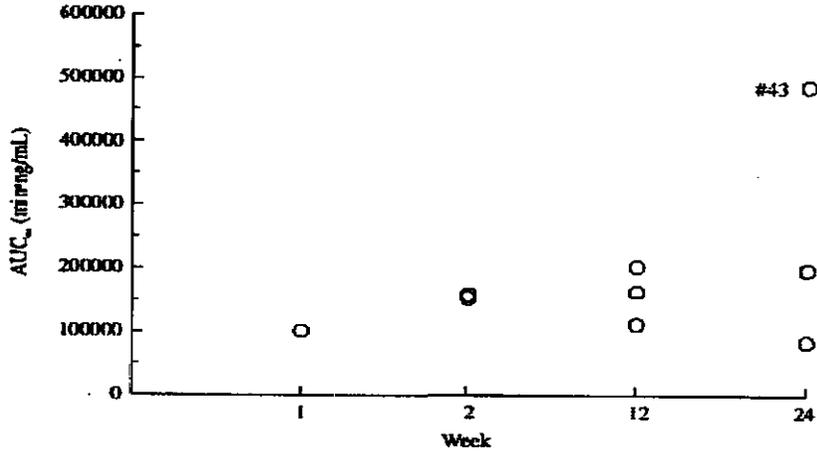
Individual Patient AUC_{0-t} values versus week of treatment and individual Patient AUC_{0-∞} values versus week of treatment are shown in the figures below.

Individual Patient AUC_{0-t} after rhASB 1.0 mg/kg/week (ASB-00-01-PK)



(The figure above was taken from page 13 of the ASB-00-01 PK Study Report.)

Individual Patient AUC_{0-∞} after rhASB 1.0 mg/kg/week (ASB-00-01-PK)



(Figure above was taken from page 13 of ASB-00-01 PK Study Report.)

For the 1.0 mg/kg/week cohort, values for AUC_{0-t} and AUC_{0-∞} appeared to increase from Week 1 to Week 2, and remain unchanged from Week 2 to Week 96, with the exception of an increase at Week 24 (see table above and figures above). Examination of the individual patient values, however, indicates that the increase in the mean as well as the large standard deviation at Week 24 was due to Patient 43 whose AUC value was approximately 2-fold higher than the other two patients in that group (see figure above).

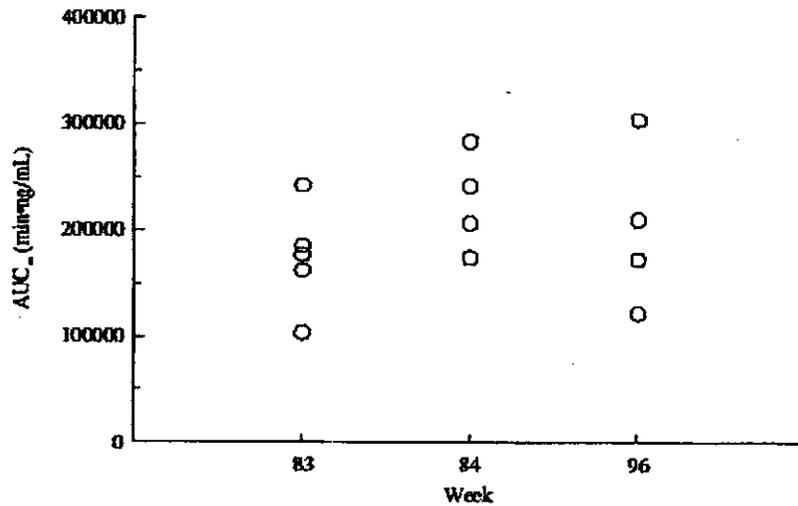
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Comparison of

Process:

Beginning with Week 84, patients received rhASB made by a modified manufacturing process and incorporated polysorbate 80 in the formulation (process). The figure below shows the individual patient AUC_∞ values after administration of rhASB at Weeks 83, 84, and 96.

Individual Patient AUC_∞: Administration of Process (Week 83) and Process (Weeks 84 and 96) rhASB [1.0 mg/kg/week dose]



(The figure above was taken from page 16 of the ASB-00-01 PK Study Report.)

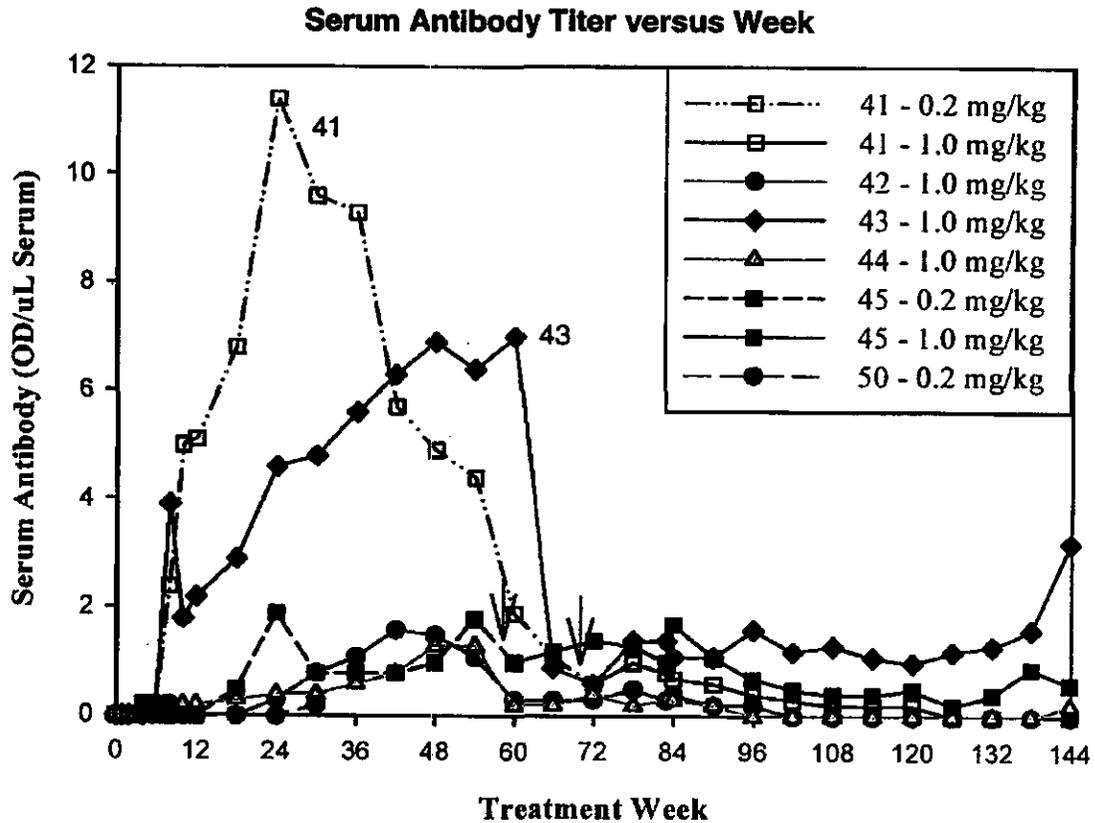
Although mean values for AUC_∞ appear to increase and those for CL to decrease approximately 25%, there is substantial overlap of the individual values and the small number of patients precludes a conclusion that the pharmacokinetic parameters for the modified process differ from that of rhASB produced by the original process (see table above and figure above). The pharmacokinetic profile of the rhASB produced by the modified process (process) appeared to be similar to that for rhASB produced by the original process (process).

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Effect of Antibody Development on Pharmacokinetics

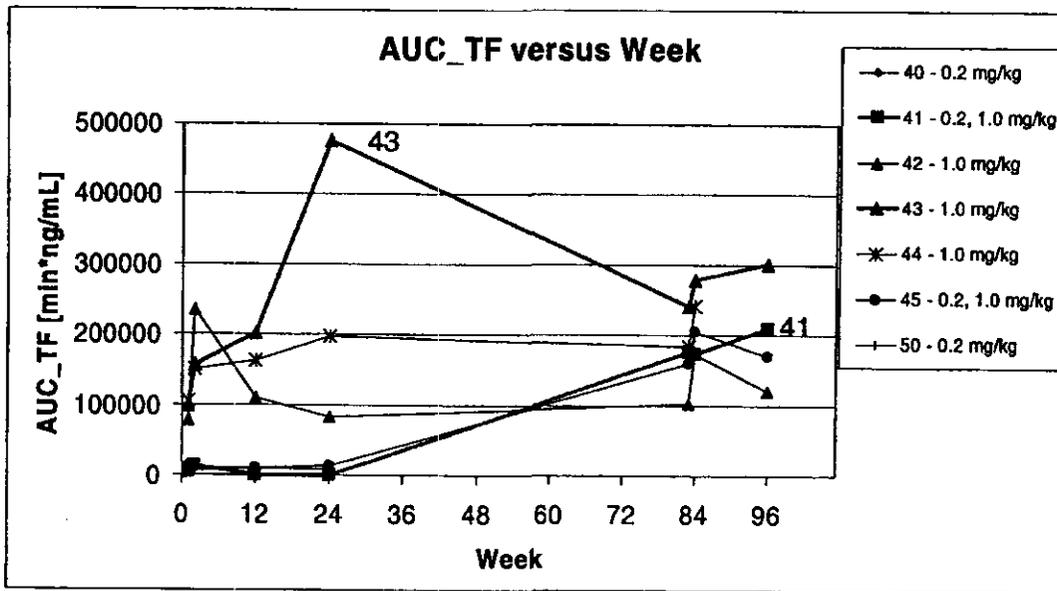
Six of the seven patients in the study developed antibodies to galsulfase. Patient 40 is the only patient that did not develop antibodies to galsulfase. However, Patient 40 received three infusions only.

The antibody titer versus week is shown in the figure below for each of the patients.



Patient 41 was changed to the 1.0 mg/kg dose at Week 69 as shown by the arrow.
 Patient 45 was changed to the 1.0 mg/kg dose at Week 59 as shown by the arrow.
 (The figure above was taken from page 120 of the ASB-00-01 Clinical Study Report)

The AUC versus week is shown in the figure below for each of the patients.



Patient 41 was changed to the 1.0 mg/kg dose at Week 69.

Patient 45 was changed to the 1.0 mg/kg dose at Week 59.

(The AUC_TF values plotted above were taken from page 22 of the ASB-00-01 PK Study Report.)

Patient 41 and Patient 43 had antibody titers that were substantially higher than the antibody titers of the other patients.

Antibody titers for Patient 41 reached a peak value of 11.4 OD/ μ L at Week 24, decreased to 1.0 OD/ μ L serum at Week 66, and were undetectable from Week 126 through Week 144. At Week 1, Patient 41 had AUC of 4,908 min*ng/mL; at Week 2, Patient 41 had AUC of 12,895 min*ng/mL. At Weeks 12 and 24, Patient 41 had concentrations below the limit of detection of the assay. By Week 83, Patient 41's AUC value had increased to values similar to those of other patients.

Patient 43 had an antibody titer of 3.9 OD/ μ L at Week 8, 4.6 OD/ μ L at Week 24, 7.0 OD/ μ L at Week 60, and 1.0 OD/ μ L at Week 66. Antibody titers remained low for the remainder of the study period, with a slight increase to 3.2 OD/ μ L at Week 144. Patient 43 had AUC value at Week 24 that was approximately 2-fold higher than the other two patients in that group (see figure above). By Week 83, Patient 43's AUC value had decreased to values similar to those of other patients.

Conclusions

1. For patients administered 0.2 mg/kg/week, the mean values for AUC_{0-t} were relatively consistent from Week 1 through Week 24.
2. For the 1.0 mg/kg/week cohort, values for AUC_{0-t} and $AUC_{0-\infty}$ appeared to increase from Week 1 to Week 2, and remain unchanged from Week 2 to Week 96, with the exception of an increase at Week 24; the increase at Week 24 was largely due to one patient with substantially higher antibody titers than those of the other patients.
3. The pharmacokinetics of rhASB are not linear between 0.2 mg/kg/week and 1.0 mg/kg/week as shown by greater than dose-proportional increases in AUC.
4. The pharmacokinetics of rhASB produced by the modified process (— process) appear similar to the pharmacokinetics of rhASB produced by the original process (— process).
5. Of the seven patients studied, six developed antibodies to galsulfase; the patient that did not develop antibodies only received three infusions of galsulfase. Two patients had antibody titers that were substantially higher than those of the other patients. One patient with high antibody titers had a greater increase in plasma AUC between Weeks 1 and 24 than other patients. One patient with high antibody titers had a decrease in plasma AUC between Weeks 1 and 24.

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Study ASB-01-04-PK

A Phase 2 Open-Label Clinical Study of the Efficacy and Safety of Recombinant Human *N*-acetylgalactosamine 4-sulfatase (rhASB) Enzyme Replacement Therapy in Patients with Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)

Methods

In Study ASB-01-04, rhASB was administered once weekly for 24 weeks at a dose of 1.0 mg/kg/week to ten MPS VI patients. Study drug was administered intravenously over approximately a 4-hour period.

Serial plasma samples for the determination of rhASB pharmacokinetics were collected at Weeks 1, 2, 12, and 24. Plasma concentrations of ASB were measured at BioMarin Pharmaceuticals, Inc. using an ELISA method. Limit of detection of the assay (LOQ) was ng/mL.

Blood samples for measurement of ASB were collected as follows for the infusions administered during Weeks 1, 2, 12, and 24.

- During the infusion: 0, 30, 90, and 180 minutes
 - End of infusion: 240 minutes
 - Post Infusion: 5, 10, 20, 30, 45, and 90 minutes
- (Note: If the duration of the infusion was >240 minutes, then an additional blood sample was collected at the end of the infusion.)

Patients who completed the first 24 weeks of treatment were offered a continuation of the therapy.

Pharmacokinetic Analysis:

Only those plasma ASB concentrations that were equal to or greater than the qualified limit of detection of the assay (LOQ: — ng/mL) were used in the pharmacokinetic analyses. Concentrations <LOQ prior to C_{max} were set equal to 0 and those after C_{max} were set to missing. Actual blood sampling times were used for all pharmacokinetic calculations. All pharmacokinetic calculations were done using SAS Version 9.0 under Windows 2000. Pharmacokinetic parameters for ASB were calculated using non-compartmental methods. Due to the short t_{1/2} of < 45 minutes observed in this study relative to the dosing frequency of once every week, each infusion was treated as a single dose for pharmacokinetic analysis.

Results

Ten patients with MPS VI, 7 females and 3 males, were enrolled in the study. Ages ranged from six to 21 years and urinary GAG levels ranged from 138.4 to 518.5 at enrollment. All ten patients were on study through Week 72.

Patients received a mean of 71.8 (SD 0.6) infusions of 1.0 mg/kg over the 72-week study period. The number of infusions ranged from 71 to 73. One patient missed two infusions and one patient missed one infusion.

Pharmacokinetic Results:

Study ASB-01-04-PK							
PK Parameters for rhASB in Patients with MPS VI, Mean (\pm SD)							
Dose = 1.0 mg/kg/wk							
Wk	N*	C _{max} [ng/mL]	AUC _{0-t} [min*ng/mL]	AUC _∞ [min*ng/mL]	CL [mL/min/kg]	V _z [mL/kg]	t _{1/2} [min]
1	10	757 \pm 270	135043 \pm 42479	137659 \pm 41550	8 \pm 3	233 \pm 223	19 \pm 16
2	9;10	1176 \pm 416	200730 \pm 72793	207810 \pm 74558	5 \pm 2	137 \pm 94	17 \pm 6
12	10	1313 \pm 546	204049 \pm 87581	205921 \pm 87989	7 \pm 5	163 \pm 197	15 \pm 11
24	7;9	1701 \pm 659	254757 \pm 88010	274570 \pm 4548	4 \pm 1	94 \pm 50	18 \pm 9

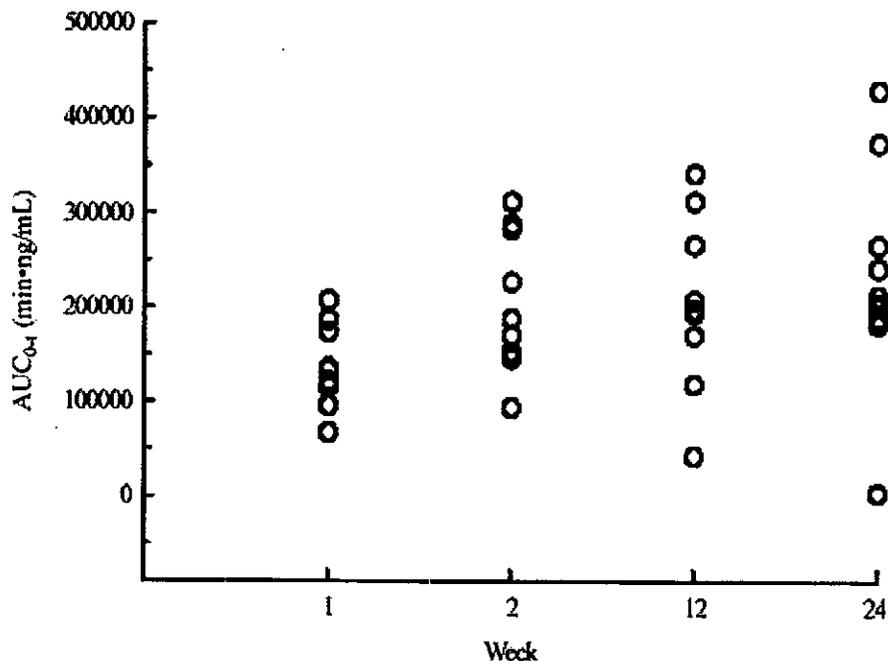
* Week 2: N=10 for AUC_{0-t}, C_{max}, T_{max}; N=9 for all other PK parameters stated.

Week 24: N=9 for AUC_{0-t}, C_{max}, T_{max}; N=7 for all other PK parameters stated.

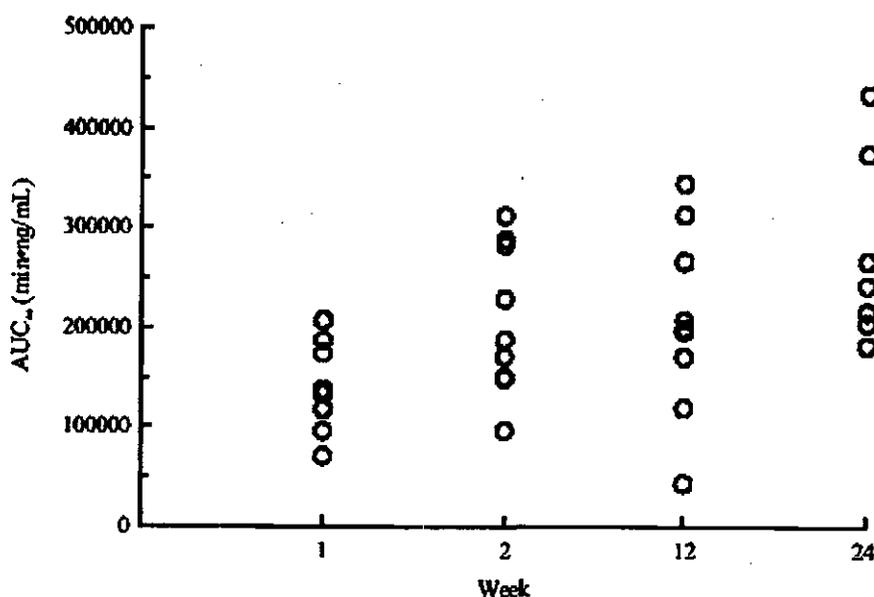
(Values in the table above were taken from Table 1, page 4 of the Clinical Pharmacology Summary.)

The mean values for AUC_{0-t} and AUC_∞ appeared to increase from Week 1 to Week 2, remain unchanged at Week 12, and then increase slightly at Week 24 (see table above). The individual patient values are shown below (see figures below).

Individual Patient AUC_{0-t} after Administration of rhASB 1.0 mg/kg/week to MPS VI Patients



(The figure above was taken from page 7 of the Clinical Pharmacology Summary.)

Individual Patient AUC_∞ after Administration of rhASB 1.0 mg/kg/week to MPS VI Patients

(The figure above was taken from page 8 of the Clinical Pharmacology Summary.)

A statistical analysis was performed to determine the effect of treatment duration on PK parameter values (see table below).

Statistical Comparison of Pharmacokinetic Parameters for rhASB Among Weeks After IV Administration of 1.0 mg/kg/week to Patients with MPS VI		
Parameter	p-value ¹	Comparison ²
AUC _{0-t}	0.0005	Week 1 < Weeks 2 - 24
AUC _∞	0.0021	Week 1 < Weeks 2 - 24
CL	0.3268	--
V _z	0.9104	--
t _{1/2}	0.6043	--

¹ p-value of the effect of week from the analysis of variance.

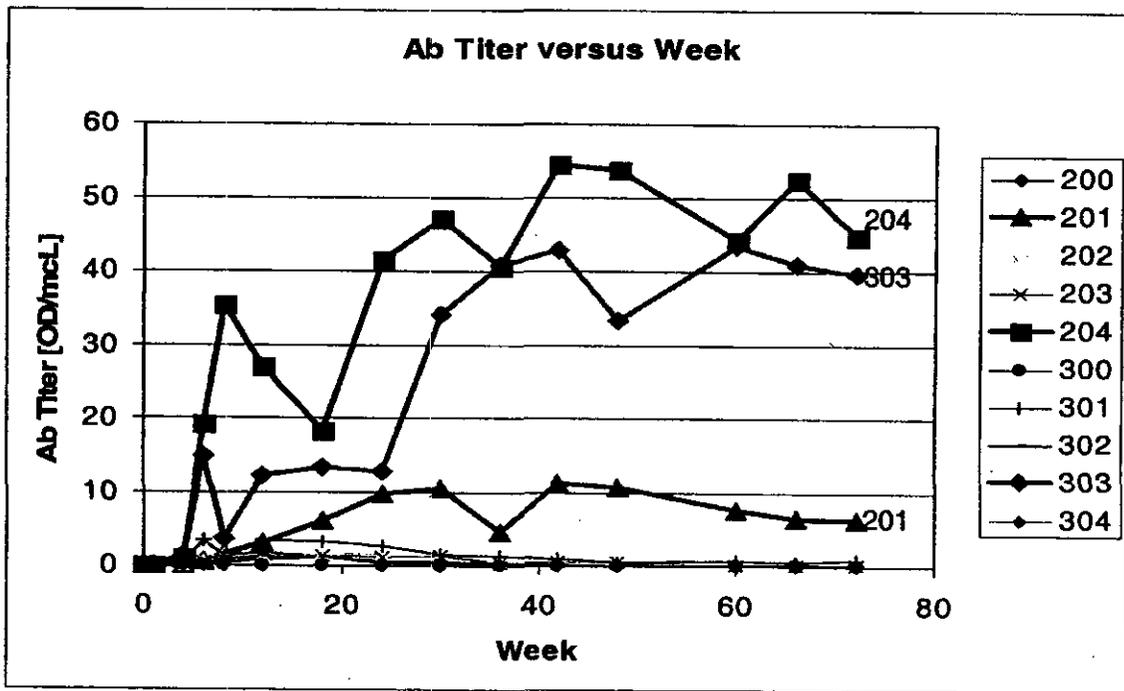
² Multiple t-tests among least squares means.

(Values in the table above were taken from page 7 of the ASB-01-04 PK Study Report.)

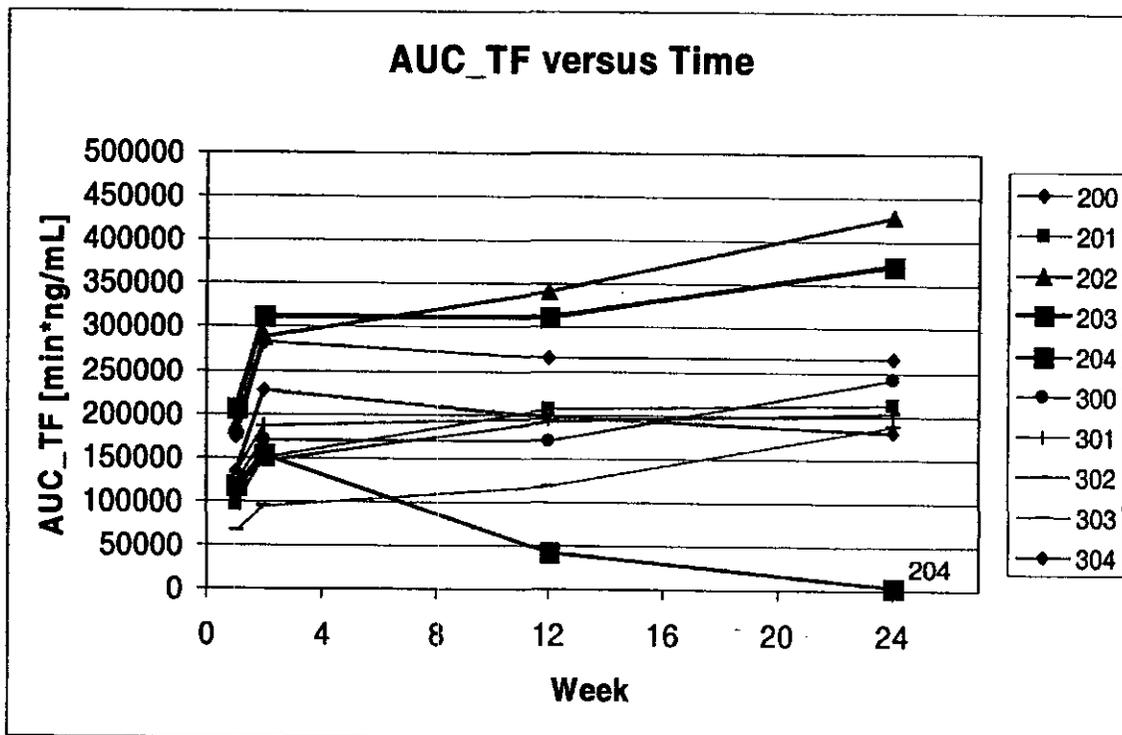
The effect of week was statistically significant for both AUC_{0-t} and AUC_∞ with Week 1 being statistically different from Weeks 2, 12, and 24; there were no significant differences for AUC_{0-t} and AUC_∞ between Weeks 2, 12, and 24. Although not significantly different, mean values for CL and V_z decreased at Week 24, consistent with the trend toward a higher AUC_{0-t} for that infusion. Mean t_{1/2} ranged from 15 to 19 minutes and did not appear to be dependent on weeks on study (see table above).

Effect of Antibody Development on Pharmacokinetics

Nine of ten patients studied developed antibodies to galsulfase. The antibody titer versus week and the AUC versus week are shown in the figures below for each of the patients.



(Ab titer values were taken from Listing 16.2.10 in the ASB-01-04 Clinical Study Report.)



(AUC_TF values were taken from the SAS dataset PRM0104.xpt.)

Patients 204, 303, and 201, had antibody titers that were substantially higher than those of the other patients. Patient 204 reached a maximum antibody titer of 54.5 OD/mcL at Week 42. Patient 303 reached a maximum antibody titer of 43.5 OD/mcL at Week 60. Patient 201 reached a maximum antibody titer of 11.2 OD/mcL at Week 42.

All patients in the study other than Patient 204 had increases in AUC from Week 1 to Week 24. AUC for Patient 204 decreased from 117,470 min*ng/mL at Week 1 to 3,786 min*ng/mL at Week 24.

Conclusions

- (1) The results of this study suggest that beginning with the second dose (Week 2), rhASB AUC appears to be independent of the duration of treatment through 24 weeks.
- (2) Mean $t_{1/2}$ ranged from 15 to 19 minutes and did not appear to be dependent on weeks on study.
- (3) Of the ten patients studied, nine developed antibodies to galsulfase. Three patients had antibody titers that were substantially higher than those of the other patients. One patient with high antibody titers had a decrease in plasma AUC between Weeks 1 and 24.

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Study ASB-03-05-PK

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Multinational Clinical Study of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) in Patients with Mucopolysaccharidosis VI

Methods

In Study ASB-03-05, rhASB was administered once weekly for 24 weeks at a dose of 1.0 mg/kg/week to 19 MPS VI patients. 20 patients received placebo.

Serial plasma concentrations for the determination of rhASB pharmacokinetics were collected from 14 of the 19 rhASB-treated patients at Weeks 1 and 24.

Plasma concentrations of ASB were measured at BioMarin Pharmaceuticals, Inc. using an ELISA method. Limit of detection of the assay (LOQ) was — ng/mL.

Blood samples for measurement of ASB were collected as follows for the infusions administered during Weeks 1 and 24.

- During the infusion: 0, 30, 90, and 180 minutes
- End of infusion: 240 minutes
- Post Infusion: 5, 10, 20, 30, 45, and 60 minutes

Pharmacokinetic Analysis:

Only those plasma ASB concentrations that were equal to or greater than the qualified limit of detection of the assay (LOQ: — ng/mL) were used in the pharmacokinetic analyses. Concentrations <LOQ prior to C_{max} were set equal to 0 and those after C_{max} were set to missing. Actual blood sampling times were used for all pharmacokinetic calculations.

All pharmacokinetic calculations were done using SAS Version 9.1 under Windows 2000. Pharmacokinetic parameters for ASB were calculated using non-compartmental methods. Due to the short t_{1/2} of < 45 minutes observed in this study relative to the dosing frequency of once every week, each infusion was treated as a single dose for pharmacokinetic analysis.

Results**Pharmacokinetic Results:**

The mean values for the PK parameters are shown in the table below.

Study ASB-03-05-PK: PK Parameters for rhASB 1.0 mg/kg/wk in Patients with MPS VI		
Mean \pm SD		
PK Parameter	Week 1 ^a	Week 24 ^b
C _{max} [mcg/mL]	0.83 \pm 0.22	2.36 \pm 1.56
T _{max} [min]	208.21 \pm 75.93	249.31 \pm 84.90
AUC _{0-t} [hr*mcg/mL]	2.21 \pm 0.60	5.71 \pm 4.02
AUC _∞ [hr*mcg/mL]	2.38 \pm 0.50	5.86 \pm 4.18
V _z [mL/kg]	118.30 \pm 74.70	316.49 \pm 752.40
CL [mL/min/kg]	7.28 \pm 1.48	7.92 \pm 14.66
t _{1/2} [min]	11.10 \pm 5.26	22.79 \pm 10.67

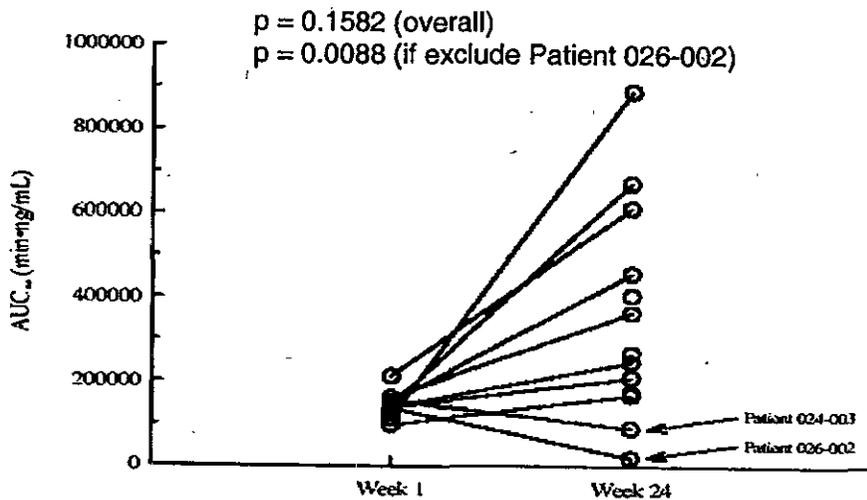
a. At Week 1: N=13 for AUC_{0-t}; N=11 for AUC_∞, CL, V_z, and t_{1/2}; N=14 for C_{max} and T_{max}.
b. At Week 24: N=13 for C_{max}, T_{max}, AUC_{0-t}, AUC_∞, CL, V_z, and t_{1/2}.
(Values in the table above were calculated from individual PK parameter values in the SAS dataset PRM0305.xpt)

The median values for the PK parameters are shown in the table below.

Study ASB-03-05-PK: PK Parameters for rhASB 1.0 mg/kg/wk in Patients with MPS VI		
Median (Range)		
PK Parameter	Week 1 ^a	Week 24 ^b
C _{max} [mcg/mL]	0.82 (0.38-1.26)	1.45 (0.24-5.46)
T _{max} [min]	207.50 (89-358)	240.00 (180-505)
AUC _{0-t} [hr*mcg/mL]	2.27 (1.01-3.53)	4.26 (0.26-14.17)
AUC _∞ [hr*mcg/mL]	2.31 (1.59-3.55)	4.47 (0.30-14.81)
V _z [mL/kg]	103.36 (55.81-322.96)	68.82 (58.77-2799.47)
CL [mL/min/kg]	7.22 (4.70-10.45)	3.73 (1.13-55.88)
t _{1/2} [min]	8.84 (5.51-21.41)	25.53 (7.80-39.89)

a. At Week 1: N=13 for AUC_{0-t}; N=11 for AUC_∞, CL, V_z, and t_{1/2}; N=14 for C_{max} and T_{max}.
b. At Week 24: N=13 for C_{max}, T_{max}, AUC_{0-t}, AUC_∞, CL, V_z, and t_{1/2}.
(Values in the table above were calculated from individual PK parameter values in the SAS dataset PRM0305.xpt)

Individual Patient AUC_∞ after rhASB 1.0 mg/kg/week



(The figure above is taken from page 9 of the Clinical Pharmacology Summary.)

A statistical analysis was performed to determine the differences in PK parameter values between Weeks 1 and 24 (see table below).

Statistical Comparison of Pharmacokinetic Parameters for rhASB After IV Administration of 1.0 mg/kg/week to Patients with MPS VI		
Parameter	p-value ¹	
	All Patients	Patient 026-002 Excluded
AUC _{0-t}	0.0670	0.0013
AUC _∞	0.1582	0.0088
CL	0.7293	0.0193
Vz	0.3658	0.8257
t _{1/2}	0.0163	0.0380

¹p-value of the effect of week from the analysis of variance.

(Values in the table above were taken from page 12 of the ASB-03-05 PK Study Report.)

The individual patient values for AUC_∞ demonstrate an increase for all but two patients (024-003 and 026-002). However, due to the inter-patient variability, the differences between Weeks 1 and 24 were not statistically significant (p = 0.1582) when all patients were considered.

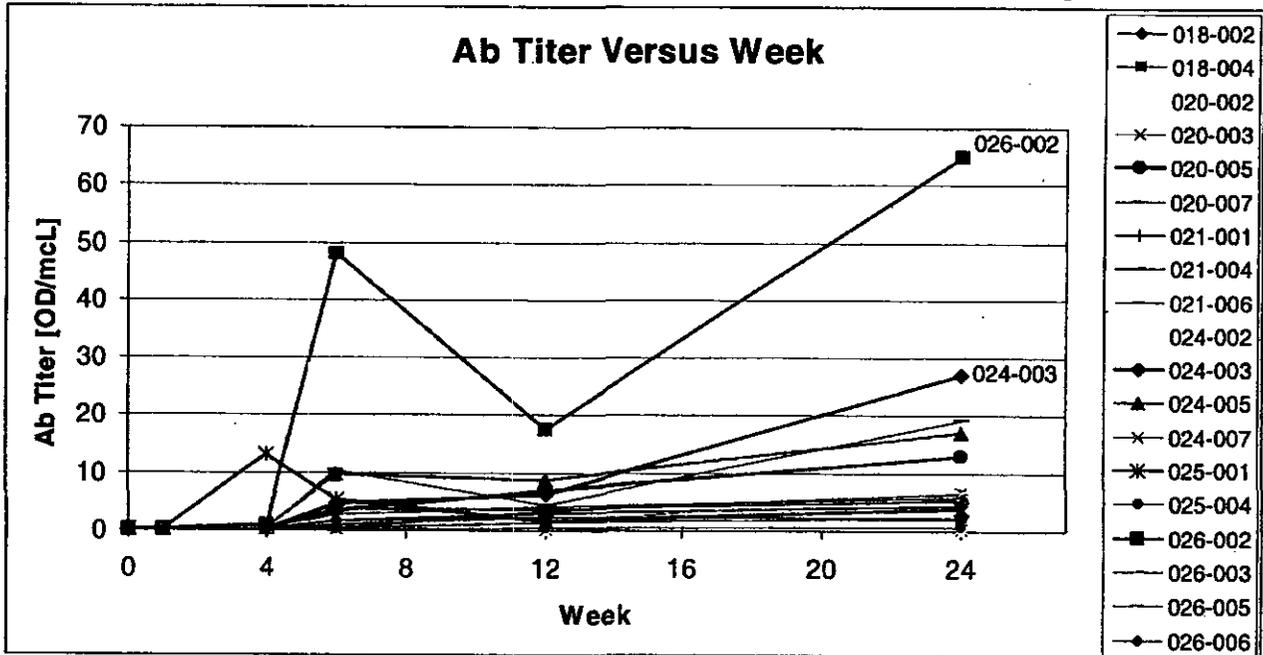
When Patient 026-002 is excluded from the analysis of AUC_{0-t} and AUC_∞, the difference between Week 1 and Week 24 is statistically significant (p = 0.0013 and p = 0.0088, respectively). Consistent with the significant increase in AUC_∞ (excluding Patient 026-002), CL was significantly lower at Week 24 than at Week 1 (excluding Patient 026-002).

The CL for Patient 026-002 at Week 24 (55.9 mL/min/kg) was substantially higher than CL for Week 1 (7.3 mL/min/kg). Therefore, the AUC_∞ for Patient 026-002 at Week 24 (0.3 h*mcg/mL) was substantially below the AUC_∞ value for Patient 026-002 value at Week 1 (2.1 h*mcg/mL) as well as the values for all other patients for both weeks (see figure above). Also, Patient 026-002 had increase in Vz from 123.0 mL/kg at Week 1 to 2799.5 mL/kg at Week 24 and had a higher value of Vz at Week 24 than all other patients for both weeks.

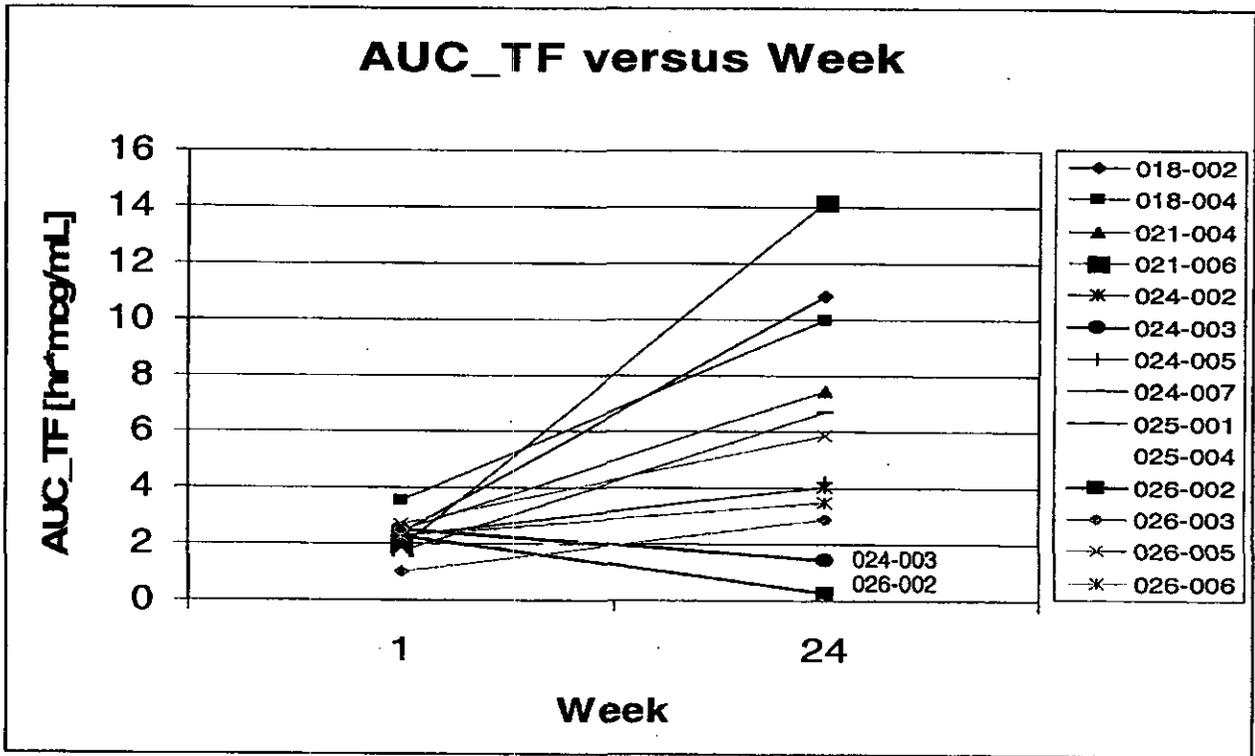
The CL for Patient 024-003 at Week 24 (11.2 mL/min/kg) was substantially higher than CL for Week 1 (6.5 mL/min/kg). Therefore, the AUC_∞ for Patient 024-003 at Week 24 (1.5 h*mcg/mL) was substantially below the AUC_∞ value for Patient 024-003 value at Week 1 (2.6 h*mcg/mL) (see figure above). Also, Patient 024-003 had increase in Vz from 139.1 mL/kg at Week 1 to 413.5 mL/kg at Week 24.

Effect of Antibody Development on Pharmacokinetics

All 19 patients treated with galsulfase in this study developed antibodies to galsulfase. The antibody titer versus week for each of the 19 patients given galsulfase, and the AUC versus week for each of the 14 patients that had PK samples taken are shown in the figures below.



(Ab titer values were taken from listing 16.2.10 on page 3840 of the ASB-03-05 Clinical Study Report.)



AUC_TF value was not determined for Patient 024-005 at Week 1.

AUC_TF value was not determined for Patient 024-007 at Week 24.

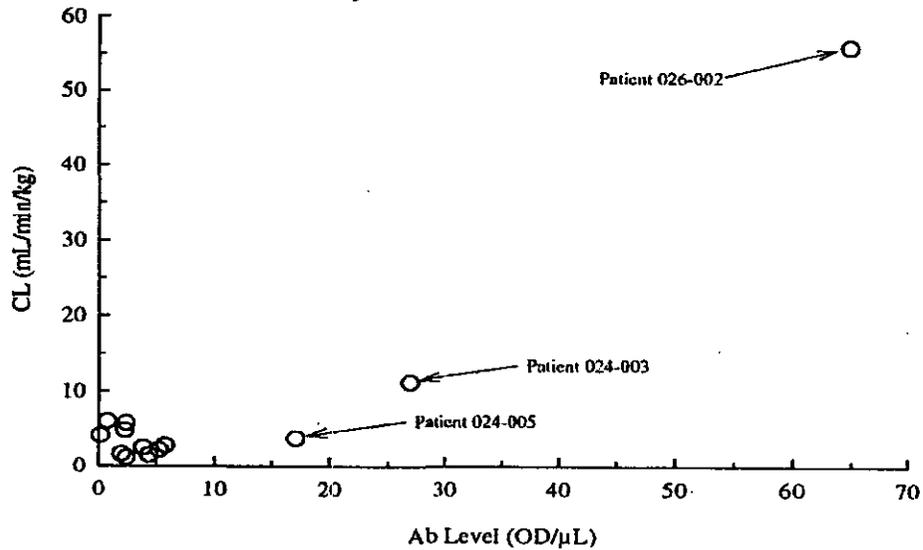
(Individual PK parameter values in the figure above were taken from SAS dataset PRM0305.xpt)

Patients 026-002 and 024-003 had antibody titers that were substantially higher than those of the other patients. Patient 026-002 reached a maximum antibody titer of 64.9 OD/mcL at Week 24. Patient 024-003 reached a maximum antibody titer of 27.0 OD/mcL at Week 24.

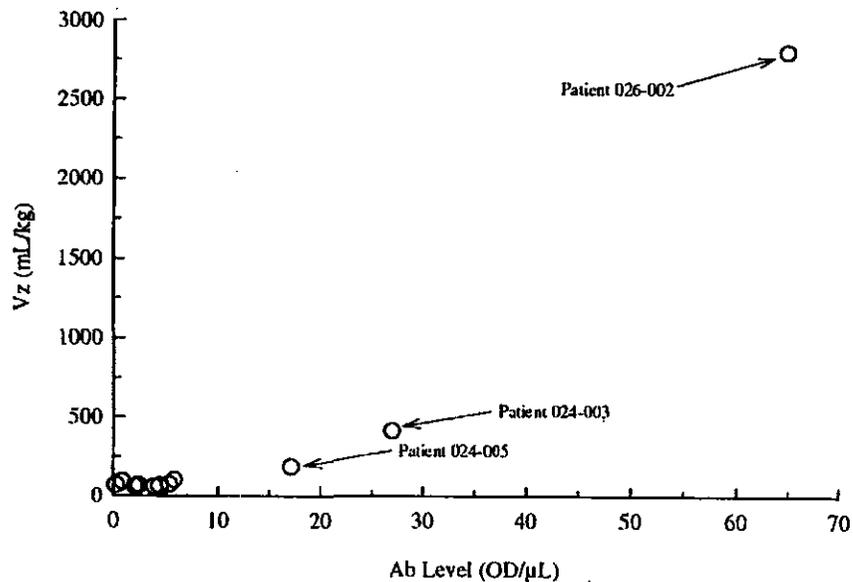
All patients in the study with AUC measured at Weeks 1 and 24 other than Patient 026-002 and Patient 024-003 had increases in AUC from Week 1 to Week 24. AUC for Patient 026-002 decreased from 2.26 hr*mcg/mL at Week 1 to 0.26 hr*mcg/mL at Week 24. AUC for Patient 024-003 decreased from 2.54 hr*mcg/mL at Week 1 to 1.45 hr*mcg/mL at Week 24.

The relationships between CL and Vz and antibody levels at Week 24 are illustrated in the figures below.

CL versus Antibody Level After 24 Weeks of rhASB 1.0 mg/kg/week



(The figure above is taken from page 12 of the ASB-03-05 PK Study Report.)



(The figure above is taken from page 13 of the ASB-03-05 PK Study Report.)

With the exception of the three patients with antibody levels greater than 10 OD/ μ L (024-003, 024-005, 026-002), neither CL nor Vz at Week 24 appeared to be related to antibody level (range of values 0.2 to 6.6 OD/ μ L).

Conclusions

1. Plasma rhASB concentrations and measures of exposure (AUC_{0-t} , AUC_{∞}) were higher at Week 24 than at Week 1, consistent with a decrease in CL.
2. Mean $t_{1/2}$ ranged from 11 to 23 minutes and did not appear to change between Week 1 and Week 24.
3. All fourteen patients with pharmacokinetic measurements developed antibodies to galsulfase. Two patients with antibody titers that were substantially higher than those of the other patients had decreases in plasma AUC between Weeks 1 and 24.
4. CL and Vz at Week 24 appeared to be related to antibody levels in those patients with a titer ≥ 10 OD/mL. It is not possible to determine if this is an effect of the antibody on the clearance and distribution of rhASB or interference of the antibody with the ELISA, resulting in apparently lower plasma concentrations and thus higher CL.

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Study ASB-XO-001

Comparison of the Clinical and Commercial Process Products of Recombinant Human N-acetylgalactosamine 4-sulfatase (rhASB) in Patients with Mucopolysaccharidosis VI

Methods

This study was an analysis of the pharmacokinetic and pharmacodynamic comparability between the clinical (Lot No. AV60304-A; produced using a _____ in the clinical facility) and commercial (Lot No. V60401-B; produced using a _____ in the commercial facility) materials in patients who had received rhASB treatment for an extended period of time.

After 179 to 188 weeks of rhASB treatment, the four (4) patients in the Phase 1/2 study (Study ASB-00-01) were transitioned from clinical process to the commercial process rhASB.

Similarly, the ten Phase 2 study (Study ASB-01-04) patients transitioned from clinical process to commercial process rhASB between Weeks 98 and 117 of treatment.

The clinical process material, Lot No. AV60304-A, was produced using a _____ . The material for commercial use, Lot No. V60401-B, was produced using a _____ .

rhASB: (1) the last infusion of clinical process material; (2) the first infusion of commercial process material the following week; and (3) the infusion of commercial process material four weeks later. Samples were collected at the following times:

Study ASB-00-01

During the infusion: 0, 15, 30, 60, 90, and 180 minutes

End of infusion: 240 minutes

Post Infusion: 5, 10, 15, 30, 45, 60, 90, 120, and 240 minutes

Study ASB-01-04

During the infusion: 0, 30, 90, and 180 minutes

End of infusion: 240 minutes

Post Infusion: 5, 10, 20, 30, 45, and 90 minutes

Doses of rhASB, patient body weight, volume infused, anti-rhASB antibody levels, plasma ASB concentrations, the calendar dates and clock times of the infusions and blood sample collection times, and urinary GAG excretions were supplied by BioMarin in Microsoft Excel workbooks.

Analysis of rhASB in Plasma: Plasma concentrations of ASB were measured at BioMarin Pharmaceutical, Inc. using a qualified ELISA method with a lower limit of detection (LOQ) of _____ ng/mL.

Analysis of GAG in Urine: Urinary GAG measurements were performed at BioMarin Pharmaceutical, Inc using a qualified method _____

Pharmacokinetic Analysis: Only those plasma ASB concentrations that were equal to or greater than the LOQ (\sim ng/mL) were used in the pharmacokinetic analyses. Concentrations $<$ LOQ prior to C_{max} were set equal to 0 and those after C_{max} were set to missing. Actual blood sampling times were used for all pharmacokinetic calculations. All pharmacokinetic calculations were done using SAS Version 9.1 under Windows 2000. Pharmacokinetic parameters for ASB were calculated using non-compartmental methods. Actual blood sampling times were used for all pharmacokinetic analyses. Due to the short $t_{1/2}$ of $<$ 15 minutes observed in this study relative to the dosing frequency of once every week, each infusion was treated as a single dose for pharmacokinetic analysis.

Statistical Analysis: Comparison of the pharmacokinetic parameters C_{max} , AUC_{0-t} , and AUC_{∞} for rhASB between the test (commercial) and reference (clinical) materials was done using an analysis of variance statistical model with subject and treatment as the classification variables, using the natural logarithms of the data. Confidence intervals (90%) were constructed for the ratios (test-to-reference) of the three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. The urinary GAG excretion was compared between test and reference using the same ANOVA but without logarithmic transformation. A 90% confidence interval was constructed for the mean difference relative to the reference mean using the two one-sided t-test procedure. All statistical analyses were done using SAS® for Windows® Version 9.1 under Windows 2000.

Results

Pharmacokinetic Results:

PK Parameters for rhASB in Patients with MPS VI (Study ASB-XO-001)							
Mean (\pm SD)							
Dose [mg/kg/wk]	Wk*	C_{max} [ng/mL]	AUC_{0-t} [min*ng/mL]	AUC_{∞} [min*ng/mL]	CL [mL/min/kg]	V_z [mL/kg]	$t_{1/2}$ [min]
1.0	N	1111 \pm 479	167805 \pm 83701	184883 \pm 87531	8 \pm 8	207 \pm 417	12 \pm 8
	N+1	1138 \pm 458	187162 \pm 74937	209069 \pm 51550	5 \pm 1	54 \pm 18	8 \pm 3
	N+6	1138 \pm 674	180273 \pm 103921	217156 \pm 73425	5 \pm 1	57 \pm 16	8 \pm 3

* After 179 to 188 weeks of rhASB treatment, the 4 patients in the Study ASB-00-01 were transitioned from clinical process to the commercial process rhASB. Between Weeks 98 and 117 of treatment, the 10 patients in Study ASB-01-04 were transitioned from clinical process to commercial process rhASB.

(Values in the table above were taken from Table 1, page 4 of the Clinical Pharmacology Summary.)

Statistical Analysis:

Statistical Analysis of PK and PD Parameters for Test (Commercial) and Reference (Clinical) rhASB after 1.0 mg/kg/week IV		
Parameter	Ratio (%) ^{1,2}	
	Estimate	90% Confidence Interval
C_{max}	96.86	84.04 – 111.64
AUC_{0-t}	103.60	92.67 – 115.83
AUC_{∞}	109.32	91.76 – 130.26
Urinary GAGs	99.5	84.47 – 114.71

¹ For pharmacokinetic parameters, geometric mean ratio of commercial to clinical; based on natural log-transformed data.

² For urinary GAGs, mean difference relative to the reference mean; data on the original scale.

The mean values for C_{max} , AUC_{0-t} , and AUC_{∞} were similar between the commercial and clinical materials (see table above). The 90% confidence intervals for the geometric mean ratio for C_{max} and AUC_{0-t} , commercial-to-clinical, for which $N = 14$, were within the 80% to 125% equivalence window (see table above). The geometric mean ratio for AUC_{∞} , which could be estimated for both treatments for 10 of 14 patients, was 109% and the upper limit of the confidence interval was $> 125\%$ (see table above).

The two process products were similar with respect to urinary GAG levels (77.8 ± 34.8 and 77.5 ± 40.1 $\mu\text{g}/\text{mg}$ creatinine, clinical and commercial, respectively), with a mean ratio of essentially 100% and a 90% confidence interval of 84% to 115% (see table above).

The C_{max} , AUC_{0-t} , and urinary GAGs were similar for the clinical and commercial materials. There was a possible 9% increase in AUC_{∞} with the commercial material.

Conclusions

- (1) The commercial process material / _____ , and clinical process material _____ , rhASB had comparable pharmacokinetics based on C_{max} and AUC_{0-t} .
- (2) The commercial process material _____ , and clinical process material _____ , rhASB had similar pharmacodynamics based on urinary GAG levels.

Study ASB-53-APK

A Pharmacokinetic Study of Two Production Lots Manufactured Via the Same Process with Different _____ of Recombinant Human Arylsulfatase B [N-acetylgalactosamine-4-sulfatase] in Dogs Following Intravenous Administration

Methods

The purpose of this study was to compare the pharmacokinetics of two lots of rhASB material, one _____, the other _____. The materials were administered to male beagle dogs as single 4-hour intravenous infusions in a crossover design. The study was conducted in compliance with Good Laboratory Practice Regulations.

rhASB was administered by a 4-hour intravenous infusion to 10 adult male purebred beagle dogs at a dose of 2.0 mg/kg. Dogs were randomized to one of two sequences: test then reference or reference then test. Lot No. P60406 (_____) was the test lot and Lot No. AV60307 (_____) was the reference lot, for the purposes of this study. Treatments were separated by a 2-day washout period. Blood samples for measurement of rhASB plasma concentrations were collected before and at 2, 4 (end of infusion), 4.033, 4.083, 4.167, 4.25, 4.33, 4.5, 4.75, 5, 6, and 8 hours after the beginning of the infusion. Plasma concentrations of rhASB were measured at BioMarin (Novato, CA) using a qualified ELISA method. The lower limit of quantitation (LOQ) was _____ µg/mL. Only those plasma rhASB concentrations that were equal to or greater than the LOQ were used in the pharmacokinetic analyses. Concentrations less than LOQ prior to C_{max} were set equal to 0 and those after C_{max} were set to missing. Pharmacokinetic parameters for rhASB were calculated using noncompartmental methods.

The pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_∞ for the test and reference lots of rhASB were compared using an analysis of variance statistical model with sequence, animal within sequence, treatment, and period as the classification variables, using the natural logarithms of the data. Confidence intervals (90%) were constructed for the ratios (test-to-reference) of the three parameters using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale.

Results

Pharmacokinetic Parameters for Lots P60406 and AV60307 of rhASB after Administration of 2.0 mg/kg to Male Beagle Dogs (n=10)		
Parameter ¹	Lot P60406 ²	Lot AV60307 ³
C _{max} [ng/mL]	368 ± 71.8	439 ± 104
T _{max} [h]	4.04	4.03
AUC _{0-t} [h*ng/mL]	1,016 ± 183	1,251 ± 261
AUC _∞ [h*ng/mL]	1,019 ± 184	1,260 ± 264
t _{1/2} [hr]	0.049 ± 0.014	0.139 ± 0.025

1. Mean ± SD except for T_{max} for which the median is reported.

2. Lot P60406 was harvested from Days 60-100.

3. Lot AV60307 was harvested from Days 1-30.

(The values in the above table were taken from page 23 of the Nonclinical Pharmacokinetics Written Summary.)

The pharmacokinetics of two production lots manufactured via the same process with different — were similar in male beagle dogs after single 4-hour intravenous infusions. Mean plasma concentrations were somewhat lower for the test lot as were mean values for C_{max}, AUC_{0-t}, and AUC_∞ (see table above).

Statistical Analysis of Pharmacokinetic Parameters for Lot P60406 (Test; —) and Lot AV60307 (Reference; —) of rhASB after Administration of 2.0 mg/kg to Male Beagle Dogs (n=10)		
Parameter	Ratio (%) ¹	
	Estimate	90% Confidence Interval
C _{max}	81.28	77.87 – 84.83
AUC _{0-t}	81.60	78.21 – 85.14
AUC _∞	84.39	79.81 – 89.24

1. Geometric mean ratio of the test to the reference. Based on natural log-transformed data.
(The values in the above table were taken from page 23 of the Nonclinical Pharmacokinetics Written Summary.)

Although the geometric means ratios (test-to-reference) for all three parameters were within the 80% - 125% window, the lower limits of the respective 90% confidence intervals were slightly below 80%.

Conclusions

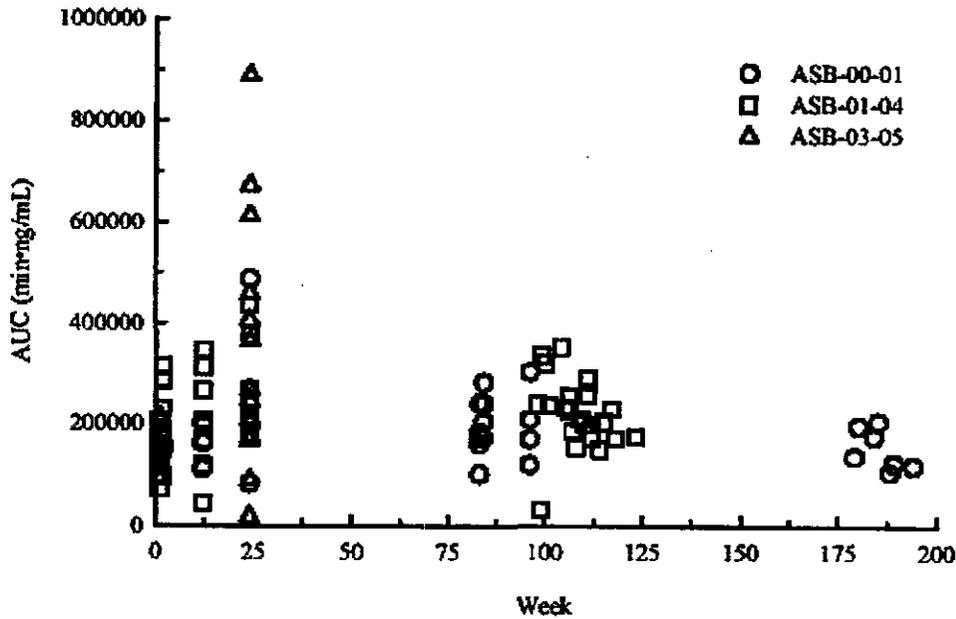
1. PK comparability of two production lots manufactured via the same process with different — was demonstrated in male beagle dogs after single 4-hour IV infusions based on geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_∞; however, the lower limits of the 90% confidence intervals were slightly below the 80 to 125% window. (90% confidence intervals for C_{max}, AUC_{0-t}, and AUC_∞ were 77.9 to 84.8%, 78.2 to 85.1%, and 79.8 to 89.2%, respectively.)

Comparison and Analyses of Results Across Studies

Effect of Duration of Treatment on rhASB Pharmacokinetics

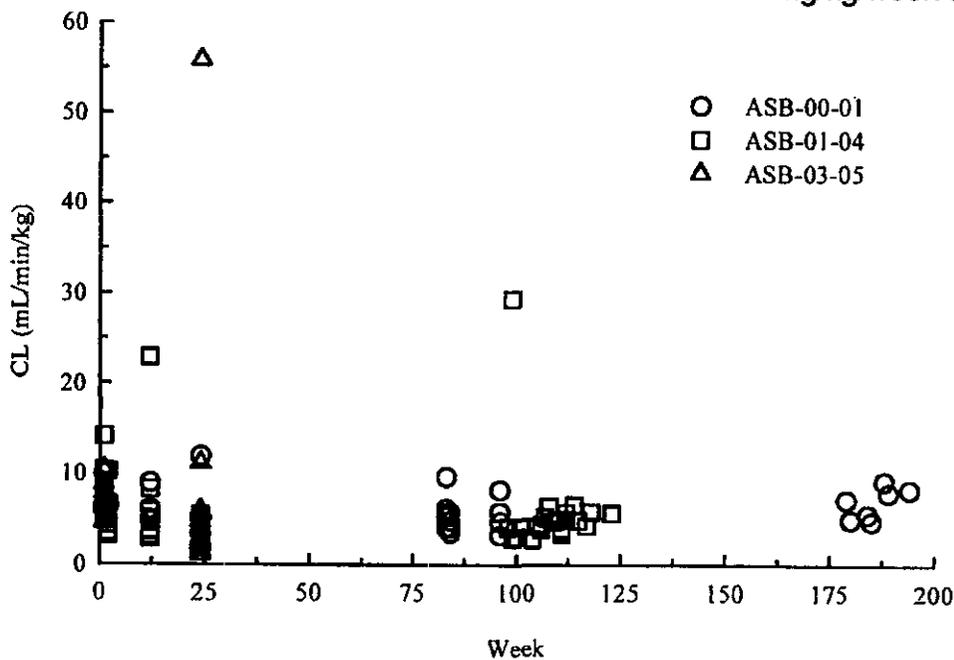
The individual patient values for AUC_{∞} , CL, V_z , and $t_{1/2}$ across studies after administration of 1.0 mg/kg/week for one to 194 weeks are illustrated in the figure below.

Individual Patient AUC_{∞} vs. Weeks on Treatment with 1.0 mg/kg/week of rhASB



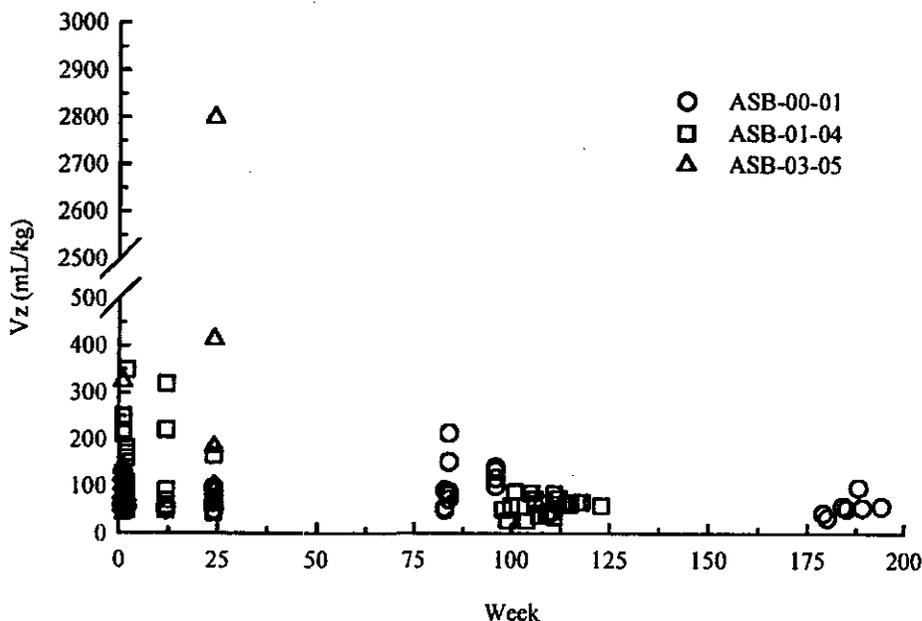
(The figure above is taken from page 12 of the Clinical Pharmacology Summary.)

Individual Patient CL vs. Weeks on Treatment with 1.0 mg/kg/week of rhASB



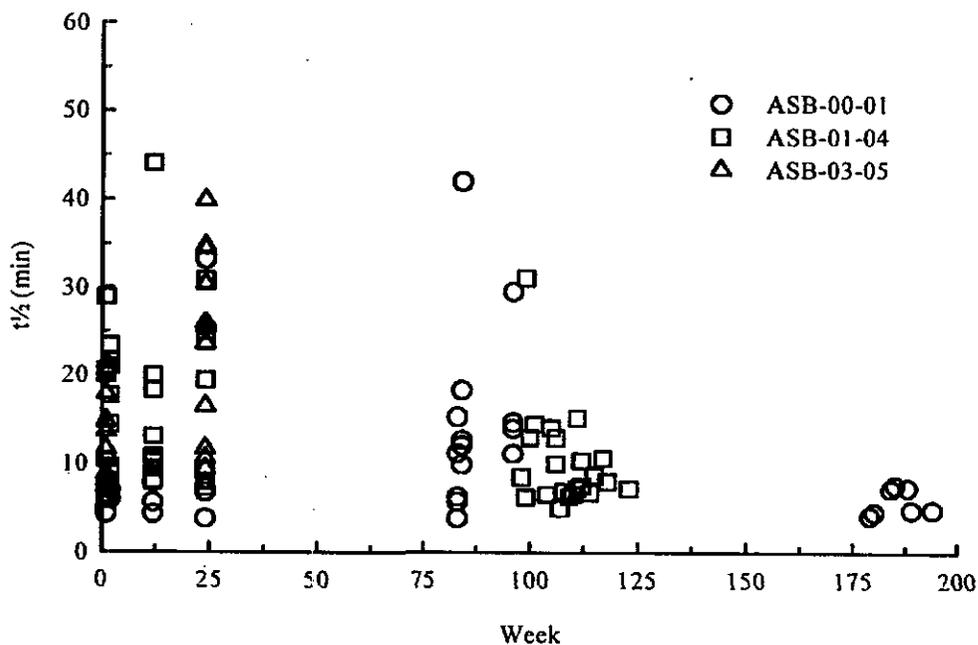
(The figure above is taken from page 13 of the Clinical Pharmacology Summary.)

Individual Patient Vz vs. Weeks on Treatment with 1.0 mg/kg/week of rhASB



(The figure above is taken from page 13 of the Clinical Pharmacology Summary.)

Individual Patient $t_{1/2}$ vs. Weeks on Treatment with 1.0 mg/kg/week of rhASB



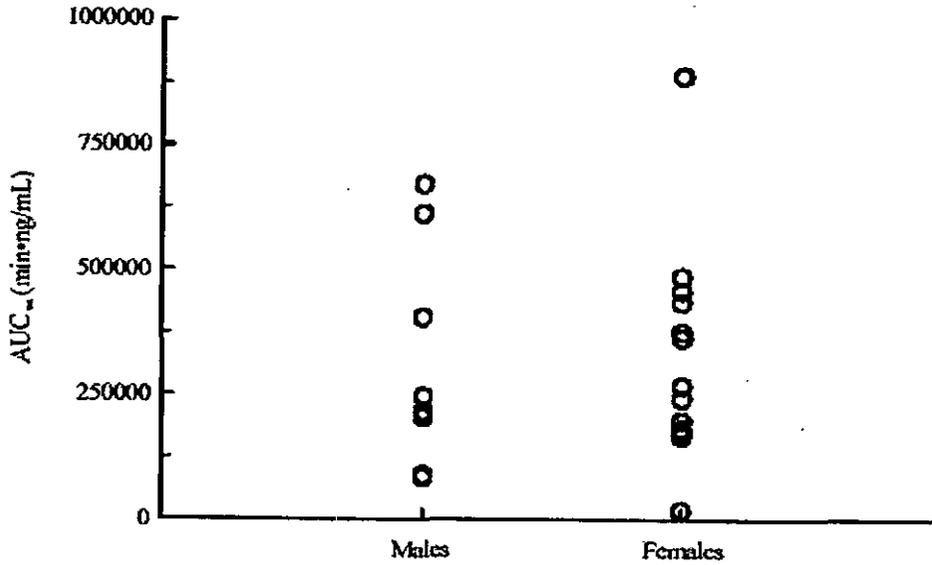
(The figure above is taken from page 14 of the Clinical Pharmacology Summary.)

Though the number of patients is small, no trends of AUC_{∞} , CL, Vz, or $t_{1/2}$ values with duration of treatment with rhASB 1.0 mg/kg from 1 to 194 weeks are apparent.

Effect of Gender on Pharmacokinetics

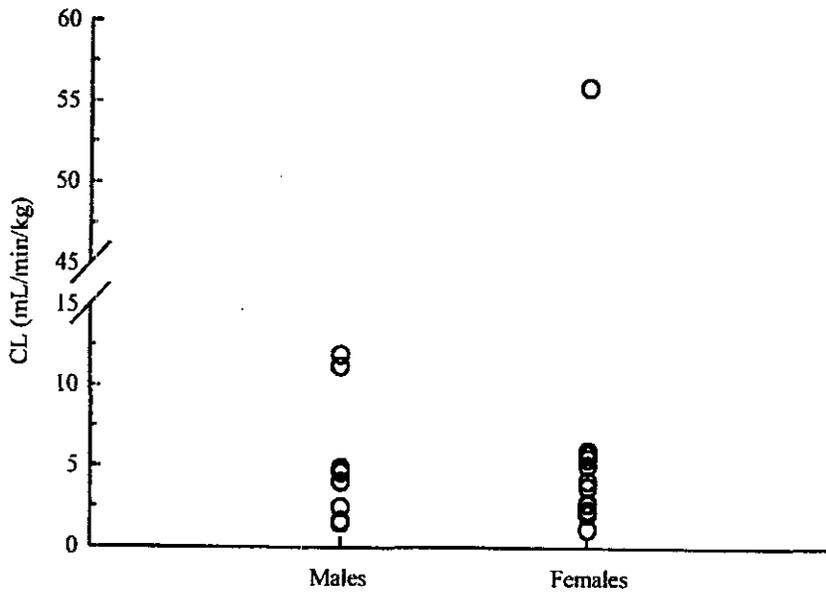
The possible effect of gender on the pharmacokinetics of rhASB was examined by graphical comparison of the individual patient values for AUC_∞, CL, Vz, and t_{1/2} at Week 24, the end of double-blind treatment in the three studies. Values for these four parameters were available for a total of 23 patients, 9 males and 14 females, across the three studies.

Individual Patient AUC_∞ by Gender after 1.0 mg/kg/week of rhASB for 24 Weeks



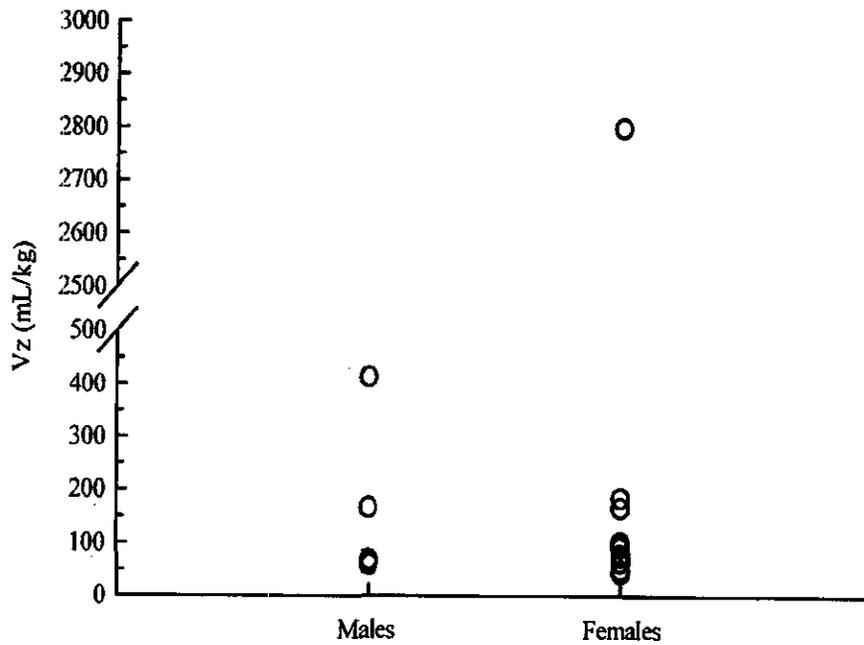
(The figure above is taken from page 15 of the Clinical Pharmacology Summary.)

Individual Patient CL by Gender after 1.0 mg/kg/week of rhASB for 24 Weeks



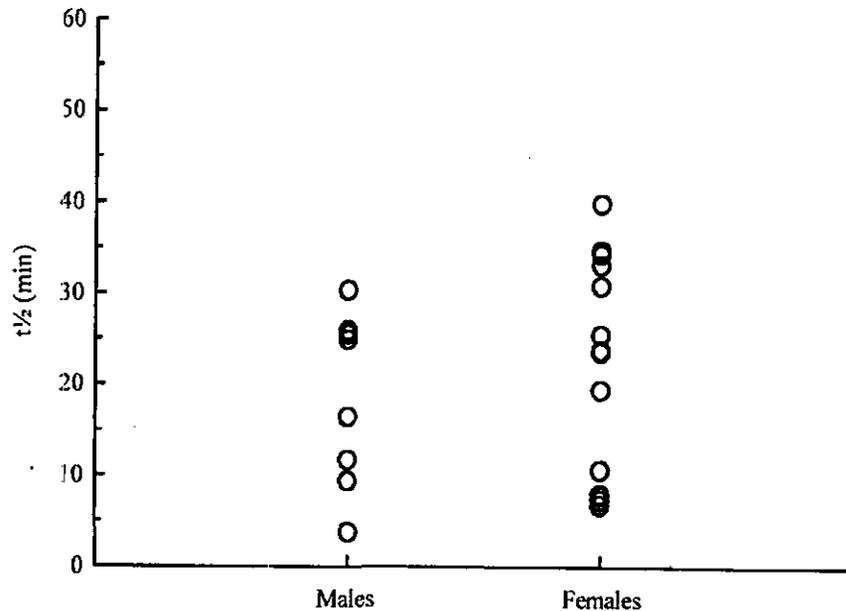
(The figure above is taken from page 15 of the Clinical Pharmacology Summary.)

Individual Patient Vz by Gender after 1.0 mg/kg/week of rhASB for 24 Weeks



(The figure above is taken from page 16 of the Clinical Pharmacology Summary.)

Individual Patient t_{1/2} by Gender after 1.0 mg/kg/week of rhASB for 24 Weeks



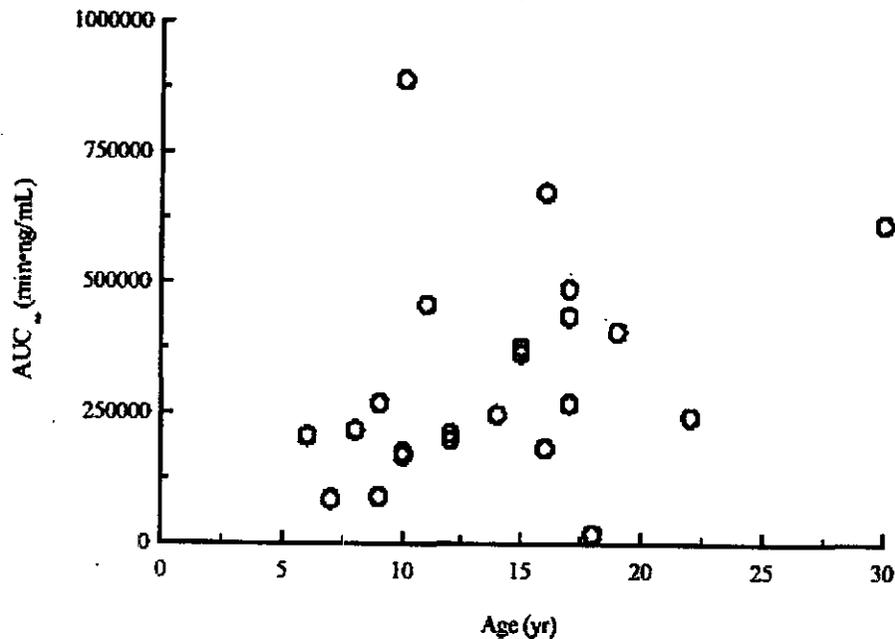
(The figure above is taken from page 16 of the Clinical Pharmacology Summary.)

Though the number of patients is small, examination of the figures indicates no apparent differences between males and females in the pharmacokinetics of rhASB after 24 weeks of treatment.

Effect of Age on Pharmacokinetics

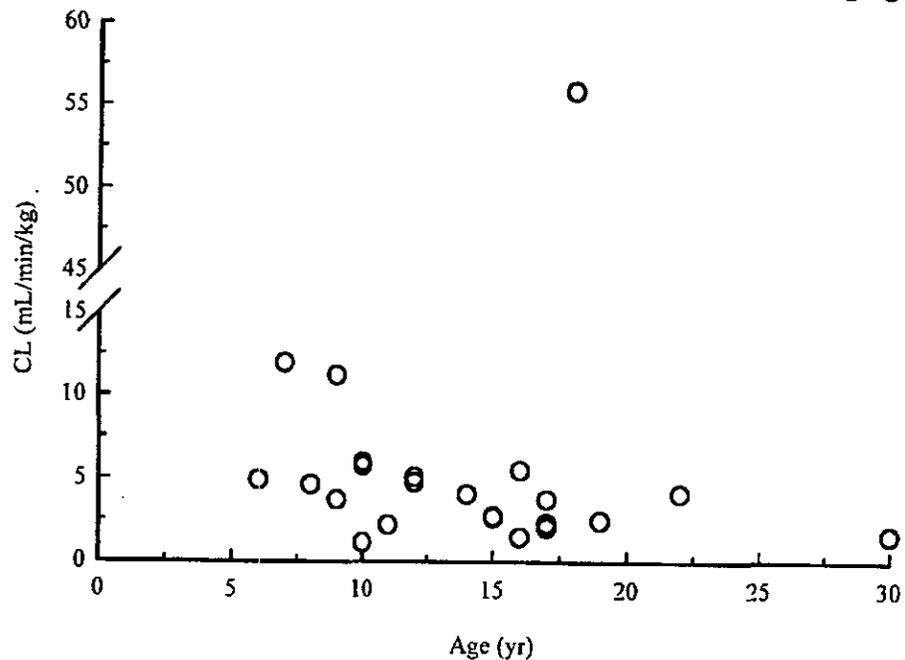
The possible effect of age on the pharmacokinetics of rhASB was examined by graphical comparison of the individual patient values for AUC_∞, CL, Vz, and t_{1/2} at Week 24, the end of double-blind treatment in the three studies. Values for these four parameters were available for a total of 23 patients across the three studies.

Relationship of Individual Patient AUC_∞ and Age after 24 Weeks of rhASB 1.0 mg/kg/week



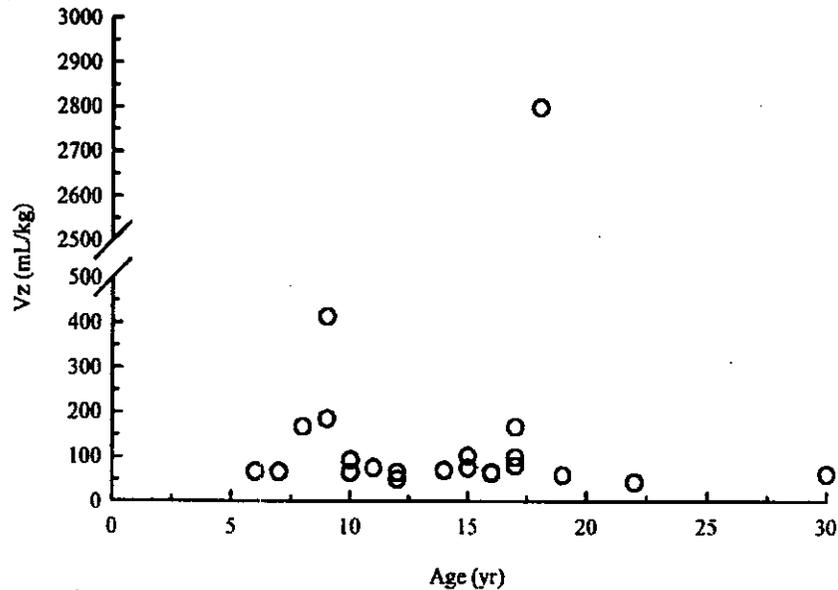
(The figure above is taken from page 17 of the Clinical Pharmacology Summary.)

Relationship of Individual Patient CL and Age after 24 Weeks of rhASB 1.0 mg/kg/week



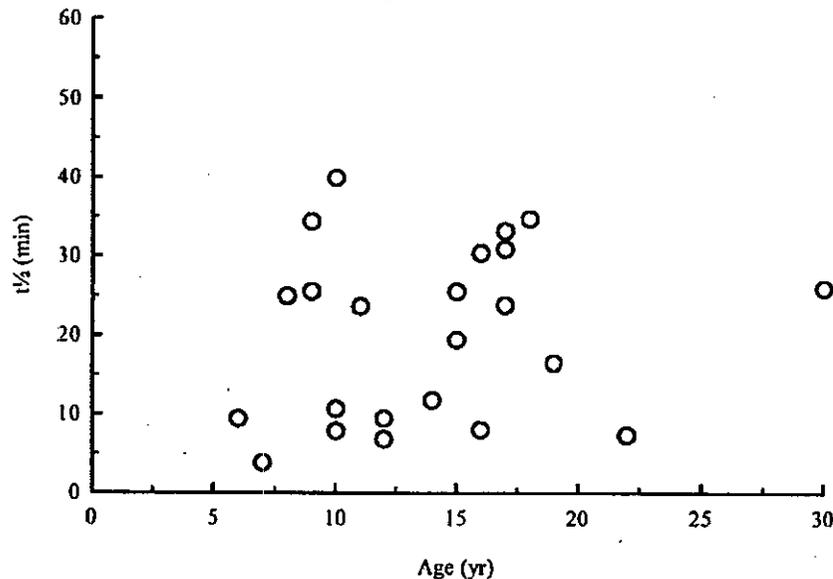
(The figure above is taken from page 18 of the Clinical Pharmacology Summary.)

Relationship of Individual Patient V_z and Age after 24 Weeks of rhASB 1.0 mg/kg/week



(The figure above is taken from page 18 of the Clinical Pharmacology Summary.)

Relationship of Individual Patient $t_{1/2}$ and Age after 24 Weeks of rhASB 1.0 mg/kg/week



(The figure above is taken from page 19 of the Clinical Pharmacology Summary.)

Though the number of patients is small, examination of the figures reveals no apparent trends in any of the pharmacokinetic parameters for rhASB as a function of age.

Conclusions

1. Though the number of patients was small, there were no apparent trends found in rhASB AUC_{∞} , CL, V_z , or $t_{1/2}$ values with duration of treatment with rhASB 1.0 mg/kg from 1 to 194 weeks.
2. Though the number of patients was small, there were no apparent trends found in rhASB AUC_{∞} , CL, V_z , or $t_{1/2}$ as a function of age or gender after 24 weeks of treatment.

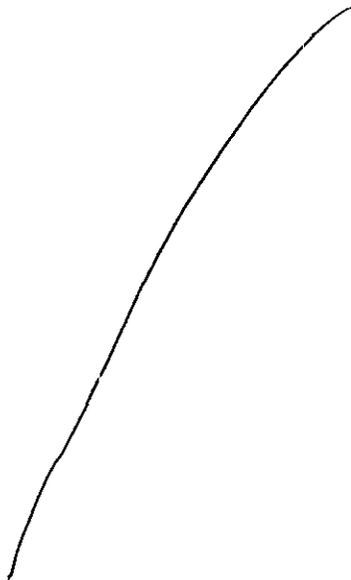
confidence intervals were slightly below the 80 to 125% window. (90% confidence intervals for C_{max} , AUC_{0-t} , and AUC_{∞} were 77.9 to 84.8%, 78.2 to 85.1%, and 79.8 to 89.2%, respectively.)

5. Demographics: Though the number of patients was small, there were no apparent trends found in rhASB AUC_{∞} , CL, V_z , or $t_{1/2}$ as a function of age or gender after 24 weeks of treatment.
6. Effect of Duration of Treatment: Though the number of patients was small, there were no apparent trends found in rhASB AUC_{∞} , CL, V_z , or $t_{1/2}$ values with duration of treatment with rhASB 1.0 mg/kg from 1 to 194 weeks.

**APPEARS THIS WAY
ON ORIGINAL**

RECOMMENDATIONS

The Label Revisions below are proposed.

Pharmacokinetics

3

The pharmacokinetic parameters of galsulfase were evaluated in 13 Phase 3 patients with MPS VI who received 1.0 mg/kg of NAGLAZYME as a 4-hour infusion weekly for 24 weeks. The pharmacokinetic parameters at Week 1 and Week 24 are shown in Table 1.

Table 1. Pharmacokinetic Parameters (Median, Range)

Pharmacokinetic Parameter	Week 1	Week 24
C _{max} (mcg/mL)	0.8 (0.4 to 1.3)	1.5 (0.2 to 5.5)
AUC _{0-t} (h-mcg/mL) ¹	2.3 (1.0 to 3.5)	4.3 (0.3 to 14.2)
V _z (mL/kg)	103 (56 to 323)	69 (59 to 2,799)
CL (mL/kg/min)	7.2 (4.7 to 10.5)	3.7 (1.1 to 55.9)
Half-life (min)	9 (6 to 21)	26 (8 to 40)

¹Area under the plasma galsulfase concentration-time curve from start of infusion to 60 minutes post infusion.

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