SWEDISH ORPHAN BIOVITRUM

A prospective, randomized, double-blind crossover study comparing rhBSSL (recombinant human Bile Salt Stimulated Lipase) added to infant formula versus placebo during one week of treatment in preterm infants born before 32 weeks of gestational age: preliminary results

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SUMMARY

Background: The rationale for enzyme replacement therapy with rhBSSL is to restore the natural lipase activity that is absent when mother´s milk is replaced with formula or human pasteurized milk.

Objectives & Material: To compare the coefficient of fat absorption, growth, safety and feeding tolerance in preterm infants treated with 0.15 g/L rhBSSL or placebo added to the infant formula. Thirty-three (33) infants with a mean birth weight of 1493 g and a gestational age of 32.4 weeks were randomized at a mean postnatal age of 3.3 weeks to receive one-week treatment with rhBSSL and placebo. 32 infants completed the study.

Key efficacy results: A mean improvement in body weight of 3.7 g/kg/day was observed during treatment with rhBSSL (mean 18.1, SD 4.0) as compared to placebo (mean 14.3, SD 6.5) (p=0.001). Analysis of additional data, including the coefficient of fat absorption, is ongoing.

Safety results: There were 18 TEAEs (treatment emergent adverse events) reported in 39% of the infants during rhBSSL treatment and 35 TEAEs reported in 52% of infants when receiving placebo. The most commonly reported AE in both groups was diaper dermatitis. One serious adverse event occurred during the study. The patient experienced meningitis during the placebo period and subsequently died. The investigator considered the SAE as not related to study drug.

Conclusion: In this first clinical study of rhBSSL added to infant formula in preterm infants there was a significant improvement in growth compared to placebo after 1 week of treatment. The safety and tolerability profile of rhBSSL added to formula was similar compared to placebo.

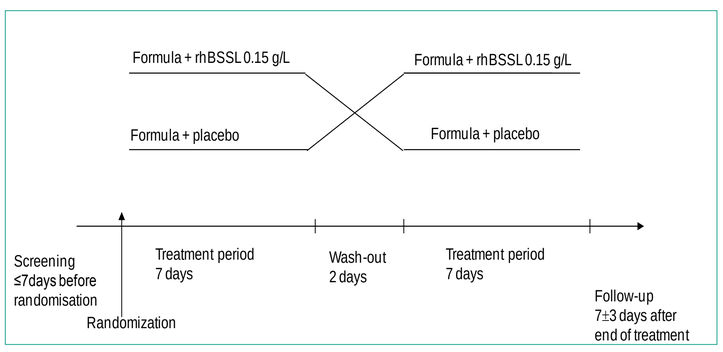
INTRODUCTION

Bile-salt-stimulated lipase (BSSL) is a naturally occurring digestive enzyme and a key for efficient fat digestion in the newborn. BSSL expression in neonatal pancreas is low compared to that of adults. This is compensated for by expression of BSSL in the lactating mammary gland and secretion of the enzyme with the milk. However, BSSL is not present in any infant formula, and is also destroyed when human milk is pasteurized.

Recombinant BSSL (rhBSSL) is being developed for enzyme replacement therapy to improve growth in preterm infants receiving pasteurized mother's milk and/or formula. The objectives of the present study were to compare the coefficient of fat absorption, growth, safety and feeding tolerance in preterm infants treated with 0.15 g/L rhBSSL or placebo.

MATERIALS AND METHODS

The study was performed according to a 2-way cross-over design (see figure).



Placebo or rhBSSL was added to the formula (specially designed by Ordesa; energy 81 kcal/100 mL; proteins 2.3 g/100 mL; fat 4.1 g/100 mL; carbohydrates 8.7 g/100 mL) according to the randomization schedule. Infants received 150 to 180 mL formula/kg body weight per day. The feeding amount on a mL/kg basis was kept constant for each individual infant throughout the study.

33 preterm infants were included in the study. Details are given in Table 1.

Table 1. Demographics at Baseline

	GA at birth (weeks)	Age (weeks)	Extrapolated GA at randomization (weeks)	Weight at randomization (g)
Mean (SD)	29.2 (1.3)	3.3 (1.2)	32.4 (0.5)	1493.5 (195.0)
Median (range)	29.1 (25.4 – 31.4)	3.1 (1.3 – 7.3)	32.6 (31.4 – 33.0)	1450.0 (1190 – 1805)

RESULTS

BODY WEIGHT:

The weights of the infants at the start and end of treatment with rhBSSL and placebo, respectively, are presented in Table 2 for infants with complete weight data.

Table 2. Growth from Day 1 to Day 7 of EachTreatment Period

	rhBSSL (N=32)	Placebo (N=32)
Mean weight (g) on Day 1	**1599.2** (236.5)	**1615.4** (245.3)
Mean weight (g) on Day 7	**1772.4** (256.7)	**1758.9** (279.1)
Growth (g)	**173.3** (41.2)	**145.5** (66.3)

The growth velocity calculated over the 7-day treatment period is presented in Table 3.

Table 3. Growth velocity (g/kg/day)

	rhBSSL (N=33)	Placebo (N=33)	Difference	p-value
LS Mean	18.1	14.3	3.74	0.001
95% CI	[16.5 ; 19.6]	[12.8 ; 15.8]	[1.58 ; 5.90]	
Median	18.4	15.5		
Minimum	9.2	-4.5		
Maximum	25.5	23.3		

SAFETY:

The number of adverse events is summarized in Table 4 and the most frequently occurring events in Table 5.

Table 4. Overall Summary of Treatment-Emergent Adverse Events

	rhBSSL (N=33)		Placebo (N=33)		Total (N=33)	
	No (%) of patients	**No of events**	**No (%) of patients**	**No of events**	**No (%) of patients**	**No of events**
Patients with any TEAE	13 (39.4)	18	17 (51.5)	35	23 (69.7)	53
Patients with any serious TEAE	0	0	1 (3.0)	1	1 (3.0)	1
Patients with any severe TEAE	0	0	2 (6.1)	12	2 (6.1)	12
Patients who died	0	0	1 (3.0)	1	1 (3.0)	1

Table 5. Most Frequently Reported Adverse Events (Number [%] of Patients)

Preferred term	rhBSSL (N=33)	Placebo (N=33)	Total (N=33)
Diaper dermatitis	4 (12.1)	5 (15.2)	9 (27.3)
Cardiac murmur	3 (9.1)	2 (6.1)	5 (15.2)
Anemia	1 (3.0)	3 (9.1)	4 (12.1)
Urinary tract infection	1 (3.0)	2 (6.1)	3 (9.1)

There was one Serious Adverse Event in the study. The patient developed meningitis on the third day of the second treatment period (placebo) and died four days later. This event was judged by investigator as not related to study drug.

There were no differences in vital signs or other safety variables during treatment with rhBSSL or placebo.

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CONCLUSIONS

In this first clinical study of rhBSSL added to infant formula in preterm infants there was a significant improvement in growth compared to placebo after 1 week of treatment.

The safety and tolerability profile of rhBSSL was similar compared to placebo.

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