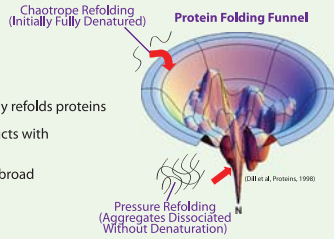


PreEMT™ Technology: An “Elegant Method”



- Purely thermodynamics
- High hydrostatic pressure disaggregates and properly refolds proteins
- Enables proprietary products with enhanced safety
- Scalable technology with broad applications

BaroFeron™

- Recombinant human interferon beta-1b for subcutaneous injection
- Manufactured from E. coli using PreEMT Technology
- Essentially free of protein aggregates in final formulation
- Formulated without human serum albumin

Methods - Bioavailability

- Single dose pharmacokinetics were assessed in Spague-Dawley Rats (naïve), cynomolgus monkeys (non-naïve), and rhesus monkeys (non-naïve)
- Serum levels of rhIFN beta-1b were measured with an ELISA method
- Neopterin levels were measured with a commercial kit qualified for use on monkey samples
- Animal studies were conducted by Charles Rivers Laboratories (in-life) with IUCAC approval
- Samples were analyzed by Prevalere Life Sciences

Sprague Dawley Rats Treatment Groups (n = 4 males/group)

Treatment					
Group #	Test Article	Dose (mg/kg)	Conc. (mg/mL)	Dose Vol. (mL/kg)	Route
1 (▲)	BaroFeron	0.2	0.10	2.0	Intravenous (IV)
2 (■)	BaroFeron	0.2	0.10	2.0	Intramuscular (IM)
3 (●)	BaroFeron	0.2	0.10	2.0	Subcutaneous (SC)
4 (○)	Commercial rhIFN beta-1b	0.2	0.10	2.0	Subcutaneous (SC)

Plasma samples obtained pre-dose, 15 and 30 minutes, and 1, 2, 6, 12 and 24 hr post-dose for all Groups, and 36 hr post-dose for Groups 3 and 4.

Pharmacokinetic Parameters for rhIFN beta-1b in Sprague Dawley Rats

Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-n} (hr*ng/mL)	AUC _{0-∞} (hr*ng/mL)	t _{1/2} (hr)
1 (▲) (BaroFeron, IV)	4617 ± 675	0.31 ± 0.13	9461 ± 2238	9574 ± 2238	3.42 ± 1.74
2 (■) (BaroFeron, IM)	31.6 ± 5.37	0.99 ± 0.69	295.9 ± 159.8	444.1 ± 188.4	9.71 ± 3.76
3 (●) (BaroFeron, SC)	43.2 ± 11.3	0.99 ± 0.02	134.6 ± 29.01	148.4 ± 31.61	1.70 ± 0.365
4 (○) (Commercial rhIFN beta-1b SC)	10.5 ± 2.19	0.75 ± 0.26	14.26 ± 1.19	41.53 ± 27.07	2.84 ± 2.73

BaroFeron™, a More Bioavailable and Less Immunogenic IFN Beta Product

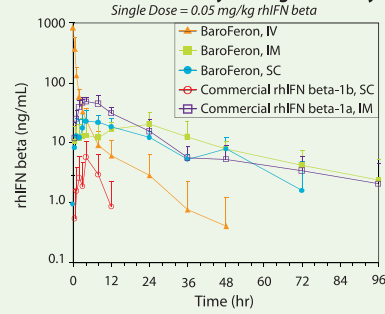
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¹BaroFold Inc., Boulder, CO ²Prevalere Life Sciences, Whitesboro, NY 13492

Non-naïve cynomolgus monkey treatment groups (n = 4 /group)

Group #	Test Article	Treatment			Route
		Dose (mg/kg)	Conc. (mg/mL)	Dose Vol. (mL/kg)	
1	BaroFeron	0.05	0.25	0.20	Intravenous (IV)
2	BaroFeron	0.05	0.25	0.20	Intramuscular (IM)
3	BaroFeron	0.05	0.25	0.20	Subcutaneous (SC)
4	Commercial rhIFN beta-1b	0.05	0.25	0.20	Subcutaneous (SC)
5	Commercial rhIFN beta-1a	0.05	0.06	0.83	Intramuscular (IM)

Plasma samples were taken pre-dose, 5 (IV only) and 30 min, 1, 2, 3, 4, 8, 12, 24, 36, 48, 72 and 96hr post-dose.

Pharmacokinetics – Cynomolgus Monkeys

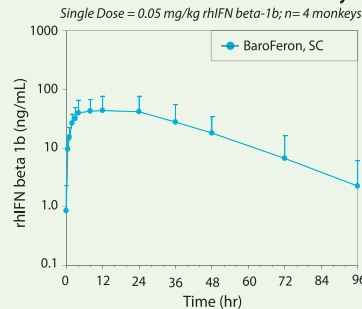


Pharmacokinetic Parameters for rhIFN beta in Cynomolgus Monkeys*

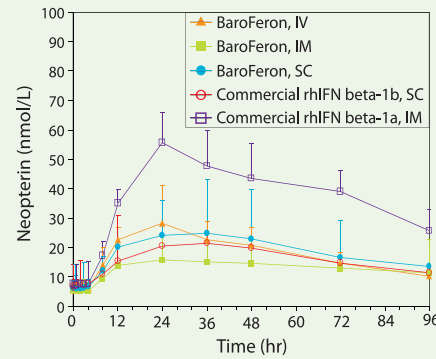
Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-n} (hr*ng/mL)	AUC _{0-∞} (hr*ng/mL)	t _{1/2} (hr)
1 (BaroFeron, IV)	846.6 ± 145.3	0.09 ± 0.00	768.2 ± 254.3	819.4 ± 276.8	8.13
2 (BaroFeron, IM)	22.74 ± 13.22	17.77 ± 11.18	913.8 ± 524.5	1092 ± 557.0	34.56 ± 12.62
3 (BaroFeron, SC)	24.22 ± 10.59	5.94 ± 2.29	605.3 ± 258.8	860.7 ± 349.5	25.55 ± 12.50
4 (Commercial rhIFN beta-1b SC)	6.16 ± 4.22	4.46 ± 2.42	43.99 ± 8.23	62.05 ± 9.91	5.02 ± 4.78
5 (Commercial rhIFN beta-1a IM)	49.88 ± 12.77	4.98 ± 1.90	1118 ± 446.7	1215.6 ± 504.7	18.79 ± 9.98

* n = 4 monkeys per group for BaroFeron, IV, IM and SC and Commercial rhIFN beta-1a, IM; n = 2 monkeys for Commercial rhIFN beta-1b, SC as a result of 2 monkeys with plasma levels below the lower limit of quantitation.

Pharmacokinetics – Rhesus Monkeys



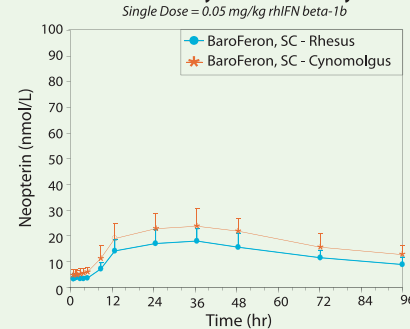
Pharmacodynamics – Cynomolgus Monkeys



Plasma Neopterin Exposure Parameters in Cynomolgus Monkeys after rhIFN beta administration

Group	C _{max} (nmol/L)	T _{max} (hr)	AUC _{0-n} (hr*nmol/L)
1 (BaroFeron, IV)	24.0 ± 5.02	26.6 ± 14.9	1201 ± 231
2 (BaroFeron, IM)	11.7 ± 3.76	51.3 ± 40.1	727 ± 291
3 (BaroFeron, SC)	19.3 ± 5.89	35.7 ± 9.85	1210 ± 419
4 (Commercial rhIFN beta-1b SC)	15.1 ± 2.97	35.7 ± 9.89	879 ± 200
5 (Commercial rhIFN beta-1a IM)	50.4 ± 11.0	26.3 ± 6.45	2924 ± 650

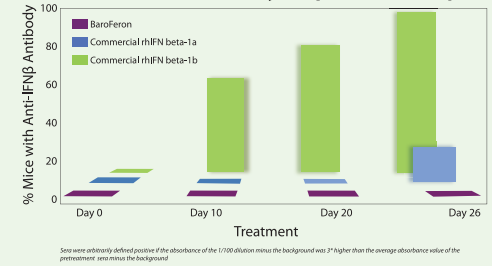
Pharmacodynamics – Monkeys



Methods - Immunogenicity

- 3 Groups
 - BaroFeron in clinical formulation
 - Commercial rhIFN beta-1b
 - Commercial rhIFN beta-1a
- 5 mice per group, 5 mcg rhIFN beta-1b per dose (QD x 5 weekly x 3), Analysis done by anti-rhIFN beta ELISA
- Study done at Utrecht University using same strain of mice from previous studies (Hermeling et al.)

% Positive Antibody Responses in IFN-β



See were arbitrarily defined positive if the absorbance of the 1:100 dilution minus the background was 2* higher than the average absorbance value of the pre-treatment sera minus the background.

Summary

- BaroFeron was well tolerated (i.e. no clinical signs noted) following single IV, IM, and SC administration
- Expected pharmacodynamic responses were achieved following the administration of BaroFeron in monkeys
- The SC bioavailability of rhIFN beta-1b in BaroFeron was 4 fold and 10 fold higher than Commercial rhIFN beta-1b in rats and cynomolgus monkeys, respectively
- The increase in bioavailability for BaroFeron could be related to differences in formulation (HSA) and/or reduced aggregation
- The IM bioavailability of rhIFN beta-1b in BaroFeron was comparable to the IM bioavailability of Commercial rhIFN beta-1a
- BaroFeron is less immunogenic than the current commercial products

Conclusions

- BaroFeron, a novel 'aggregate-free' preparation of rhIFN beta-1b, has greater bioavailability administered SC than commercial product.
- The greater SC bioavailability and longer elimination half-life of rhIFN beta-1b in BaroFeron as compared to commercial product may lead to:
 - Less frequent administration of BaroFeron
 - Potential for equal or greater efficacy at lower rhIFN beta-1b dose of BaroFeron
- The lack of aggregates in BaroFeron may result in reduced immunogenicity compared to the commercial product.