

Phase 2a Study to Evaluate the Safety and Tolerability and Anti-Viral Effect of 4 Doses of a Novel, Controlled-Release Interferon Alfa-2b (Locteron™) Given Every 2 Weeks for 12 Weeks in Treatment-Naive Patients with Chronic Hepatitis C (Genotype 1)

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INTRODUCTION

Controlled-release recombinant interferon alfa-2b (Locteron™) is a novel approach to delivery of interferon (IFN) given every 2 weeks offering an improved tolerability combined with a high level of hepatitis C virus (HCV) RNA reduction in this trial.

STUDY OBJECTIVE

A phase 2a, open-label randomized, dose-ranging study was conducted in treatment-naïve patients with genotype 1 chronic HCV infection to evaluate the safety, tolerability and anti-viral effect of Locteron™.

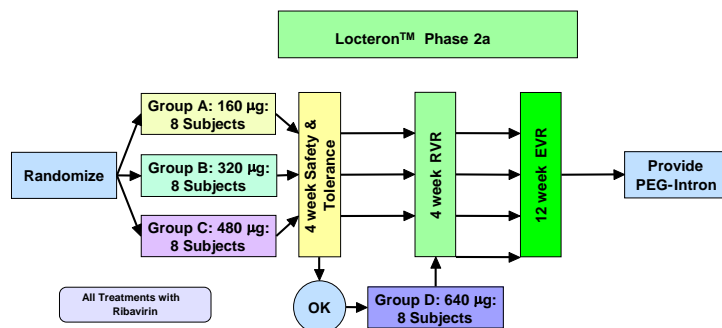
METHODS

Thirty-two patients were randomized to receive subcutaneous injections of Locteron™ 14 days apart over 12 weeks in 4 dose cohorts (8 per cohort) of 160, 320, 480 and 640 µg, with the 640 µg group starting after safety evaluation of the other cohorts. All subjects received weight-based ribavirin.

Analysis of IFN-α2b in human serum samples was performed by a modified ELISA from GE HealthCare, UK, using standards and quality controls prepared from IFN-α2b (BLX-883). LLOQ for IFN-α2b using the ELISA was 2.5 pg/mL (A. Kromminga, IPM, Hamburg, Germany). HCV RNA assay was performed using COBAS TaqMan with an LLOQ of 28 IU/mL.

Viral kinetics were modeled mathematically from a full PK-PD model according to the individual pharmacokinetic profile of Locteron™ for all patients. The compartmental model was based on a differential equation system including a time-varying efficiency factor ϵ according to the respective serum levels of Locteron™.

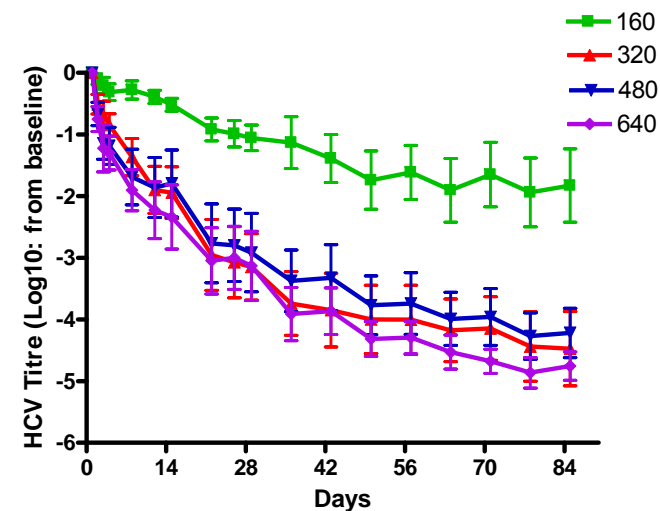
STUDY SCHEMA



BASELINE DEMOGRAPHICS

	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
Gender: Male (%)	3 (38%)	7 (88%)	6 (75%)	4 (50%)
Race: Caucasian (%)	8 (100%)	8 (100%)	8 (100%)	8 (100%)
Age (Yr): Mean (Median)	39.0 (34)	35.0 (35)	38.0 (38.5)	39.8 (39)
Weight (Kg): Mean (Median)	73.9 (76)	83.8 (83.5)	78.4 (78)	78.5 (76)
HCV RNA (log IU/mL): Mean (Median)	6.36 (6.29)	6.47 (6.41)	6.55 (6.63)	6.37 (6.34)
HCV RNA: HCV RNA > 800,000 IU/mL (%)	6 (75%)	5 (63%)	5 (63%)	6 (75%)
ALT (U/L): Mean (Median)	88 (66)	143 (115)	128 (109)	63 (65)

RESULTS: ANTI-VIRAL EFFECT



Mean HCV RNA (IU/mL)	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
Baseline	5,780,525	16,463,250	12,962,750	5,123,750
4 weeks	802,463	130,152	241,511	34,234
8 weeks	896,443	85,810	75,044	410
12 weeks	961,226	79,275	13,656	97

RESULTS: ANTI-VIRAL EFFECT

Initial Response	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
12 weeks mean HCV RNA decline (Log ₁₀)	1.8	4.5	4.2	4.7
RVR (%): HCV RNA undetectable at 4 weeks (<28IU/mL)	0 (0%)	2 (25%)	3 (37.5%)	2 (25%)
EVR (%): HCV RNA drop from baseline at least 2 logs	3 (37.5%)	7 (87.5%)	8 (100%)	7* (100%)

* Locteron™ 640 EVR: 7 out of 7 patients, one patient discontinued in week 9 with 3.1 log drop in HCV RNA

RESULTS: SAFETY AND TOLERABILITY

Flu-Like Adverse Event	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
Arthralgia	2 (25%)	3 (37.5%)	6 (75%)	4 (50%)
Chills (rigors)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)
Fever (pyrexia; T ≥ 38.0°C)	1 (12.5%)	1 (12.5%)	0 (0%)	4 (50%)
Headache	4 (50%)	2 (25%)	2 (25%)	5 (62.5%)
Myalgia	3 (37.5%)	4 (50%)	2 (25%)	4 (50%)

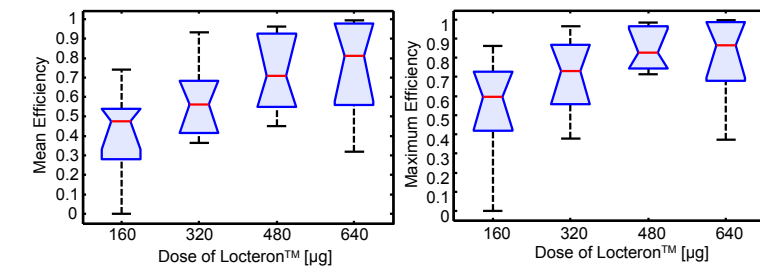
Clinical Adverse Event ¹	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
Alopecia	2 (25%)	0 (0%)	1 (12.5%)	1 (12.5%)
Depression	1 (12.5%)	0 (0%)	0 (0%)	3 (37.5%)
Dry cough	1 (12.5%)	0 (0%)	3 (37.5%)	2 (25%)
Dry mouth	2 (25%)	1 (12.5%)	2 (25%)	0 (0%)
Dry skin	4 (50%)	2 (25%)	4 (50%)	1 (12.5%)
Dyspepsia	2 (25%)	0 (0%)	1 (12.5%)	0 (0%)
Exacerbation: gastritis or duodenal ulcer	0 (0%)	0 (0%)	1 (12.5%)	2 (25%)
Irritability	1 (12.5%)	1 (12.5%)	1 (12.5%)	3 (37.5%)
Pruritus	2 (25%)	0 (0%)	1 (12.5%)	1 (12.5%)
Scleral icterus	1 (12.5%)	2 (25%)	0 (0%)	0 (0%)
Sleep disorder	1 (12.5%)	3 (37.5%)	4 (50%)	4 (50%)
Stomatitis	0 (0%)	0 (0%)	0 (0%)	2 (25%)
Taste alteration	3 (37.5)	2 (25%)	2 (25%)	5 (62.5%)
Thyroid, abnormal	0 (0%)	0 (0%)	0 (0%)	2 (25%)
Weakness	4 (50%)	4 (50%)	4 (50%)	7 (87.5%)

¹Table shows clinical adverse events occurring in more than 1 subject in any dose cohort.

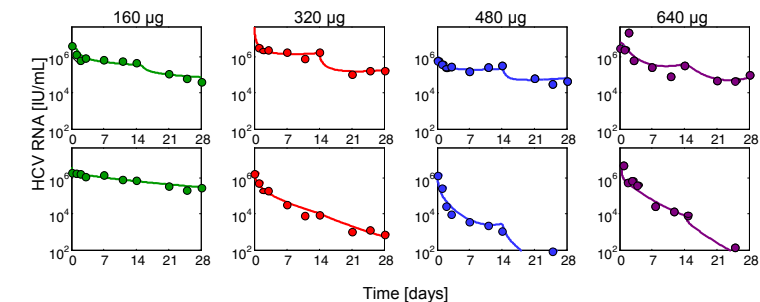
RESULTS: HCV MODELING

Viral kinetic modeling also demonstrated a clear dose-dependent effect on anti-viral mean and maximal efficiency (Jonckheere-Terpstra-Test: p=0.003 and p=0.006, respectively); further illustrated in the box plots below.

Efficiency estimated from viral kinetic model	Dose Group			
	160 µg (N = 8)	320 µg (N = 8)	480 µg (N = 8)	640 µg (N = 8)
Mean Efficiency (Mean ± SD)	41.7 ± 22.6 (%)	57.8 ± 19.2 (%)	72.2 ± 20.2 (%)	75.1 ± 26.4 (%)
Maximal Efficiency (Mean ± SD)	54.4 ± 27.3 (%)	70.6 ± 20.9 (%)	84.6 ± 11.2 (%)	80.4 ± 22.6 (%)



Furthermore, median half-life of free virus of 2.1 hours as well as the half-life of infected cells of 2.78 days are in concordance with previous viral kinetic results with interferon-based treatment combined with ribavirin. Individual viral kinetic data for 2 typical patients (out of 8) of each of the 4 dose groups are shown in the following figures. No or only a small rebound of HCV RNA could be observed at the end of the dosing periods.



CONCLUSIONS

In this study, Locteron™, a controlled-release formulation of unmodified IFN-α2b, administered every 2 weeks to treatment-naïve patients with chronic hepatitis C (genotype 1) demonstrated strong anti-viral activity combined with an improved safety and tolerability profile compared to currently marketed IFNs and those in development. Viral kinetic analysis demonstrated a dose-dependent anti-viral efficiency during the entire 12-week treatment period.