

Novel sustained release formulation of IFN-alfa-2b-XL, improves tolerability and demonstrates potent viral load reduction in a phase I/II HCV clinical trial

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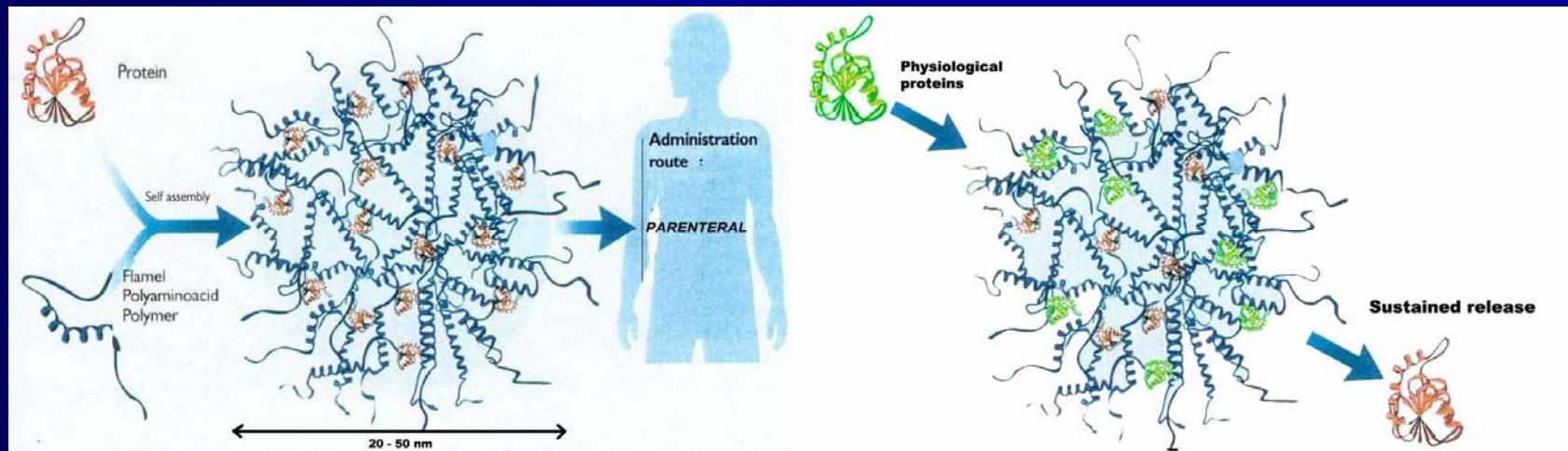
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Molecular Model of IFN alfa-2b-XL

In Vitro

In Vivo



Background (1)

- Treatment with IFN alfa is associated with dose dependent adverse events
- Systemic toxicity is due to the large variation and Cmax of plasma IFN levels
- Biological effect is also related to the dose and the pharmacokinetic profile

Background (2)

- In preclinical studies, IFN-XL **reduces** post-injection **peak concentration** (C_{max})
- Reducing C_{max} and sustaining therapeutic levels of IFN-XL, **may improve tolerability and efficacy** in HCV patients.

Objectives

- Evaluation of **safety and tolerability** of a single dose administration of **IFN-XL** compared to **Viraferon[®]** in HCV patients.
- Analysis of **pharmacokinetic** and **pharmacodynamic** properties of a single dose of IFN-XL.
- Analysis of **HCV clearance**

Inclusion criteria

- Adult chronic hepatitis C patients
- HCV RNA > 780 UI/mL
- All genotypes
- Naive or non responder (wash out 3 months)
- ALAT/ASAT < 2.5 ULN
- BMI >18 and < 32 Kg/m²
- No decompensation
- HIV and HBsAg negativity

Study design

Phase I/II, dose escalating, open label, controlled, randomized study

4 French centers

4 groups (12-14 volunteers/group):

Group 1: 3 MIU TIW interferon alfa-2b (**Viraferon**[®]) (200 µL/site)

Group 2: 9 MIU Interferon alfa-2b **XL** (150 µL/site)

Group 3: 18 MIU Interferon alfa-2b **XL** (300 µL/site)

Group 4: 27 MIU Interferon alfa-2b **XL** (450 µL/site)

No ribavirin was administered

Assessments

- **Safety**

Clinical and laboratory tolerability: body temperature, RBC, WBC, neutrophils, platelet counts

- **Pharmacokinetics**

IFN-alfa-2b serum concentrations:

0, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 hours (D2)

36, 48 hours (D3) post-dosing and 4, 5, 6 and 8 days

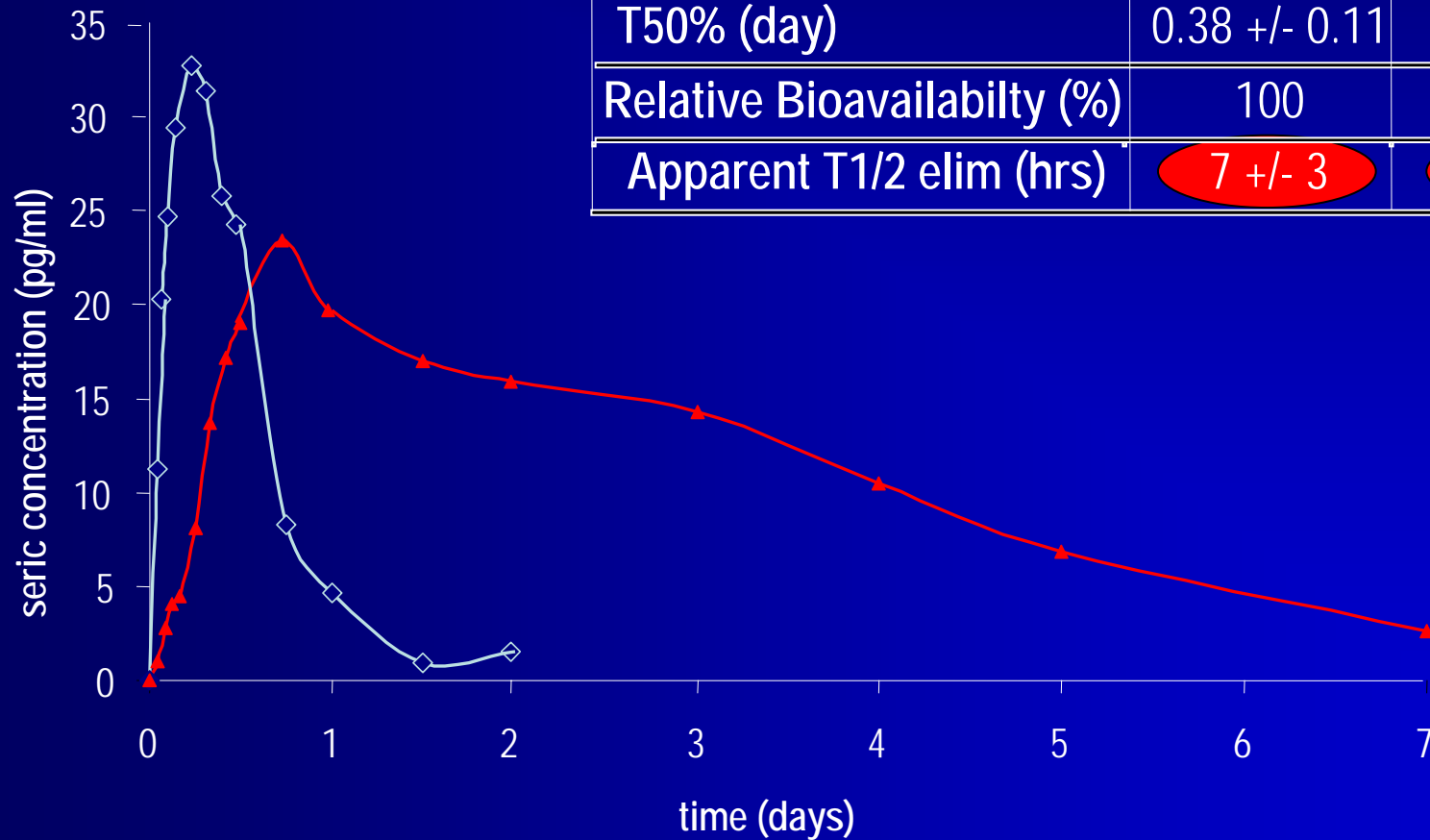
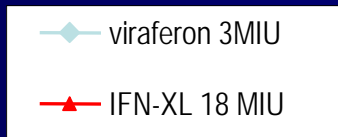
- **Pharmacodynamics**

Serum Neopterin, 2',5'-OAS, b2-microglobulin at screening, predose, 12, 24 (D2), 48 (D3) hours and 4, 5, 6 and 8 days

- **Viral load**

At screening, predose, 1, 3, 6, 12, 24 hours (D2), 36, 48 hours (D3) and 4, 5, 6 and 8 days post-dosing by bDNA

Serum Medusa[®] concentrations



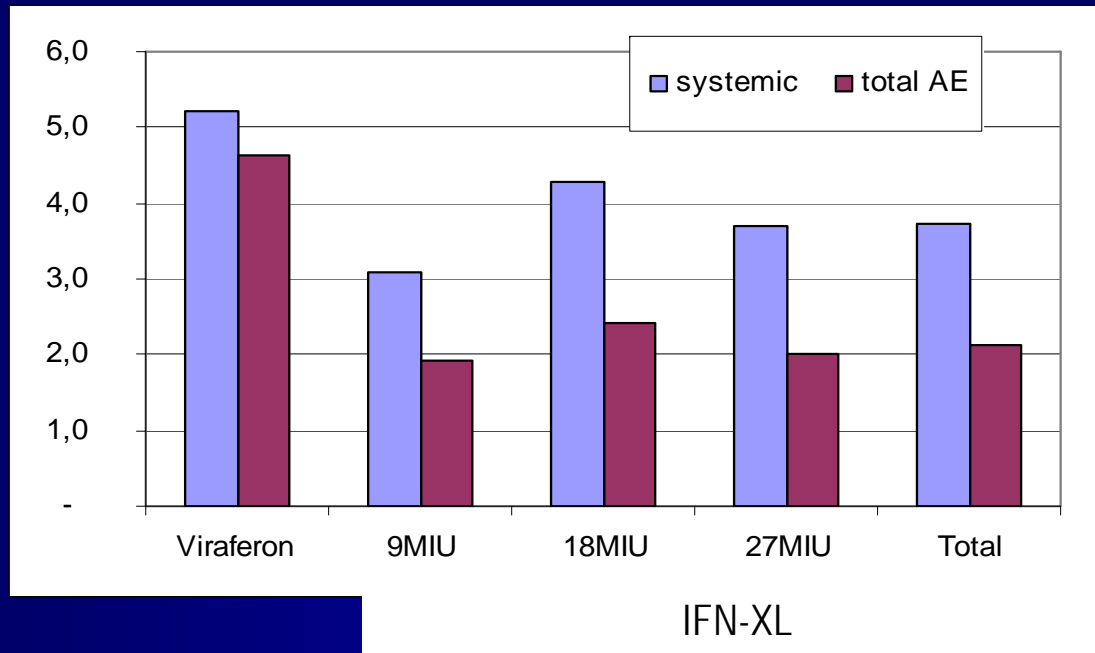
	Viraferon	IFN-XL
cmax	42 \pm 14	27 \pm 9
AUC last (pg/mL*day)	19 \pm 8	77 \pm 29
T50% (day)	0.38 \pm 0.11	2.41 \pm 0.66
Relative Bioavailabilty (%)	100	66
Apparent T1/2 elim (hrs)	7 \pm 3	57 \pm 34

IFN XL: Safety

	viraferon		IFN-xi							
	(3*3MIU)		9MIU		18MIU		27MIU		Total	
N	14		12		14		13		39	
Hematological										
NEUTROPENIA	5	36%	3	25%	3	21%	2	15%	8	21%
LYMPHOPENIA	4	29%	1	8%	3	21%	3	23%	7	18%
Influenza like Illness										
HEADACHE	11	79%	3	25%	12	86%	6	46%	21	54%
PYREXIA	8	57%	3	25%	3	21%	4	31%	10	26%
ASTHENIA	2	14%	3	25%	2	14%	3	23%	8	21%
CNS										
IRRITABILITY	2	14%	0	0%	0	0%	0	0%	0	0%
INSOMNIA	0	0%	0	0%	1	7%	0	0%	1	3%
General										
MUSCULOSKELETAL STIFFNESS	9	64%	4	33%	0	0%	3	23%	7	18%
CHILLS	4	29%	0	0%	0	0%	0	0%	0	0%
BACK PAIN	3	21%	1	8%	1	7%	2	15%	4	10%
HYPERHIDROSIS	2	14%	0	0%	0	0%	0	0%	0	0%
NAUSEA	2	14%	1	8%	0	0%	0	0%	1	3%
MYALGIA	1	7%	0	0%	3	21%	2	15%	5	13%

IFN-XL is well tolerated: adverse events were transient and slight to moderate in severity.

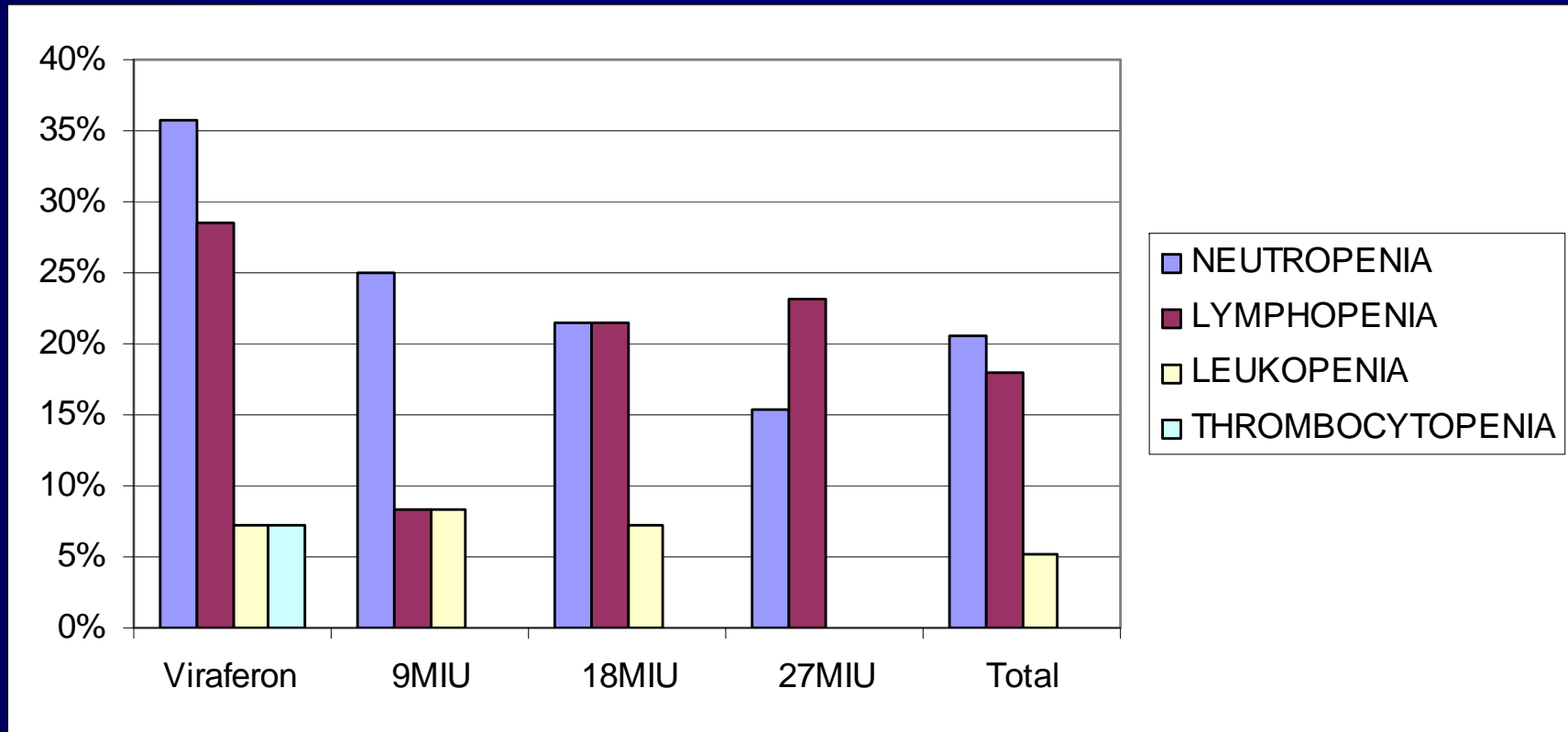
Safety summary



IFN-XL presented much better tolerance than Viraferon given three times a week:

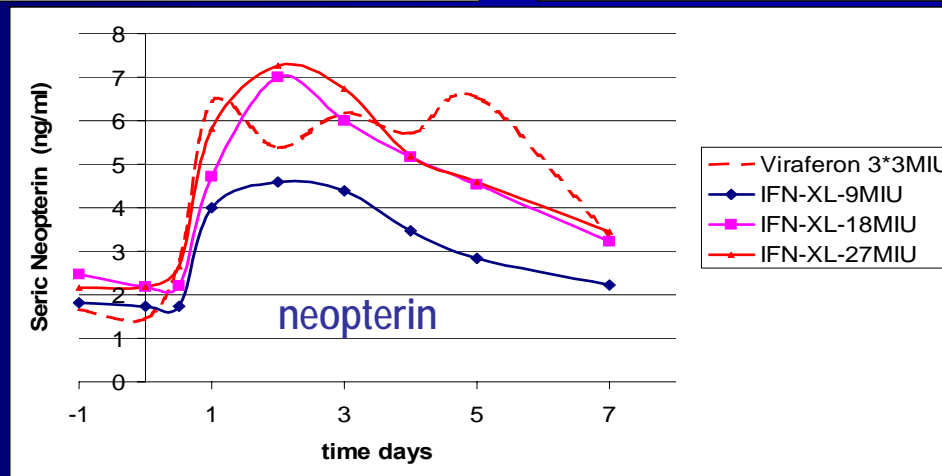
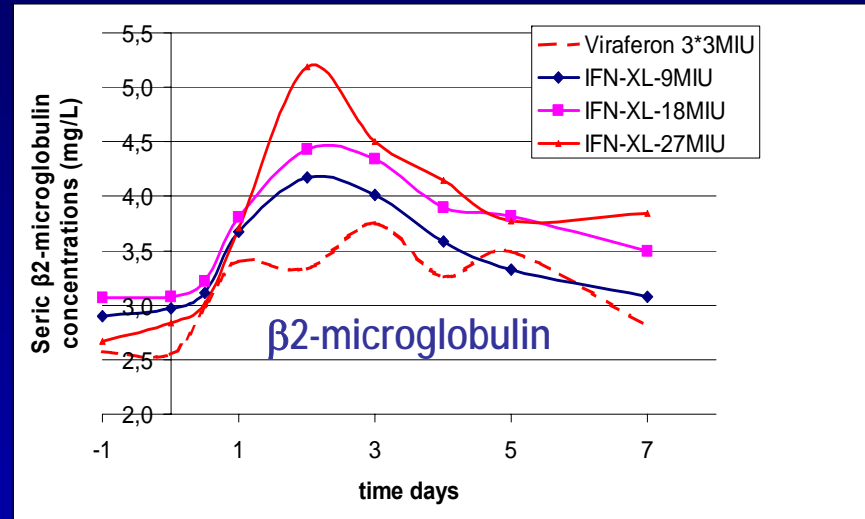
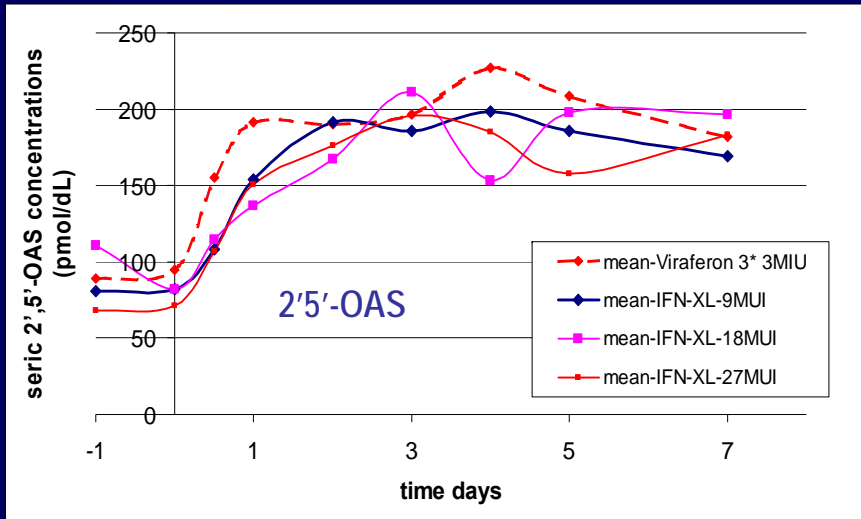
3.7 AE / patient compared to 5.2 respectively

IFN XL: Hematology



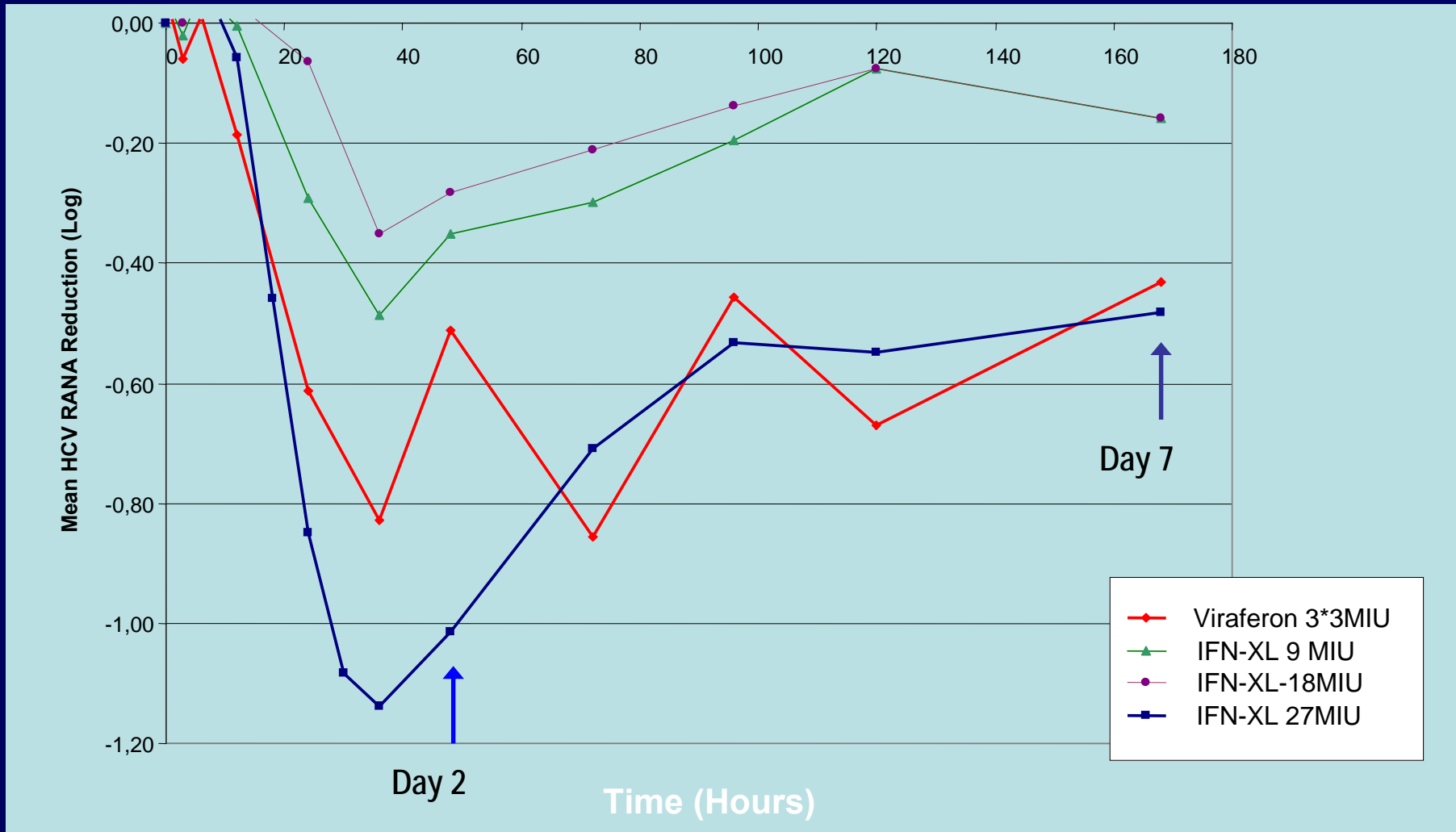
IFN-XL displayed a lower rate of hematological Adverse Events

INF XL: Biomarkers



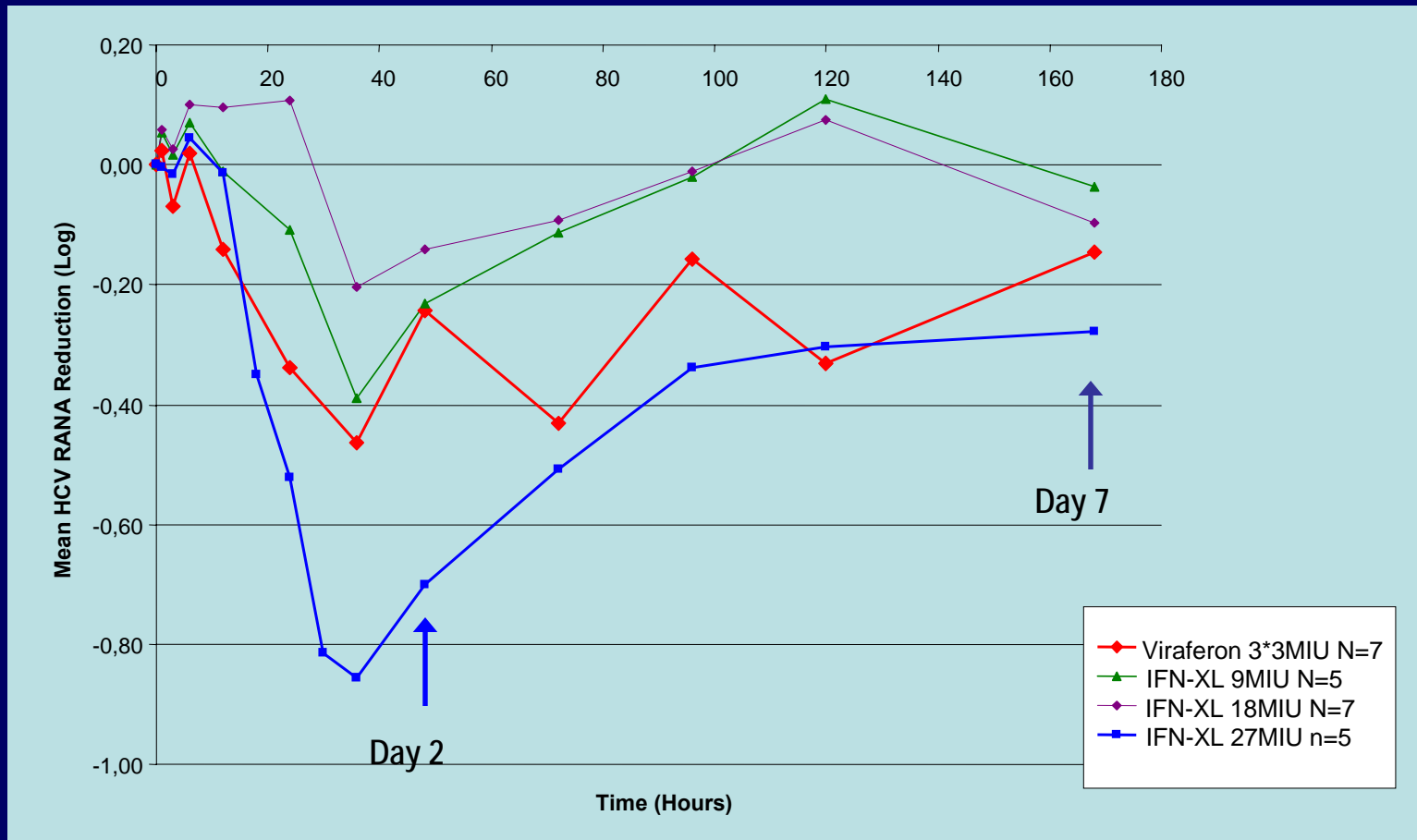
At the 3 doses, IFN-XL is efficient to induce seric biomarkers such 2,5-OAS, neopterin and beta2-microglobulin.

IFN XL: Viral Load Result



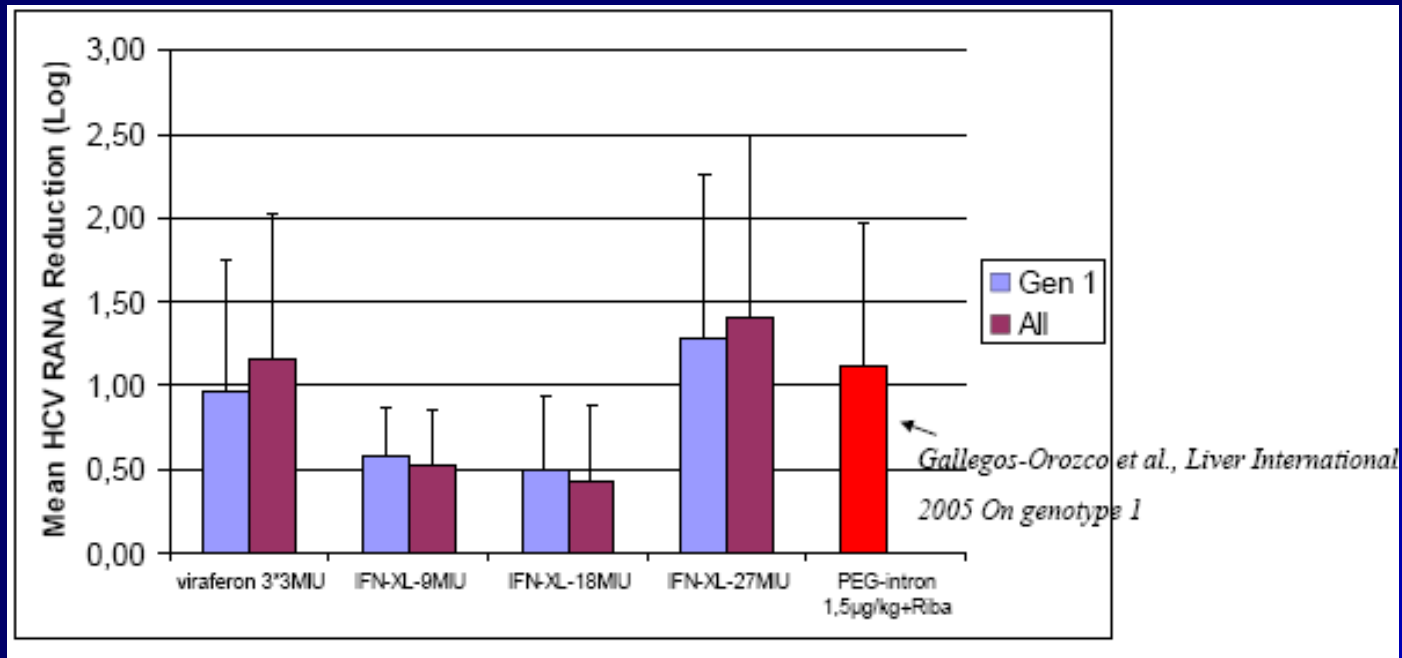
Compared to the Viraferon[®], 27MIU cohort presents a higher viral load decrease at D2 and equivalent at D7

Viral load in non responder genotype 1 patients



- Viral load decrease in non-responding genotype 1 patients:
- Strong viral load decrease with IFN XL

IFN XL: Viral Load Result (Nadir)



- A robust antiviral response is obtained for 27MIU cohort
- In this cohort 50% (6/12) had a HCV RNA decrease by more than 1 log (similar to Viraferon® cohort: 43% (6/14))

Summary (1)

- IFN-XL is well tolerated across all treatment groups
- One single administration of IFN-XL leads to IFN release over 7 days
- At all doses, viral kinetics is biphasic, comparable to that of PEG-IFN-alfa
- A robust antiviral response is obtained for 27 MIU cohort:
 - 50% had a HCV RNA decrease > 1 log
 - similar to Viraferon®

Summary (2)

- IFN-XL has the potential to **reduce adverse events** and may **improve tolerability** and **efficacy** compared to Standard IFN
- Further clinical studies of this novel IFN in patients with hepatitis C are now in progress, with the goal to use **PEG-IFN as comparator**

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