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# Antiviral activity and tolerance of a novel interferon-alpha-2b sustained release (IFN-alpha-2bXL) compared to Peg-IFN-alpha-2b: a phase Ib trial in HCV patients

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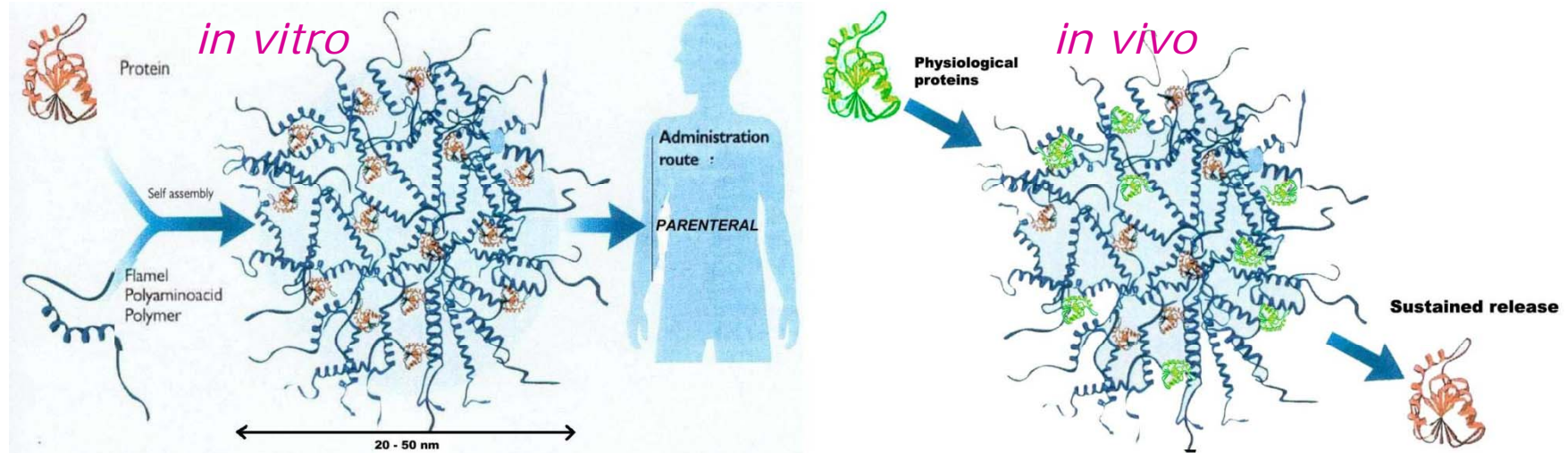
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# The Medusa® technology



## ▪ The Medusa® polymer

- Made of natural aminoacids (polyglutamate / Vitamine E)
- Hydrophobic nanodomains → self-assembles in water → nanoparticles
- Non-covalent association of the protein → controlled release

➤ Release profile depends on the polymer/protein ratio and concentration

## ▪ IFN alfa

- dose dependent adverse events
- biological activity related to plasma IFN levels

➤ In preclinical studies, slow release Medusa® IFN $\alpha$ -2bXL reduces Cmax

# Rationale for IFN-alpha-2bXL development

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- **Objectives**

- **↓ toxicity by ↓ Cmax of IFN $\alpha$ 2b**

- **Improve efficacy** by:

Maintaining IFN $\alpha$ 2b levels above a minimum therapeutic concentration

- **IFN-alpha2bXL approach using Medusa® technology**

- **Native interferon** with full affinity to its receptors

- **Increases the serum half life of IFN** by increasing the bio-absorption time

- **Reduces Cmax related Adverse Events** thus allowing administration of higher doses

# Background and aims

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- In a **previous single dose ranging phase I study**, slow release Medusa® formulation of human IFN (IFN $\alpha$ 2b-XL) was shown to be safe, with **promising antiviral activity**
- **IFN $\alpha$ -2bXL was shown to reduce peak serum IFN concentrations and provide sustained release of IFN**, with the potential to improve efficacy and tolerability
- **The aim of the present trial was to confirm the antiviral activity and safety of two doses of IFN $\alpha$ 2bXL (18/27MIU)**, as compared with **Peg-IFN $\alpha$ 2b**.

# Trial Design

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## ■ Study objectives

- Compare the anti-HCV activity of
  - IFN $\alpha$ 2b-XL 18/27 MIU
  - vs marketed PEG IFN $\alpha$ 2b (Viraferon® PEG)
- Assess the safety profile of both products

## ■ Material and Methods

- Randomized, 3 parallel HCV groups
- Two weekly administrations:
  - IFN $\alpha$ 2b-XL 18MIU
  - IFN $\alpha$ 2b-XL 27MIU
  - Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg

## ■ Viral load assessment

- 1<sup>st</sup> administration: 0, 3, 6, 12, 18, 24, 36, 48, 72, 96 and 120 hours
- 2<sup>nd</sup> administration: 0, 6, 12, 24, 36, 48, 72, 96, 120 and 168 hours

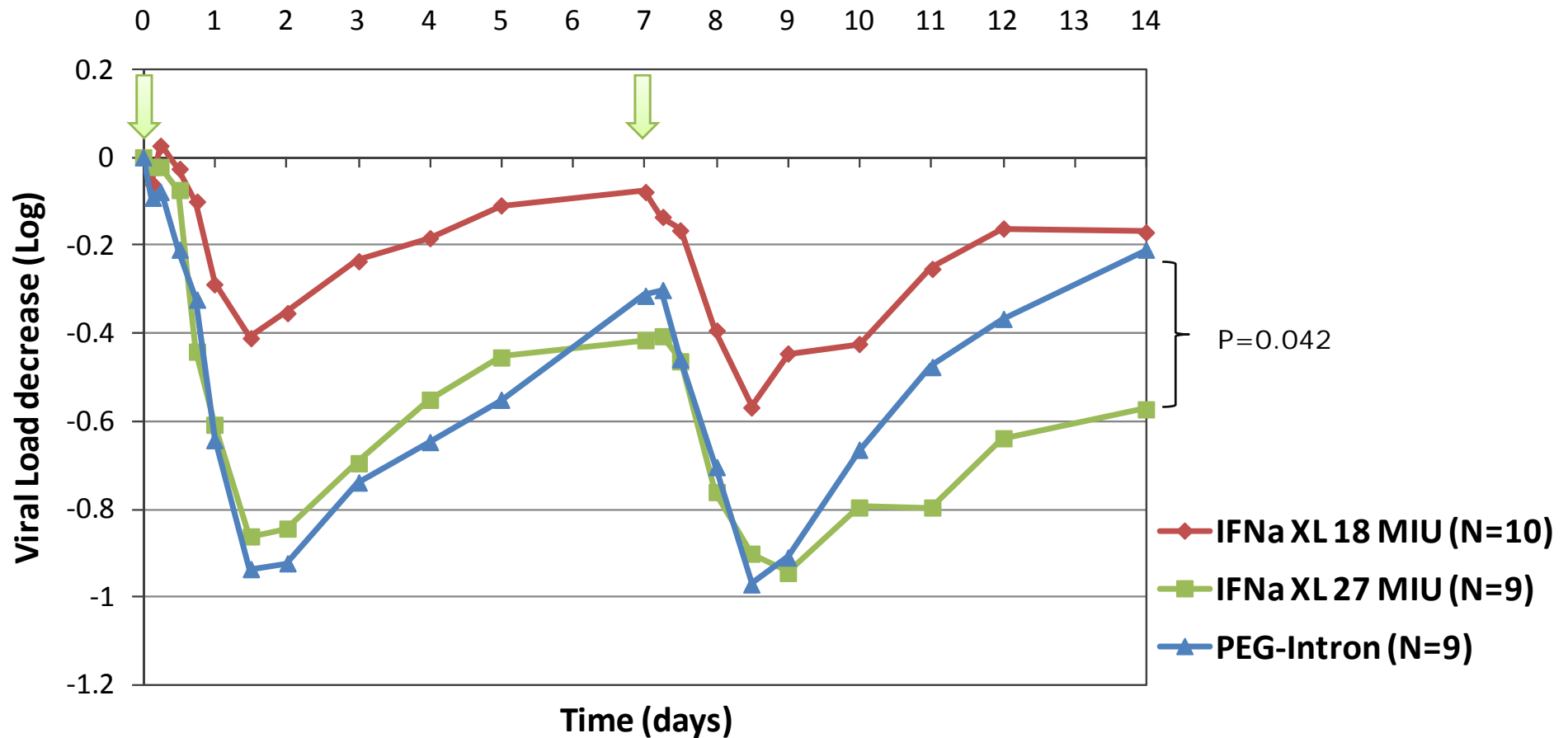
# Study population

	IFN $\alpha$ -2bXL 18MIU (n=11)	IFN $\alpha$ -2bXL 27MIU (n=12)	Peg-IFN $\alpha$ -2b 1.5 $\mu$ g/Kg (n=14)	Between groups difference (p)	
<i>Number of patients (%) / Mean [min – max]</i>					
<b>Gender M / F</b>	8/3	7/5	10/4	0.745	
<b>Age (years)</b>	50.1	46.1	46.8	0.673	
<b>BMI (Kg/m<sup>2</sup>)</b>	24.4 [18.0 - 29.8]	23.7 [18.8 - 31.2]	23.0 [19.8 - 26.4]	0.716	
<b>Treatment status at inclusion</b>	<b>Naive</b>	1 (9.1)	1 (8.3)	<b>6 (42.9)</b>	<b>0.073</b>
	<b>Non Responder to Peg-IFN</b>	7 (63.6)	9 (75.0)	<b>6 (42.9)</b>	0.257
	<b>Relapser to Peg-IFN</b>	3 (27.3)	2 (16.7)	<b>1 (7.1)</b>	0.396
<b>HCV genotype</b>	<b>Gen 1</b>	10 (91.0)	10 (83.4)	<b>10 (71.4)</b>	0.988
	<b>Gen non-1</b>	1 (9.1)	2 (16.6)	<b>4 (28.5)</b>	
<b>Baseline Viral Load (log<sub>10</sub> IU/mL)</b>	6.1 [5.1 - 6.9]	5.8 [3.5 - 6.9]	5.9 [4.5 - 6.8]	0.606	
<b>ALAT (IU/L)</b>	80.55	73.58	78.57	0.487	

- **No statistical differences but more naïve patients in Peg-IFN population (most of them genotype 3)**



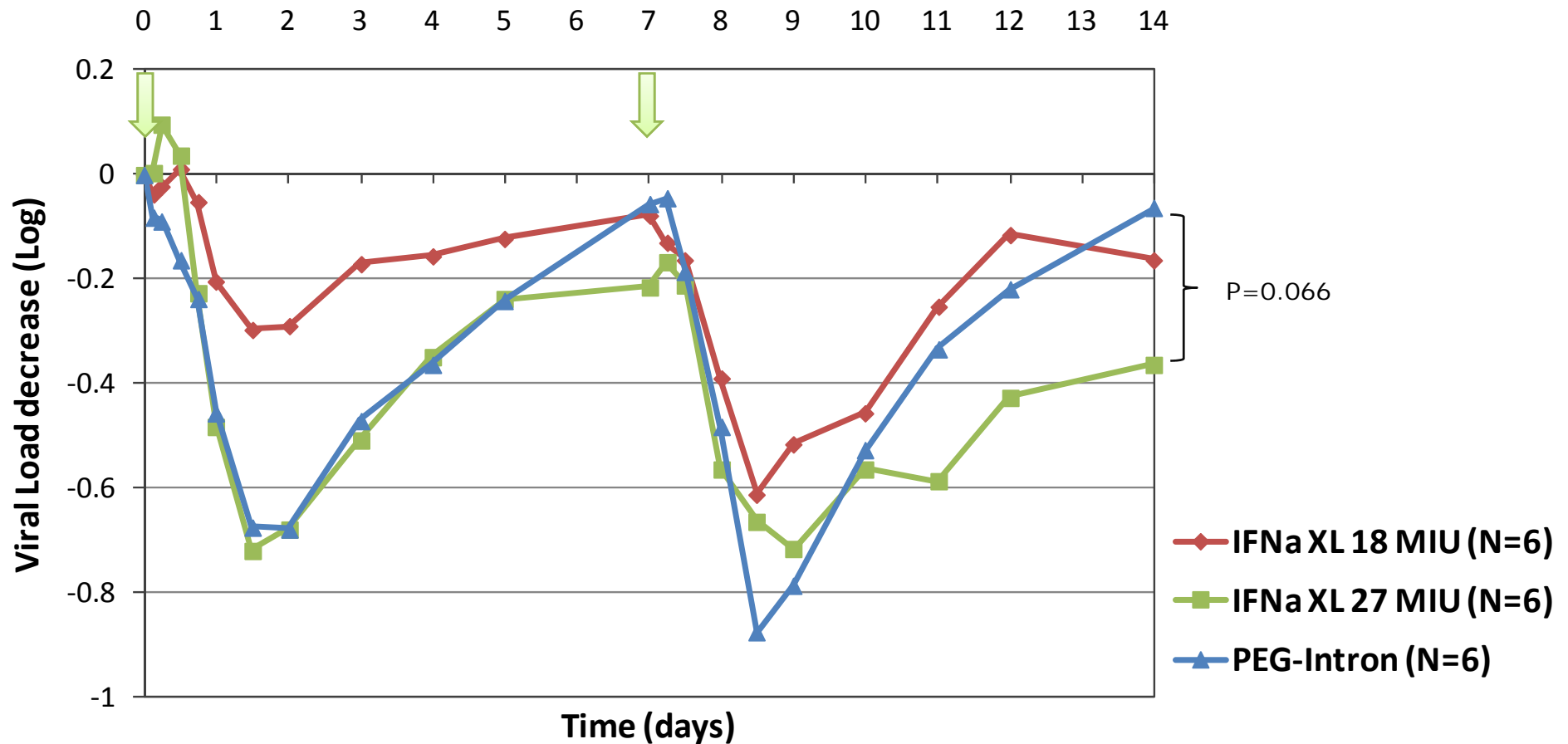
## Viral Load decrease in Genotype 1 patients (including non-responder, relapser to Peg/ribavirine, and naïve)



- During the first administration the antiviral activity of IFN $\alpha$ -2bXL 27 MIU is similar to Peg-IFN $\alpha$ -2b
- During the second administration IFN $\alpha$ -2bXL 27 MIU shows a significantly better antiviral activity than Peg-IFN $\alpha$ -2b (-0.21 Log vs -0.57 Log N=9 p=0.042)



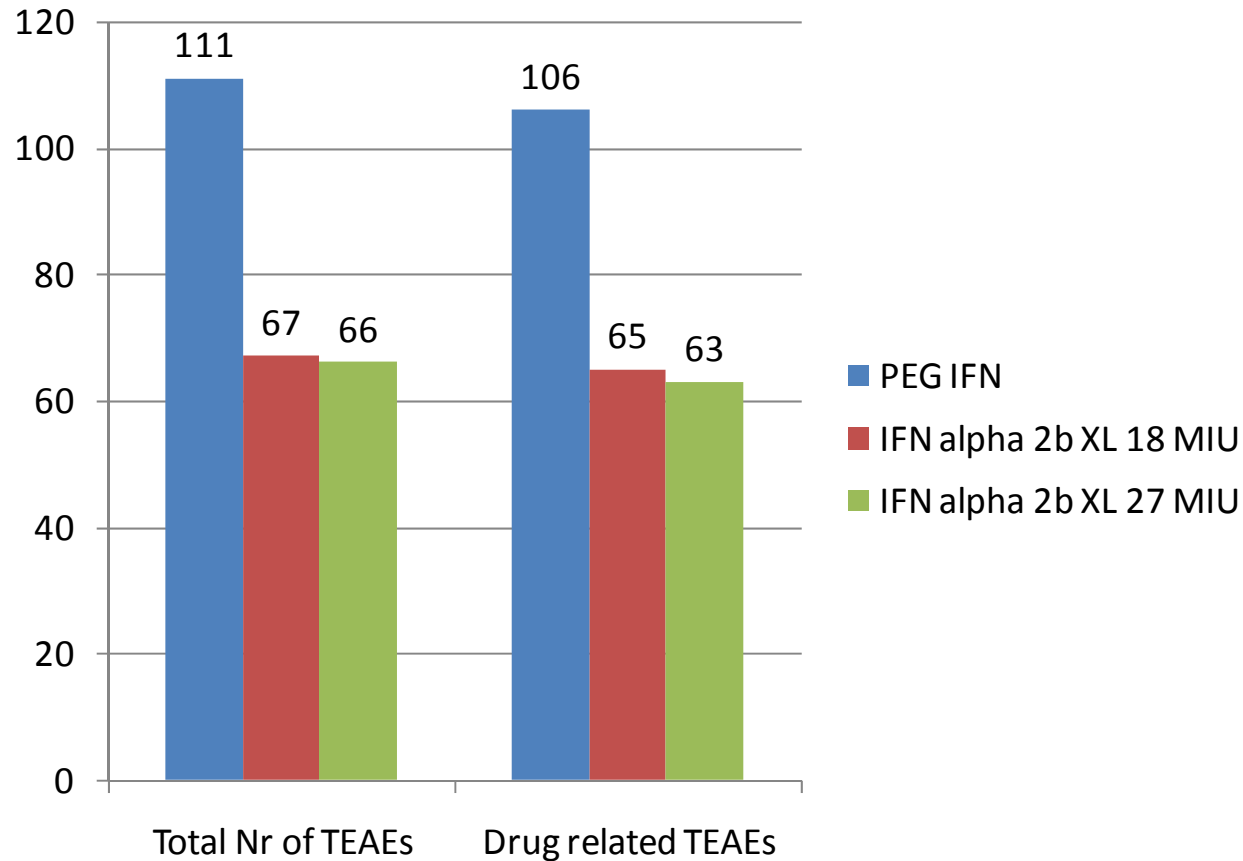
## Viral Load decrease in non responder Genotype 1 patients



- During the first administration, **similar activity** is obtained between Peg-IFN $\alpha$ 2b and IFN-XL 27MIU.
- However, it is interesting to notice the **better activity obtained at the end of second week** (nearly significant).

# Safety

## Overall summary of adverse events



- **Better tolerance with IFN $\alpha$ 2bXL than with Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/Kg:  
**5.3 vs 7.6 TEAEs/patient****

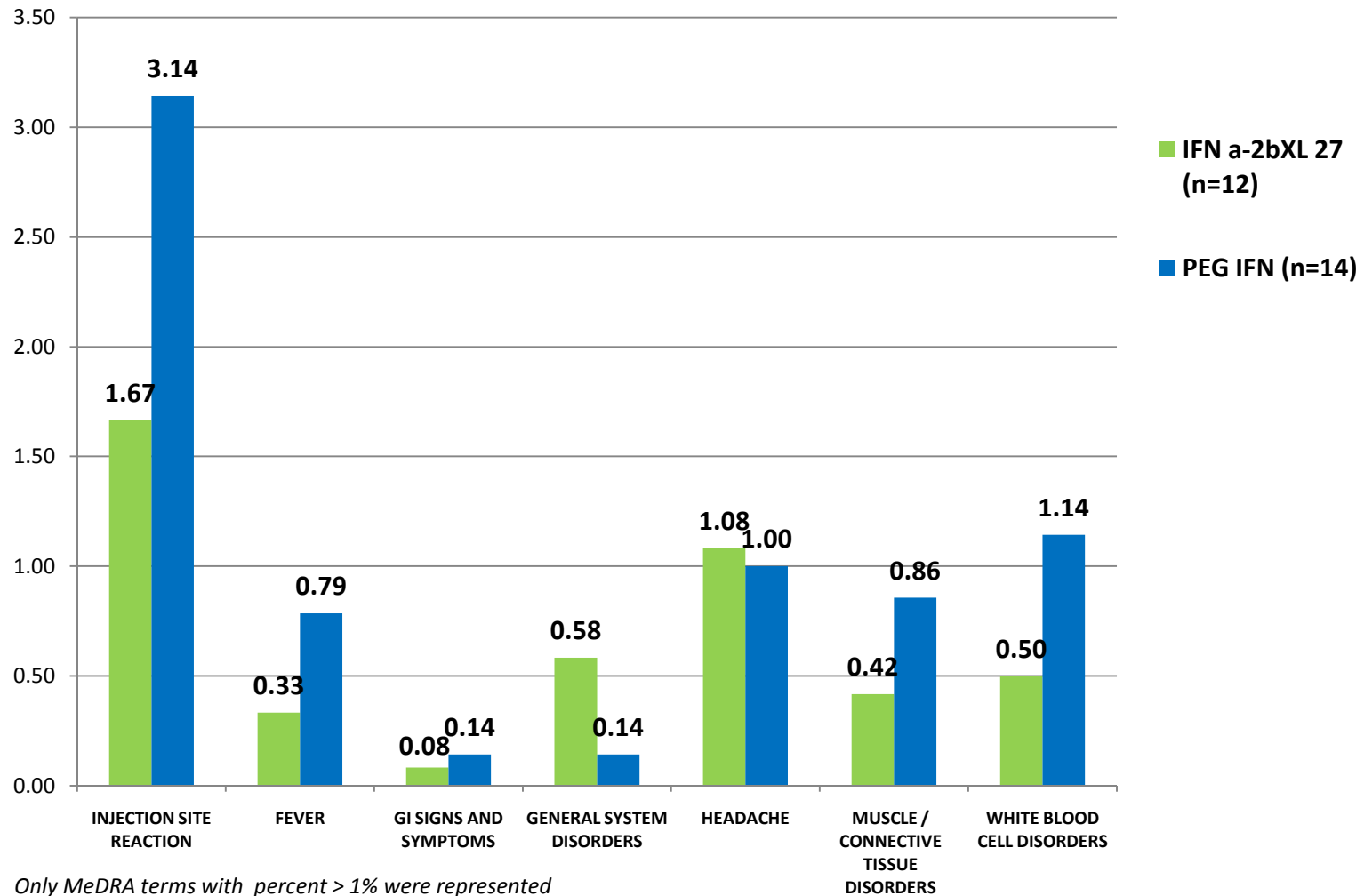
- **Safety profile of IFN $\alpha$ 2bXL is not dose-related**

TEAE: treatment Emergent Adverse event



# Clinical Safety

TEAEs / patient (only possibly or probably related)



- Less injection site reactions with IFN $\alpha$ -2bXL 27 MIU than with Peg-IFN $\alpha$ -2b 1.5  $\mu$ g/Kg
- Systemic tolerance better or at least similar to that of Peg-IFN $\alpha$ -2b 1.5  $\mu$ g/Kg



# Conclusions 1

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- **IFN $\alpha$ 2bXL 18/27 MIU** has been administered to 23 hepatitis C patients, and exhibited:
  - A **favorable safety profile: 5.3 AEs / patient vs 7.6 AEs** for Peg-IFN $\alpha$ 2b
  - A **dose-dependent slow release activity** over one week
  - A **superior antiviral activity** than Peg-IFN $\alpha$ 2b (**-0.57Log vs -0.21Log p=0.042** at D14 in Genotype 1 patients)

# Conclusions 2

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➤ **This new proof of concept study**  
**does confirm the**  
**superior tolerability/anti-viral ratio**  
**of IFN $\alpha$ 2bXL for Hepatitis C treatment**

# Acknowledgements

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