

# LB 9 Four weeks of IL-7 (CYT107) added to peginterferon (pegIFN) and ribavirin (RBV) is safe, induces a broad immune response and HCV viral clearance in genotype 1 and 4 patients non responders to pegIFN and RBV (Study ECLIPSE 2)

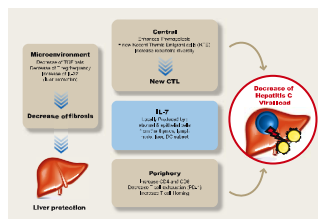
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## Background and rationale

IL-7 properties match especially well with T cell abnormalities reported in HCV infection:

- **lymphopoietic effect** (thymopoiesis); IL-7 may potentially expand the frequency of rare HCV specific CD4 or CD8 T cell precursors
- may **enhance T cells response**; the magnitude of CD4 and CD8 T cell responses, usually blunted in HCV infected patients who cannot clear the virus
- **broaden the T cell response**; both by making available new naïve T cells and by broadening the T cell repertoire
- may **foster the differentiation of protective memory** CD4 and CD8 T cells, which is typically impaired in chronic viral infections (PD-1)
- **anti-TGFβ** activity of IL-7 might significantly contribute to decreasing the excessive "T-reg" frequency.



## Objectives

Evaluate the tolerance, immunological and antiviral effects of CYT107 in HCV-infected patients non-responders to Standard of Care (SoC)

➢ **Safety at W12 of biologically active doses of CYT107** added to pegylated interferon-alpha (PegIFN-α) and ribavirin (SoC)

➢ **Pharmacokinetics**

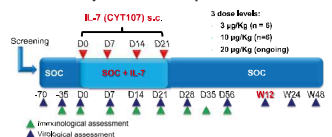
## Immunological effects:

- CD3, CD4, CD8 and subpopulations of lymphocytes (naïve, memory, Treg)
- T cell Repertoire diversity
- T cell Homing

## Antiviral effects

## Methods

**Study design : open-label dose-escalating study multicentric phase I/II a**



- **SoC** was initiated 6-10 weeks before initiation of CYT107, and continued as add-on during at least 12 weeks.
- **Assignment to a DL was doubled from 6 to 12 patients**,
  - if a reduction of HCV Viral Load  $\geq 2$  log or HCV undetectable at W12 after CYT107 initiation (D0) was observed in at least 2 of 6 patients,
  - if more than 1 patient from the initial cohort at this DL experienced a DL.

## Patient Population and Baseline Demographics

### Patient population

- **The treatment-experienced HCV (genotype 1 and 4) adult patients enrolled were prior non responders defined as:**
  - Absence of EVR, or
  - Absence of end of treatment response defined by detectable HCV RNA at the end of treatment (24 weeks or 48 weeks)
- **Key exclusion criteria included:**
  - Previous receipt of polymerase or protease inhibitor or any substance with immunological properties

- Co-infection with HIV or HBV
- Body mass index (BMI) > 30kg/m<sup>2</sup>
- Auto-antibodies with a titer > 1/80
- Alpha-fetoprotein > 200 ng/mL
- ALT and/or AST > 5 x ULN [grade 2]
- Any history of malignancy,
- Auto-immune disease, transplantation.

**Table 1 : Baseline patient demographics and disease characteristics**

	3 µg/Kg (n = 6)	10 µg/Kg (n = 12)
Gender (F/M)	1/5	3/9
Race		
• Caucasian	5	7
• North-African	1	3
• African	1	2
Age, years ; median (range)	47 (42 - 61)	50 (41 - 59)
BMI (Kg/m <sup>2</sup> ) ; median (range)	24 (23 - 29)	26 (21 - 30)
HCV genotype (n)		
• Genotype 1	6	8
• Genotype 4	0	4
Total duration of previous SoC, wks ; median	62 (16 - 108)	76 (14 - 286)
HCV RNA at baseline (Scr1), (log <sub>10</sub> IU/ml) ; median (range)	6.29 (5.59 - 6.83)	6.17 (5.87 - 6.42)

## Results

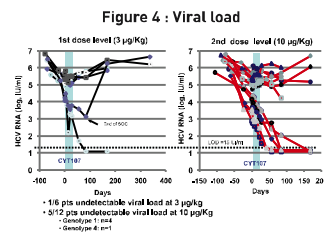
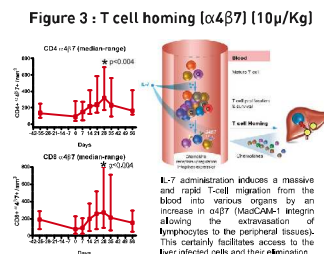
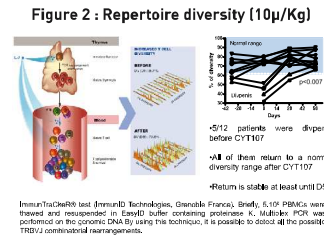
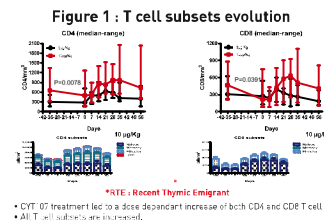
Presentation of the 3µg/kg and 10µg/Kg dose levels

### Safety and tolerability

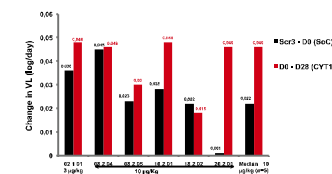
- One SUSAR (abdominal pain, grade 2) was considered as possibly related to CYT107 and/or to SoC. This SAE did not lead to the stop of the patient treatment.
- No other serious Adverse Events, DLT or clinically relevant abnormalities in biological parameters related to CYT107 treatment were reported.
- 78,6 % of AEs were of grade  $\leq 1$ , primarily injection-site reactions.

**Table 2 : Treatment Adverse Events (n patients, % of patients)**

	3 µg/Kg/wk (N= 6)	10 µg/Kg/wk (N= 12)
• Local reactions at injection site (erythema, pruritus, induration, pain)	5 (83.3%)	11 (91.7%)
• Asthenia	0	3 (25%)
• Flu-like syndrome	0	1 (8.3%)
• Fever	0	2 (16.7%)
• Splenomegaly	0	1 (8.3%)
• Neutropenia	0	0
• Lymphocytopenia	0	1 (8.3%)



**Figure 5 : Comparison of Viral Load Changes (log/day)-CYT107 vs. SoC**



Conclusion: the slopes of viral decrease were larger after CYT107 administrations (D0-D28) than during the SoC treatment (SoC+D0)

## Conclusions

In chronic HCV- patients, non-responders to pegIFN + RBV,

- CYT107 was generally well-tolerated when co-administered for 4 weeks to pegIFN/RBV,
- CYT107 expanded both CD4 and CD8 T cells, an effect known to provide an efficient and stable immune response,
- CYT107 contributed to an increase of T cell homing in lymphoid organs
- CYT107 induced a normalization of the diversity of the TCR repertoire in most patients
- At 10µg/kg/wk in combination with pegIFN and RBV, these immune effects were associated with a HCV RNA drop to undetectable levels in a significant number of patients.

**These results suggest the need for future studies combining DAAs and CYT107 in patients with CHC.**

## References

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## Acknowledgements

We thank all the study participants, the study-investigative teams and Cytheris collaborators.