

# **Anti-viral Proof of Concept Study of Miravirsen, an Oligonucleotide Targeting miR-122, in Treatment of Naïve Patients with Genotype 1 Chronic HCV Infection**

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M.R. Hodges on behalf of the study investigators and Santaris Pharma

NIH RNA Oligonucleotides Conference

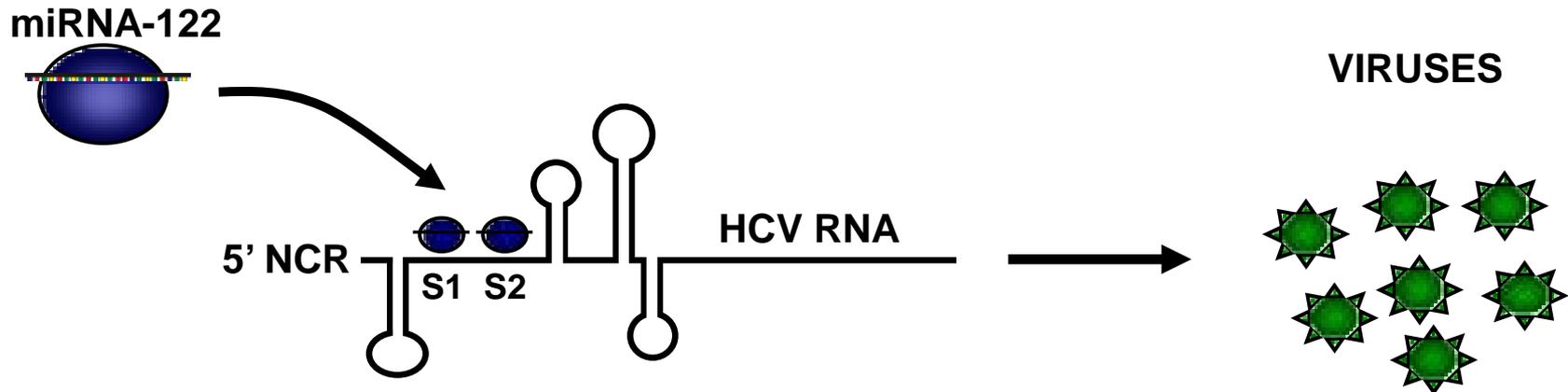
Emerging Clinical Applications

NIH, Rockville, Maryland, December 15-16 2011

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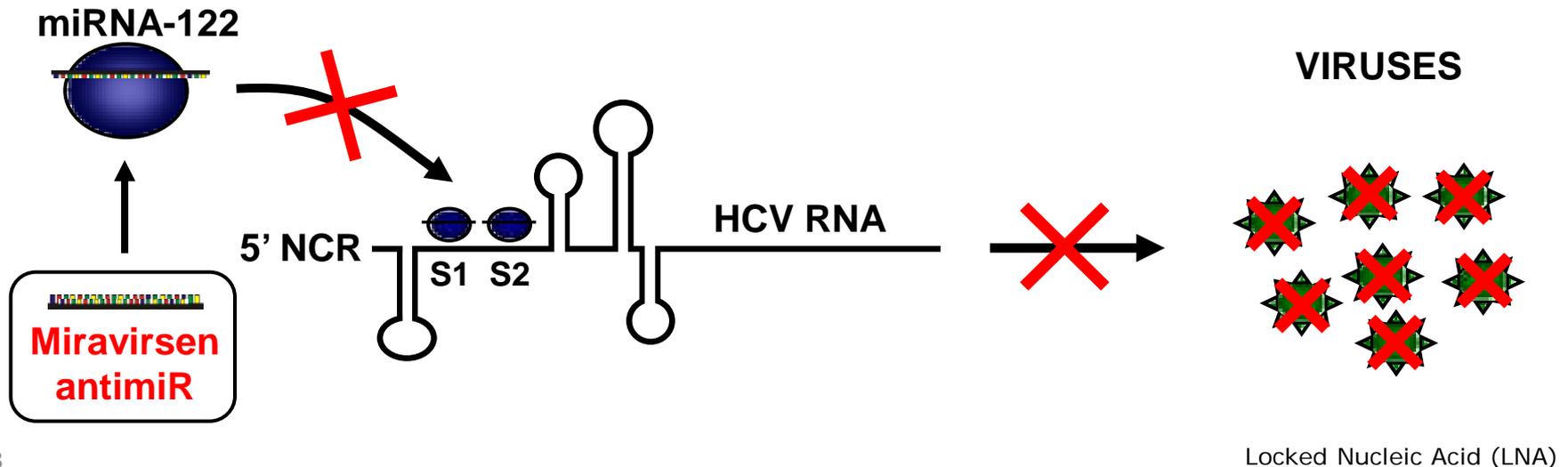
# Introduction

- microRNAs are small non-coding RNAs that post-transcriptionally regulate gene expression by inhibiting translation and promoting degradation of target mRNAs
- miR-122 is a liver specific microRNA critical for hepatitis C virus accumulation in the liver<sup>1</sup>



# Miravirsen Mode of Action

- Miravirsen is a LNA modified phosphorothioate anti-sense oligonucleotide targeting and blocking miR-122
  - First drug to exploit a microRNA target for therapeutic use
  - As a host targeting agent miravirsen poses a high barrier to resistance
  - Miravirsen should work in all HCV genotypes because miR-122 binding sites are conserved



# Rationale for Clinical Use

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## Pre-clinical studies<sup>1-2</sup>

- Miravirsen reduced HCV replication in vitro (EC<sub>50</sub> 0.67 μM)
- Presence of miR-122/drug heteroduplex
- Miravirsen produced long-lasting suppression of HCV viremia with no escape mutations detected in the miR-122 seed regions of the HCV RNA

## Healthy volunteers

- Miravirsen is safe and well tolerated
- No dose limiting toxicities were identified
- Terminal elimination half-life in plasma of 30 days supports infrequent dosing

# Study Objectives

SPC3649-203

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## Primary study objective:

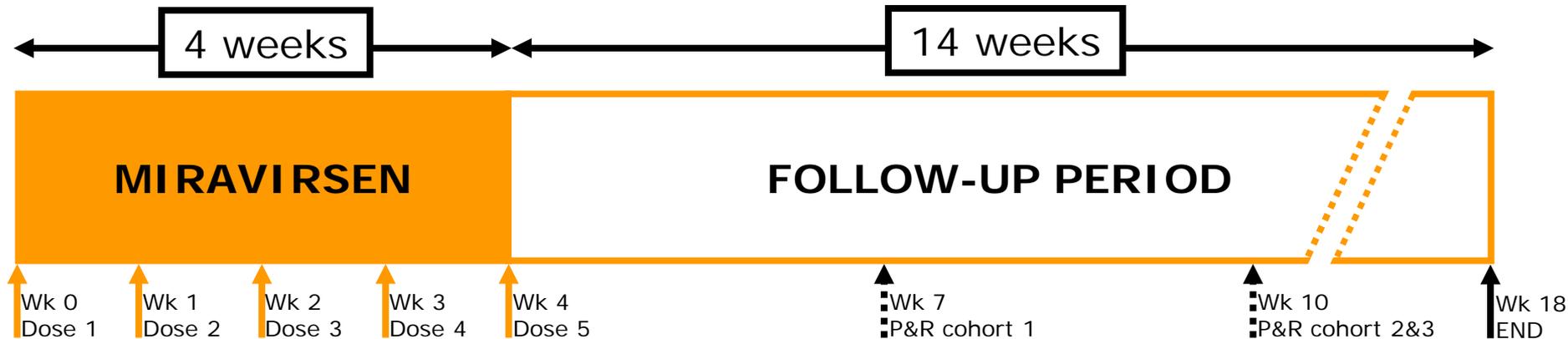
- Safety and tolerability of multiple doses of miravirsen given to chronic HCV genotype 1 infected patients

## Secondary study objectives:

- Assess effects on HCV RNA load
- Plasma exposure and PK/PD relationships
- Sequencing HCV seed regions for miR-122

# Study Outline

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-  4 weeks miravirsen s.c., simple saline solution
  - 3 dosing cohorts : 3, 5 and 7 mg/kg x weekly doses
  - 36 patients : 12 patients per dosing cohort (9 active and 3 placebo)
-  14 weeks of follow-up with regular visits
  - 3 mg/kg cohort : pegIFN/RBV was allowed 3 weeks after last dose
  - 5 & 7 mg/kg cohort : pegIFN/RBV was allowed 6 weeks after last dose
-  Dose Selection
  - Weekly doses expected to reach target hepatic exposure required for anti-viral activity

# Key Entry Criteria

## SPC3649-203

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- Male or female, aged 18-65
- Chronic hepatitis C infection
  - Genotype 1
  - HCV RNA > 75,000 IU/mL
- Naïve to interferon-based treatment regimens
- Compensated liver disease
- No clinically significant abnormalities in safety laboratory tests or medical history

# Baseline Characteristics (n=36)

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Characteristic	
Age, mean (SD)	47.5 (11.7) yrs
Male (%)	22 (61%)
BMI, mean (SD)	27.1 (5.2) kg/m <sup>2</sup>
White/Black/Asian	86%/11%/3%
HCV RNA, mean (SD)	6.12 (0.53) log <sub>10</sub> IU/mL
Genotype: 1a/1b/1a&1b	67%/22%/11% <sup>1</sup>
IL28B status: CC/CT/TT	33%/47%/19%
ALT, mean (SD)	79.4 (44.9) U/L

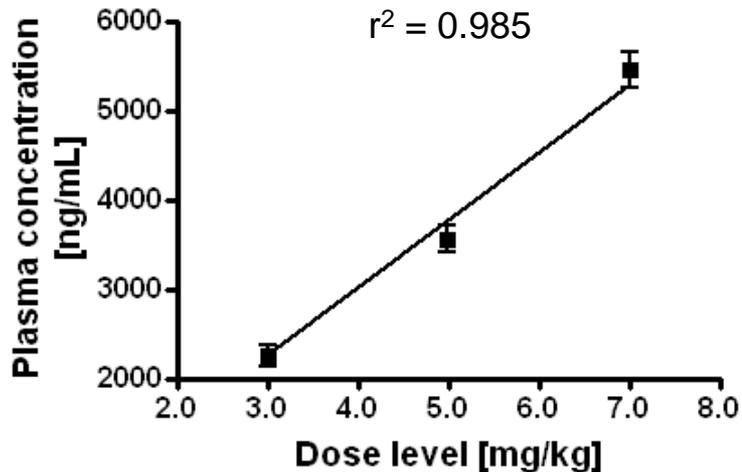
None of the patients had cirrhosis

1: one patient included as GT1a had mixed GT 1a and 3a

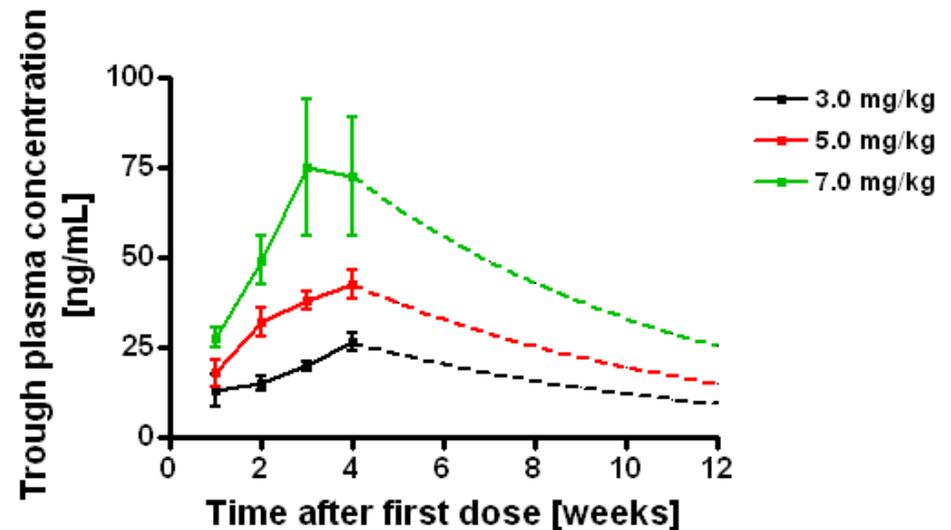
# Plasma Pharmacokinetics

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Mean plasma concentration ( $\pm$  SD) of miravirsen 2h after dose



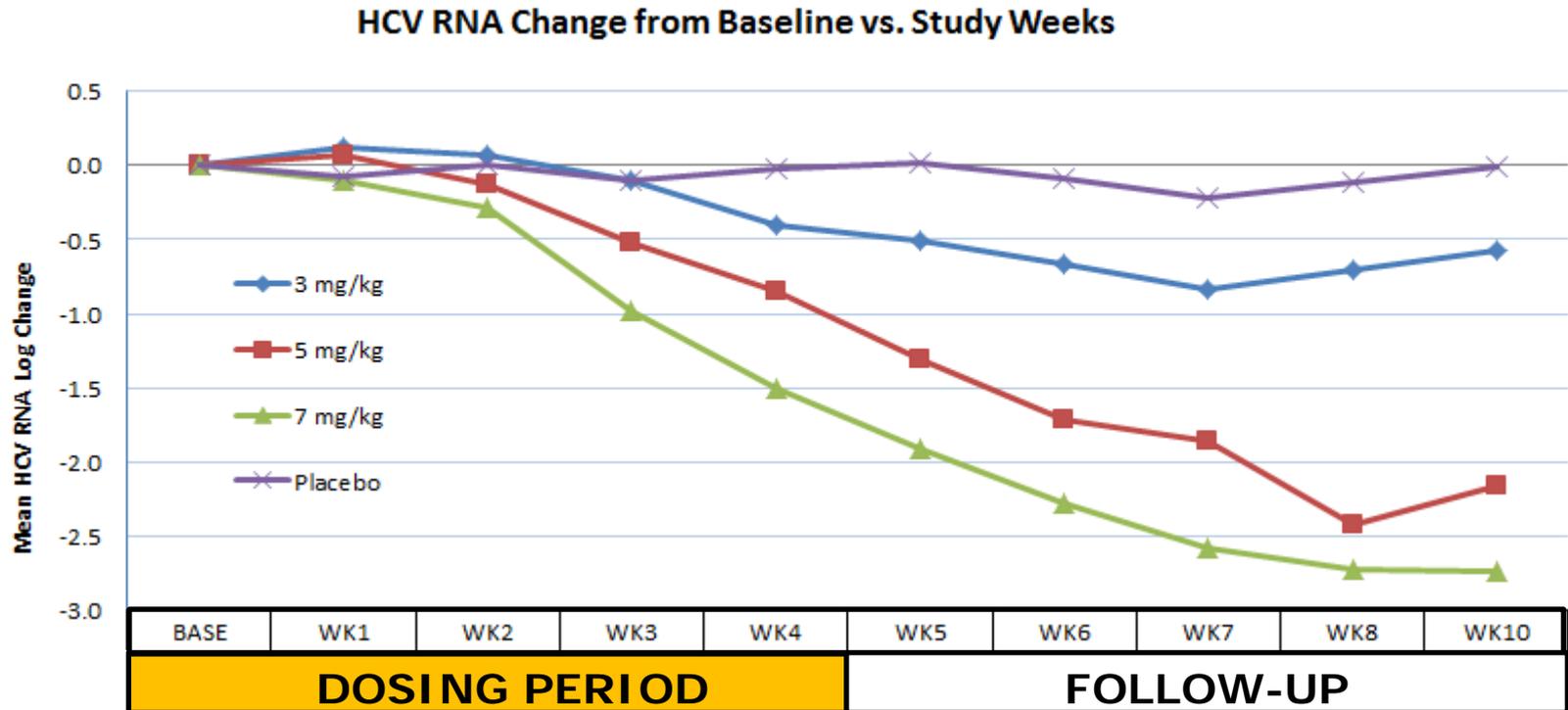
Trough concentrations of miravirsen one week after dose and after treatment period (estimated)



- Miravirsen shows dose proportional plasma PK
- Trough concentrations increase over time (as an index of liver exposure)
- Slow elimination from liver contributes to sustained activity

# HCV RNA Decline (before P&R)

## SPC3649-203 All Cohorts



No HCV RNA during Peg-IFN/Ribavirin included in graph; Cohorts cut at week 10

Dose Group	Mean HCV RNA decline IU/mL (SEM) at week 10	p value (t) MIR vs placebo
placebo	-0.01 (0.19)	-
3 mg/Kg	-0.57 (0.13)	0.034
5 mg/Kg	-2.16 (0.58)	0.007
7 mg/Kg	-2.73 (0.55)	<0.001

# Maximum HCV RNA Decline (before P&R)

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	Number Subjects	<1 log	≥1 log	≥ 2 log	≥3 log	HCV RNA < LOD
Placebo	9	8	1	0	0	0
3 mg/Kg	9	3	6	1	0	0
5 mg/Kg	9	2	7	6	4	1
7 mg/Kg	9	1	8	6	4	4

No HCV RNA during Peg-IFN and ribavirin included in table. In cohorts 3, 5 mg/kg data up to end of study, cohort 7 mg/kg data up to week 14. LOD = limit of detection 23 IU/mL.

- Miravirsen shows dose dependent antiviral activity
- No clear trend in relation between miravirsen induced viral decline and IL28B genotype or HCV genotype 1a/1b
- No escape mutations detected in the miR-122 seed regions of HCV RNA up to the end of follow-up so far in any of the treatment cohorts

# Safety, General

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### Adverse events

- No dose-limiting toxicities
- AEs mostly mild; no AE resulted in discontinuation
- 1 SAE (unrelated to treatment) in a patient who received 7 mg/kg

### Liver tests

- AST, ALT and GGT tend to decrease with miravirsen treatment in all dose groups

### Injection-site events

- Injection site reactions are uncommon (2 patients with local erythema and itching in cohort of 7 mg/kg)

# Miravirsen Study Summary

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- Miravirsen is the first microRNA targeting agent to be administered to patients
  - Safe, well tolerated with no dose-limiting toxicities
  - Dose dependent plasma trough levels
  - Prolonged dose dependent anti-viral activity well beyond the end of therapy, consistent with 30 day terminal half-life
  - No evidence of viral resistance to miravirsen
- Miravirsen has the potential to eradicate chronic HCV infection as part of non-IFN regimens or as monotherapy
- Further trials in all HCV genotypes, with longer duration of miravirsen therapy, alone and in combination with DAAs are planned

# Acknowledgements

## Clinical Trial Sites

*Erasmus MC University Hospital, Rotterdam, The Netherlands*

*Academic Medical Center, Amsterdam, The Netherlands*

*J.W. Goethe University Hospital, Frankfurt, Germany*

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