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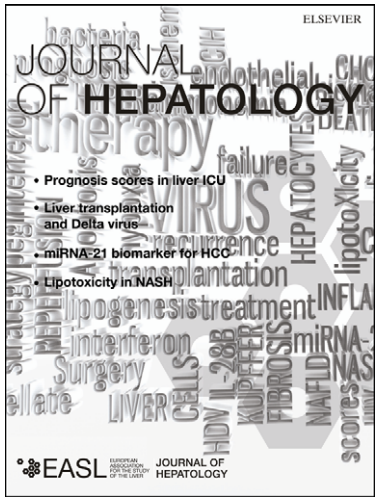

Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period

Zoe Mariño, Gonzalo Crespo, Massimo D'Amato, Nadia Brambilla, Giampaolo Giacovelli, Lucio Rovati, Josep Costa, Miquel Navasa, Xavier Forns

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Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period.

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Abbreviations: HCV: hepatitis C virus; SIL: silibinin; IV: intravenous; LT: liver transplantation; VL: viral load; RNA: ribonucleic acid; CVR: complete virological response; SVR: sustained virological response; PVR: partial virological response; PCR: Polymerase Chain Reaction; LOQ: limit of quantification; LOD:

limit of detection; SAEs: serious adverse events; AEs: adverse events; NS5B: non-structural protein 5B; MELD: model for end-stage-liver-disease.

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Abstract

Background and Aims: Hepatitis C recurrence after liver transplantation (LT) is the main problem of most transplant programs. We aimed to assess the antiviral activity and safety of intravenous silibinin (SIL) administered daily during the peri-transplant period. **Methods**: This was a single-centre, prospective, randomized, double-blind, placebo-controlled study including 14 HCV-infected patients awaiting LT. Eleven patients received SIL and 3 placebo, for a maximum of 21 days before LT and 7 days after LT. **Results**: Among the patients who received more than 14 days of pre-LT treatment, the median decrease in viral load (VL) was 2.31 log_{10} (range 0.6-4.2) in the SIL-treated group (n=9) *versus* 0.30 log_{10} (0.1-0.6) in the placebo group (n=3) (p=0.016). During the post-LT treatment, HCV-RNA levels were consistently and significantly (p=0.002) lower in the SIL group compared to placebo and decreased below the limit of quantification in 2 patients and below the limit of detection in 2 additional patients (all in the SIL-treated group). Peri-transplant treatment with SIL was well tolerated. **Conclusions**: This proof-of-concept study in patients in the waiting list for LT indicates that daily intravenous silibinin has evident antiviral properties and is well tolerated in the peri-LT period. A longer treatment regimen with silibinin (alone or in combination with other agents) should be assessed in clinical trials for the prevention of hepatitis C recurrence.

Introduction

Liver transplantation (LT) is the treatment of choice for HCV-infected patients with end-stage liver disease or hepatocellular carcinoma. Unfortunately, infection of the graft occurs universally in patients with detectable HCV-RNA at the time of LT [1]. Moreover, hepatitis C recurrence leads to graft cirrhosis in a significant proportion of patients within the first years after transplantation [2]. Eradication of hepatitis C virus before, or inhibition of HCV replication after LT, are among potential strategies to prevent hepatitis C recurrence in the graft [3]. Nevertheless, pegylated interferon and ribavirin therapy in patients awaiting LT has a low applicability and efficacy, as well as numerous adverse events (some of them life-threatening) [4, 5]. In addition, interferon cannot be administered immediately following LT.

Ferenci et al [6] have recently shown potent dose-dependent antiviral activity of intravenous silibinin in patients with chronic hepatitis C not responding to prior standard antiviral therapy. Moreover, treatment was safe, with only a transient increase in serum bilirubin levels in accordance to that observed in different publications [7, 8].

In this study, we explored the antiviral efficacy and safety of intravenous silibinin in a small cohort of HCV-infected patients awaiting LT.

Patients and methods

This is a single-centre, prospective, randomized, double-blind, placebo-controlled study (NCT01535092). HCV-infected patients enlisted for LT due to end-stage liver disease or hepatocellular carcinoma were considered to participate in the study protocol. Detailed inclusion and exclusion criteria are shown in the supplemental methods section. The aim of the study was to determine if Legalon® SIL was effective in the prevention of HCV graft infection, i.e. to induce a complete virological response [CVR] (defined as undetectable HCV at any time during the study, potentially including sustained virological response - SVR), or at least, to induce a partial virological response (PVR, ≥ 2 $\log_{10}$ viral load decrease). Finally, we aimed to assess the safety profile and tolerability of the drug.

Patients were randomized to receive 20 mg/kg/day IV Legalon® SIL (Rottapharm|Madaus, Monza, Italy) or placebo according to a 3:1 active: control ratio for a maximum of 21 consecutive days before LT (Pre-LT treatment period). Treatment was started when, based on the historical data of our center waiting list, we estimated that LT was likely to occur in less than one month. The latter was considered likely when patients from blood groups 0 and A reached the second or third position in the waiting list. At this point, patients were given information and were asked to consent to study participation. In addition to pre-LT treatment, patients received treatment for further 7 days after LT starting on the same day of the surgical procedure (from day 0 to day 6 after LT; Post -LT treatment period), totalling a maximum of 28 days of treatment with Legalon® SIL/ placebo. Infusions were administered daily in the hospital over 2-

4 hours under the supervision of a nurse. Clinical and laboratory assessments were performed daily during the treatment period; viral load (VL) was determined at every visit by real time PCR (COBAS TaqMan HCV Test, v2.0 Roche Molecular System Inc Branchburg, NJ 08876 USA; LOQ 25 IU/mL, LOD 15 IU/mL) according to the protocol schedule (see supplemental methods section). Patients were then followed up for 24 weeks after LT (Follow-up period). The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and all patients gave written informed consent before screening.

During the study period (September 2010- October 2011) 46 HCV-infected patients underwent LT in our unit; 16 patients consented to participate and were screened for the study. Out of the 16 patients included, 14 were randomized to receive IV SIL (n=11) or placebo (n=3) and they all received at least one dose of study medication (median: 20 days, range 1- 21). Twelve of these patients (9 SIL; 3 placebo) were treated for ≥14 consecutive days during the pre-LT period. Three (3) patients randomized to SIL withdrew from the study before LT: 1 patient died due to hepatocellular carcinoma progression and 2 others withdrew due to a serious adverse event (SAE) (n= 1) or an adverse event (AE) (n= 1) (Table 2). Therefore, 11 of the 14 patients underwent LT. One (1) additional patient was then withdrawn from the study 2 days after LT due to primary graft failure, leading to 10 randomized patients undergoing LT and completing the post-LT period. These 10 patients constitute the prospectively defined Intention-to-Treat Population (subgroup of Transplanted patients) for the efficacy analysis (7 patients who received SIL and 3 placebo), while the safety will be reported for all the 14 randomized patients who received at least one dose of the study

medication (Safety Population) (Figure 1). The key characteristics of the study cohort are summarized in Table 1.

Results

Efficacy analysis

The median VL decrease from baseline to the end of pre-LT treatment in the SIL group (n=9) was 2.31 log $_{10}$ (0.6-4.2) *versus* 0.30 log $_{10}$ (0.1-0.6) for the placebo group (n=3) (p=0.016, Mann-Whitney U test). Interestingly, at the end of the pre-LT treatment period 6 (67%) patients in the SIL group achieved a ≥ 2 log decrease in viral load (PVR) *versus* no patient in the placebo group (p= 0.18, Fisher Exact Test). In one patient HCV-RNA levels decreased below the LOD and in a second one below the LOQ, both in the SIL group (Figure 1 and Table 1).

The time interval between the end of pre-LT treatment and LT ranged between 0 and 38 days. Only 3 patients (all in SIL group – Table 1 and Figure 2) underwent LT while on therapy. In those patients in whom there was a gap between pre-LT and post-LT treatment, the VL increased again (Figure 2A). Already with the first infusion after LT (day 0 = day of LT), VL was lower in the SIL group (n=7) compared to placebo (n=3) and remained consistently lower during the entire 7-day post-LT treatment period (p=0.002, repeated measurements ANOVA) (Figure 2B). At the end of the post-LT treatment period VL was 1.95±1,13 (log_{10} UI/mL, mean ± SD) in SIL and 3.87±1.57 in placebo treated patients; in other words, VL was ≥2 log lower than at the screening time in all patients receiving SIL *versus* no patient in the placebo group (Fisher's Exact Test, p=0.008). Interestingly, VL was below LOQ in 4 of the 7 SIL-treated

patients *versus* none in the placebo group, with 2 patients being even below LOD (CVR).

As depicted in Figure 2B, VL increased after the end of the short post-LT treatment and, although numerically lower in the SIL group compared to placebo at all study time points (weeks 1-4, 8, 12 and 24 after LT), the differences were not statistically significant. No patient achieved SVR at the end of the study.

Safety analysis

Safety was analyzed in all 14 randomized patients receiving at least one dose of the study medication. The number and profile of AEs observed in this study was in line with those anticipated in patients awaiting LT or with the known pattern for SIL (e.g. heat sensation, chills, abdominal pain). Most of AEs were mild (76%) or not related to the study drug (74%) and more frequently reported during the pre-LT period (56%) (Table 2).

A transient and reversible increase in bilirubin was observed in 1 patient that could be attributable to SIL. Overall, while bilirubin values in the placebo group (n= 3) remained fairly constant over time before LT, in patients in the SIL group, bilirubin levels increased from 3.8±3.7 at baseline to 4.7±4.0 mg/dl at the time of LT. Following LT, mean bilirubin values at the end of treatment were numerically higher in patients who received SIL than those receiving placebo (SIL: 6.1±3.1 mg/dl *vs* Placebo: 3.2±4.1 mg/dl). However, by the end of the study, total bilirubin values were similar between groups.

Discussion

Ferenci et al have recently shown potent dose-dependent antiviral activity of intravenous silibinin in patients with chronic hepatitis C not responding to prior standard antiviral therapy [6]. Moreover, HCV infection of the graft has been prevented by the administration of IV silibinin during the peritransplant setting in 2 patients (one infected with genotype 3 and another with mixed 1a/4, both with baseline VL below 30000 UI/ml) [7, 8]. In vitro, silibinin has been shown to exert anti-HCV effects by direct inhibition of NS5B polymerase activity [9], as well as by blocking virus entry and transmission by targeting the host cell [10]. In a recently published study [11], viral kinetics modelling based on daily measurements of HCV VL in patients receiving IV SIL has supported both in vitro findings [9, 10], and suggested a major dose-dependent effect of silibinin by blocking viral production and a moderate effect on viral entry (and/or cell-to-cell spread). Thus, it appeared reasonable to explore the safety and efficacy of silibinin in patients awaiting LT and/or immediately after the surgical procedure, in a controlled study.

Our study confirmed the potent antiviral activity of SIL in difficult to treat patients (i.e. decompensated cirrhotics). Viral load decreased > 2 $\log_{10}$ in two thirds of patients who underwent at least 2 weeks of SIL therapy before LT and reached levels below the LOQ in two of them. Due to logistics and safety reasons, pre-transplantation therapy was not maintained more than 21 days and thus, only a small proportion of patients underwent LT while on therapy. As expected, in a majority of patients, VL rebounded after treatment interruption. Following LT, a short course of SIL also demonstrated antiviral efficacy and good safety profile,

with the majority of patients reaching levels below the LOQ and 2 out of 7 even below the LOD. Given the short post-LT treatment duration, it is not surprising that viral loads increased again at the end of the 7-day post-LT therapy.

This study has some limitations. One is the small number of patients included. This was due to the exploratory nature of the study and its difficulty to accurately predict the time of liver transplantation for an enlisted patient. However, even within this small cohort, we have shown a consistent antiviral effect and a good safety profile in this difficult-to-treat population. Another limitation is the use of an intravenous route in the pre-LT setting. Intravenous administration of SIL following LT and for a longer period of time may be an easier approach that should be explored to prevent or delay HCV infection of the graft. Although direct acting antivirals will probably replace interferon-based treatment in HCV-infected patients awaiting LT, there are still no data of any interferon-free regimens in decompensated cirrhosis and none of them could be probably administered immediately after LT.

In summary, this proof-of-concept randomized, double-blind, placebo controlled study in patients in the waiting list for LT treated indicates that daily intravenous silibinin has evident antiviral properties and is well tolerated in the peri-LT period. Thus, a longer treatment regimen with silibinin (alone or in combination with other agents) especially following LT, should be assessed in clinical trials for the prevention of hepatitis C recurrence.

Table 1: Clinical and virological features of the study cohort (randomized patients, n= 14):

Patient ID	Study medication	Age	Sex M/F	HCV Genotype	MELD at screening	Previous antiviral treatment response	Screening VL (log_{10})	Pre-LT period (days)	VL at pre-LT EOT (log_{10})	Time EOT-LT (days)	VL at LT (log_{10})	VL at post-LT EOT (log_{10})	Absolute decrease in VL [d]
S02	Leg® SIL	38	M	1b	19	NR	5,52	21	4,95	7	5,25	3,00	2.52
S03 [a,b]	Leg® SIL	59	F	1b	10	na ve	5,18	1	N/A	No LT	N/A	N/A	N/A
S04	Leg® SIL	47	F	1a	19	na ve	6,50	21	4,20 *	30	6,27	3,54	2.97 *
S06 [b,c]	Leg® SIL	57	F	3a	16	NR	4,29	14	<LOQ *	No LT	N/A	N/A	N/A
S07	Leg® SIL	68	F	1b	26	NR	4,38	14	2,12 *	0	2,29	<LOD	3.53 *
S09	Leg® SIL	53	M	1b	11	NR	5.98	21	2,55 *	38	6,37	2,78	3.20 *
S11	Leg® SIL	55	M	1b	12	NR	5,24	16	2,53 *	0	2,79	<LOQ	3.94 *
S12	Leg® SIL	69	F	1b	20	NR	5,02	21	<LOD *	10	4,10	<LOD	4.17 *
S13	Leg® SIL	58	M	1b	11	NR	4,08	19	2,15	0	1,95	<LOQ	2.78 *
S15 [b]	Leg® SIL	68	M	1b	20	NR	5,90	18	4,11	No LT	N/A	N/A	N/A
S16 [b]	Leg® SIL	57	M	4c	25	na ve	4,83	4	3,64	0	3,88	<LOQ	3.53 *
S01	Placebo	41	M	1b	25	NR	4,46	21	3,90	2	4,15	2,81	1.65
S10	Placebo	52	M	1a	22	NR	4,94	21	4,86	15	5,41	3,12	1.83
S14	Placebo	62	M	1b	10	NR	5,95	21	5,70	6	6,25	5,67	0.28

Table 1 footnote

[a] Prematurely discontinuation from the study due to adverse events after the first dose administration. [b] Patients not included in the efficacy analysis (<14 days pre-LT treatment and/or no LT). [c] *Exitus vitae* (hepatocellular carcinoma progression) while on the waiting list. [d] Referred to VL change between screening period and post-LT EOT.

Abbreviations: M: male; F: female; VL: viral load; EOT: end of treatment. LOD: Limit of Detection; LOQ: Limit of Quantitation; for the purpose of calculations Undetectable HCV-RNA (<LOD) was considered 0.85 Log and Detectable HCV-RNA below the limit of quantification (<LOQ), 1.30 Log, respectively. Patients achieving ≥ 2 log VL decrease during therapy are marked with (*).

Table 2: Safety report (randomized patients, n= 14):

Treatment Emergent AEs (Preferred Term, MedDRA version 14.1)	Legalon SIL			Placebo		
	OVERALL STUDY (n=11)	Pre LT (n=11)	Post LT (n=8)	OVERALL STUDY (n=3)	Pre LT (n=3)	Post LT (n=3)
	% (n)	n	n	**%** (n)	n	n
Nausea	**54,6 %** (6)	6	0	**66,7 %** (2)	1	1
Feeling Hot	**54,6 %** (6)	6	0	**0,0 %** (0)	0	0
Pyrexia	**45,5 %** (5)	5	1	**33,3 %** (1)	1	0
Phlebitis	**45,5 %** (5)	5	0	**33,3 %** (1)	1	0
Hyperglycaemia	**45,5 %** (5)	2	3	**66,7 %** (2)	0	2
Hypertension	**45,5 %** (5)	0	5	**33,3 %** (1)	0	1
Chills	**36,4 %** (4)	4	1	**0,0 %** (0)	0	0
Abdominal pain	**36,4 %** (4)	3	1	**0,0 %** (0)	0	0
Asthenia	**36,4 %** (4)	3	2	**0,0 %** (0)	0	0
Oedema peripheral	**36,4 %** (4)	3	1	**0,0 %** (0)	0	0
Back pain	**36,4 %** (4)	1	3	**0,0 %** (0)	0	0
Abdominal discomfort	**27,3 %** (3)	3	0	**33,3 %** (1)	0	1
Diarrhoea	**27,3 %** (3)	3	0	**33,3 %** (1)	0	1
Feeling of body temperature change	**27,3 %** (3)	3	0	**0,0 %** (0)	0	0
Myalgia	**27,3 %** (3)	3	0	**0,0 %** (0)	0	0
Dizziness	**27,3 %** (3)	3	0	**33,3 %** (1)	1	0
Hepatic encephalopathy	**27,3 %** (3)	3	0	**33,3 %** (1)	1	0
Vomiting	**27,3 %** (3)	2	1	**0,0 %** (0)	0	0
Headache	**27,3 %** (3)	2	1	**0,0 %** (0)	0	0
Insomnia	**27,3 %** (3)	2	1	**33,3 %** (1)	1	0
Diabetes mellitus	**27,3 %** (3)	0	3	**33,3 %** (1)	0	1

Table 2 footnote

* Due to the size of each treatment group, every occurred TEAE is common (>1 in 100) even if it occurred in 1 patient only. Therefore the threshold used for the definition of the "most commonly" reported TEAEs to be included in this summary table is the occurrence in at least 3 patients in at least one treatment group.

Abbreviations: TEAEs: Treatment Emergent AEs. Number (and %) of patients who "most commonly" * reported treatment emergent AEs in the whole study cohort (Safety population, n=14) in both treatment groups and by study phase. The percentage and number of patients are reported for the overall study period, while only numbers are shown for the pre-LT and post-LT treatment periods, respectively.

Figure and Table legends.

Figure 1. Study patients flow-chart.

Figure 2. Time course of HCV-RNA levels during the study period.

(A) Time course of HCV-RNA levels in individual patients. The first continuous vertical line represents time of pre-LT treatment initiation; discontinuous line depicts time of pre-LT treatment finalization; bold line (time point 0) represents time of LT; the second continuous line represents time of post-LT treatment finalization. Viral load is depicted in the y axis in a $\log_{10}$ scale; time is shown in the x axis in days. (B) Averaged time curve (mean ± SD) by treatment group in patients who received at least 14 days of pre-LT treatment and underwent LT. Time between pre-LT end of treatment and LT has been compressed for simplification purposes. Abbreviations: SCR: screening phase; TREAT: treatment (pre-LT and post-LT) phase; FUP: follow-up phase; LOD: limit of detection; LOQ: limit of quantification; OLT: orthotopic liver transplantation.

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Figure

Figure 1:

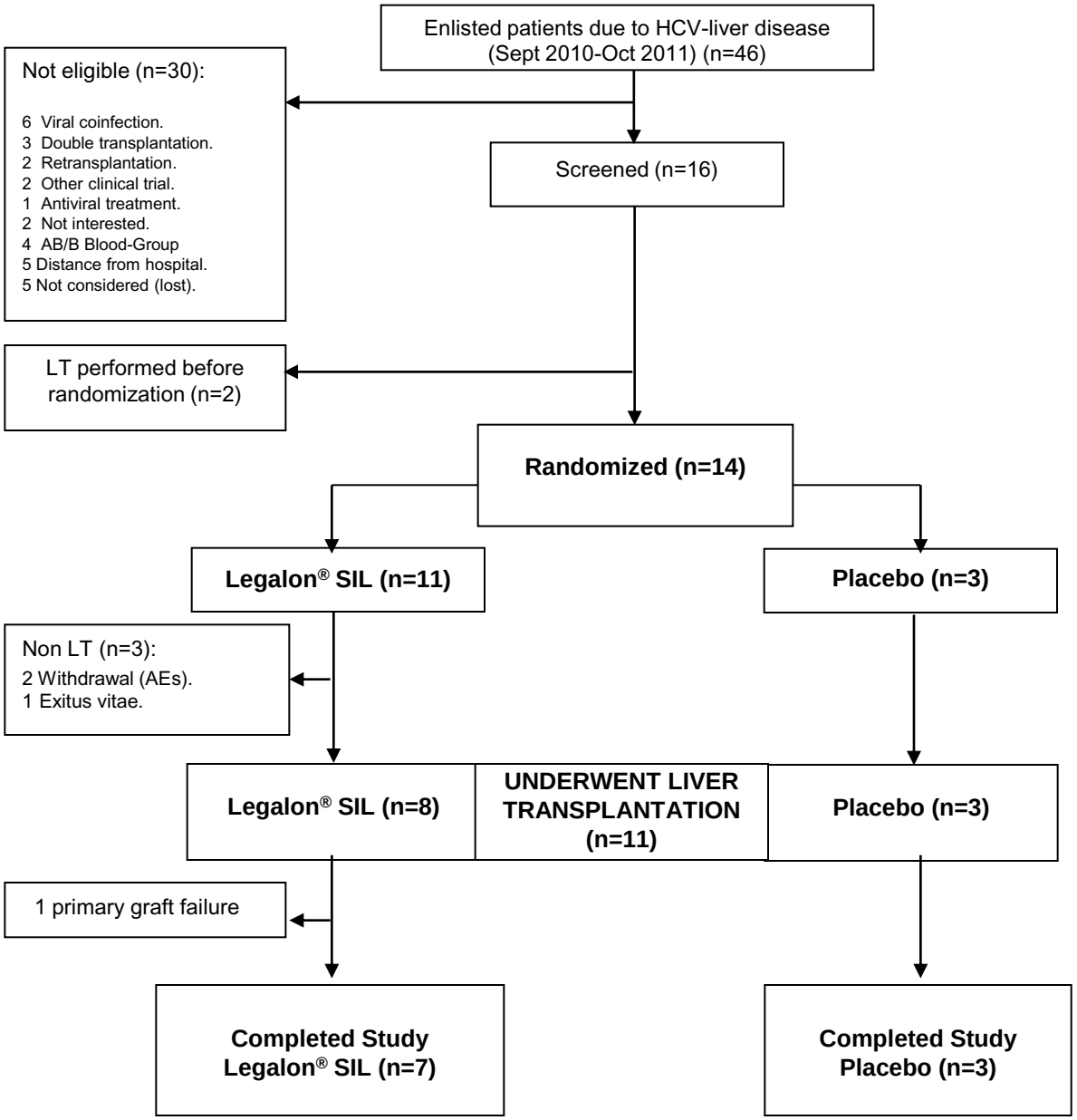
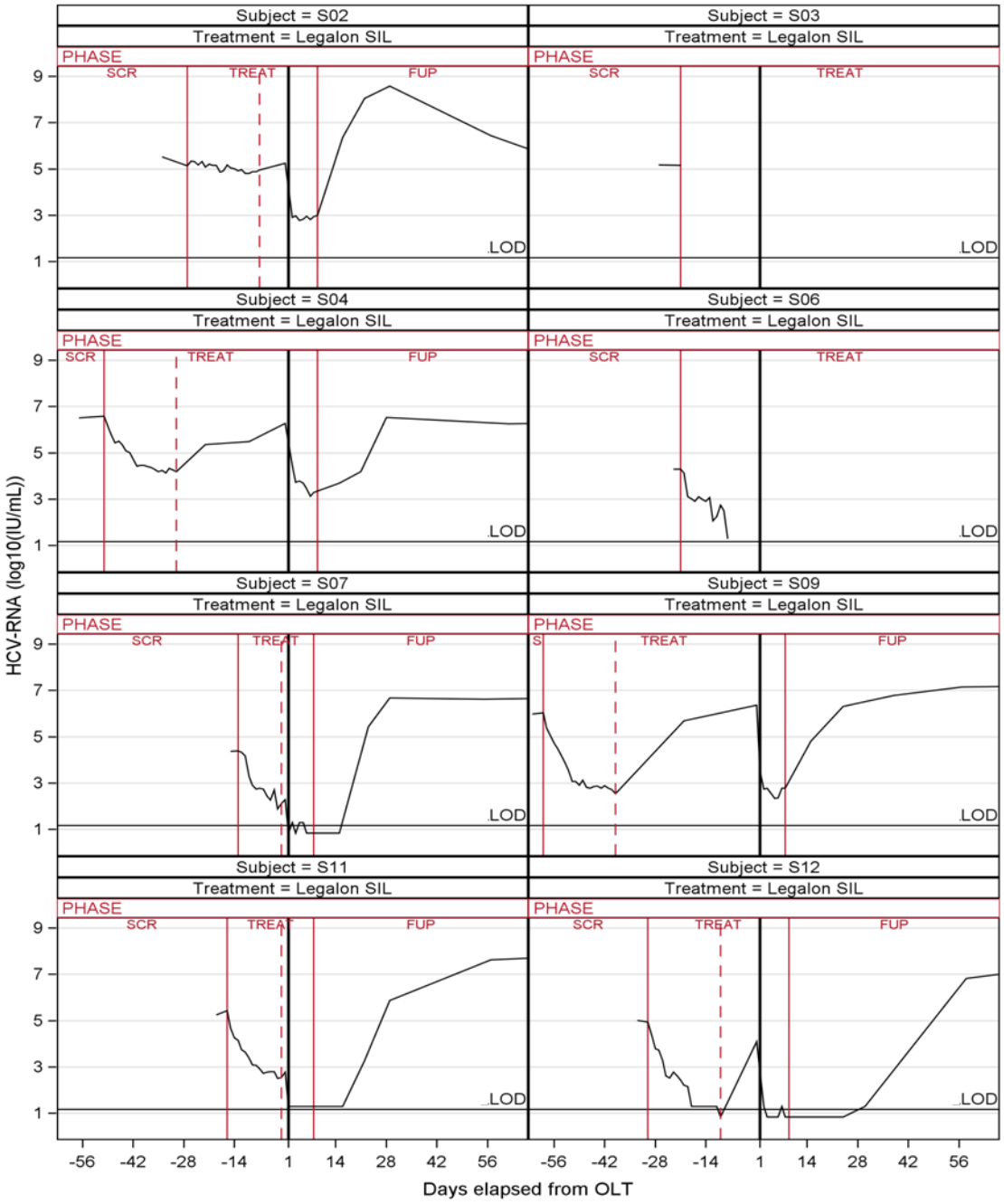


Figure 2A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Treatment = Legalon SIL
PHASE
SCR
TREAT
FUP
LOD
HCV-RNA (log10(IU/mL))
Days elapsed from OLT
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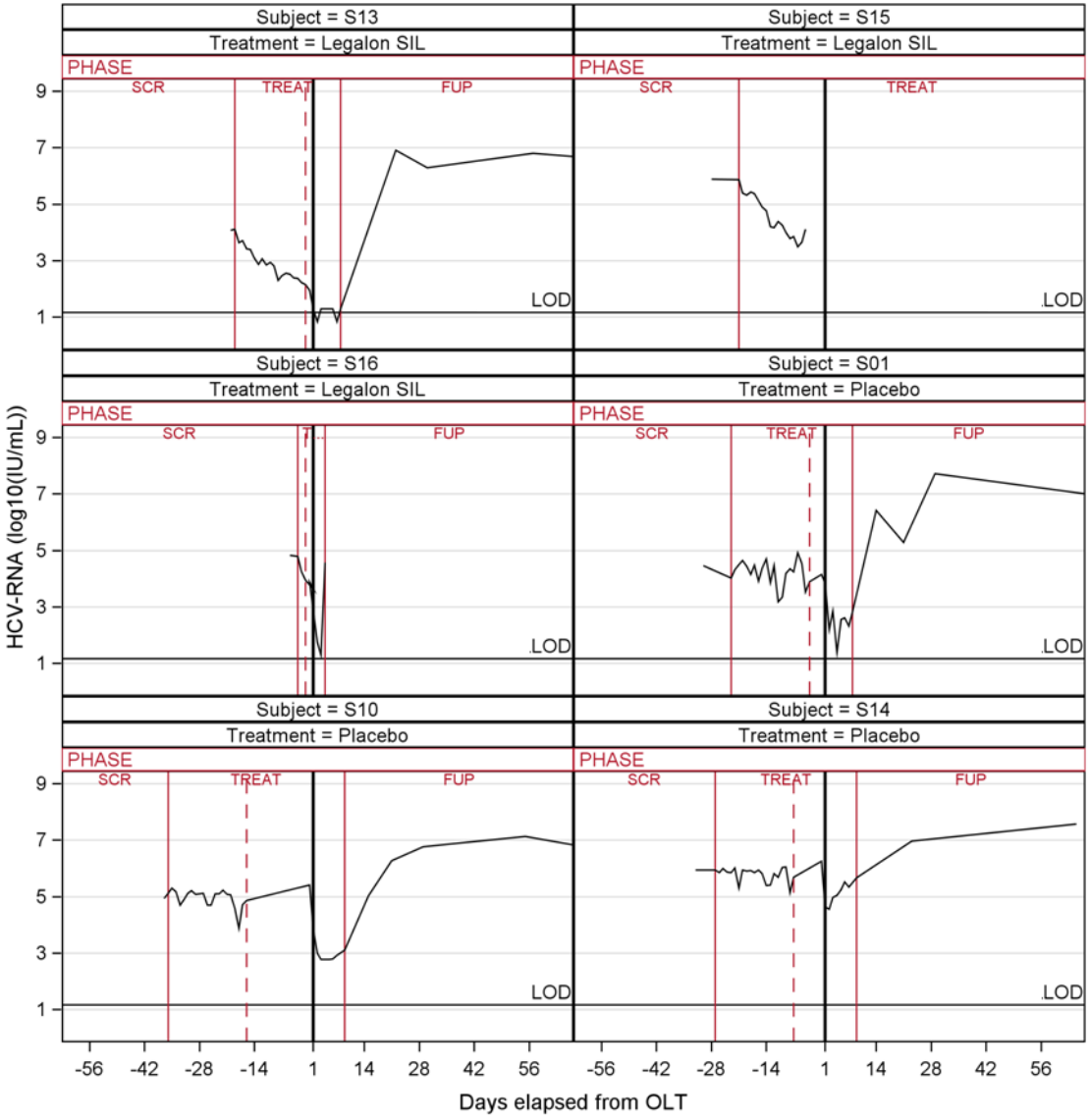
-42
-28
-14
1
14
28
42
56
1
3
5
7
9

Figure 2A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Treatment = Placebo
Subject = S14
Treatment = Placebo
PHASE
SCR
TREAT
FUP
LOD
HCV-RNA (log10(IU/mL))
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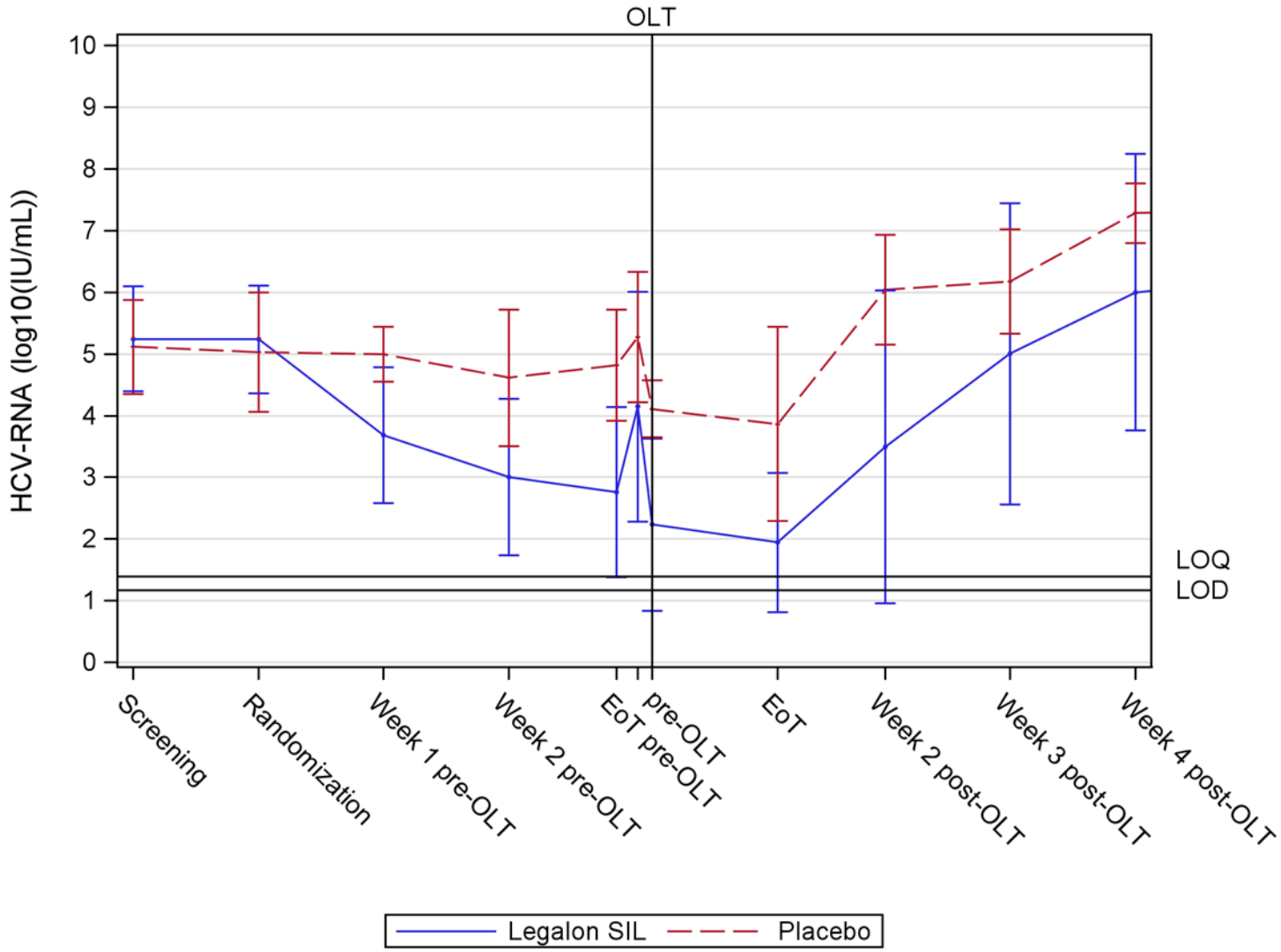
3
1
-56
-42
-28
-14
1
14
28
42
56
Days elapsed from OLT

Figure 2B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9
8
7
6
5
4
3
2
1
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LOQ
LOD
Screening
Randomization
Week 1 pre-OLT
Week 2 pre-OLT
EoT pre-OLT
pre-OLT
EoT
Week 2 post-OLT
Week 3 post-OLT
Week 4 post-OLT
Legalon SIL
Placebo