Optimization of an Interferon-free Hepatitis C Virus Therapy Regimen Containing the HCV NS3/4A Protease Inhibitor Faldaprevir, the Non-nucleoside NS5B Inhibitor Deleobuvir, and Ribavirin for Genotype-1b-infected Patients

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IDWeek 2013

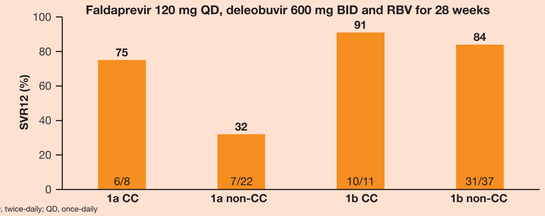
INTRODUCTION

- New direct acting antivirals (DAAs) currently in development for treatment of chronic hepatitis c virus (HCV) are being tested in conjunction with and without both pegylated interferon-alpha and ribavirin (PegIFN/RBV)
  - Faldaprevir is an NS3/4A HCV protease inhibitor currently in phase 3 trials, with a pharmacokinetic profile that supports once-daily (QD) dosing
  - Deleobuvir is an HCV NS5B polymerase inhibitor with a pharmacokinetic profile that supports twice-daily (BID) dosing

RATIONALE

- The aim of SOUND-C3 was to optimize IFN-free treatment with faldaprevir, deleobuvir, and RBV following the SOUND-C2 study:
  - SOUND-C2 investigated the safety, efficacy, and treatment duration of faldaprevir 120 mg QD, deleobuvir 600 mg BID or TID with or without RBV for 16, 28, or 40 weeks in 362 HCV GT1-infected patients
    - Cirrhotic patients were included and accounted for 9% of the total population
  - In SOUND-C2, patients infected with HCV GT-1b who received faldaprevir 120 mg QD, deleobuvir 600 mg BID, and RBV achieved an SVR12 rate of 85%
  - Patients infected with HCV GT-1a and carrying the IL28B CC genotype achieved a similar SVR12 to those with GT-1b (Figure 1)
  - In SOUND-C2 the deleobuvir BID regimen had a 28-week duration; the BID regimen was tested for 16 weeks in SOUND-C3[1]

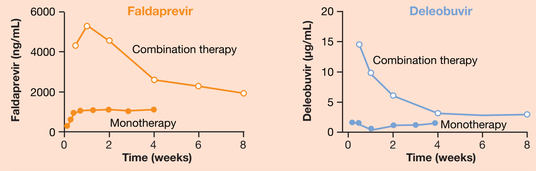
Figure 1. SOUND-C2: SVR12 by HCV GT-1 subtype and IL28B genotype



BID, twice-daily; QD, once-daily

- Pharmacokinetic and pharmacodynamic analysis in SOUND-C2 indicated an interaction between faldaprevir and deleobuvir that increased plasma concentrations of each drug (Figure 2)[2]

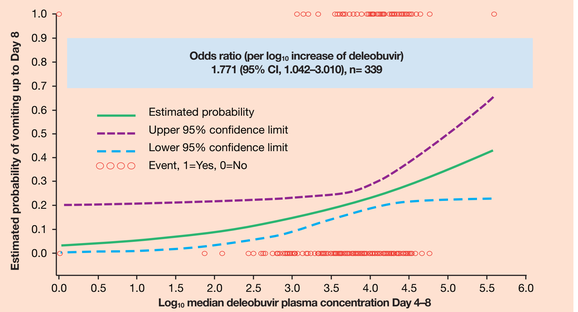
Figure 2. Pharmacokinetics of faldaprevir and deleobuvir in SOUND-C2



	UGT1A1	OATP	P-gp	MRP-2	BCRP
Faldaprevir	Inhibitor	Substrate	Substrate Inhibitor	Substrate	Inhibitor
Deleobuvir	Substrate	Inhibitor	Substrate Inhibitor	Inhibitor	Substrate

- SOUND-C2 included a loading dose of deleobuvir 1200 mg on Day 1 leading to high plasma concentrations that were associated with an increased incidence of gastrointestinal (GI) adverse events (AEs) (Figure 3)[3]

Figure 3. Delobuvir plasma levels correlate with GI AEs in SOUND-C2



METHODS

- The Phase 2b SOUND-C3 study (N=32) tested the BID regimen from SOUND-C2 for a period of only 16 weeks (Figure 4); the primary endpoint was SVR12 and patients with compensated liver cirrhosis were eligible and accounted for 13% of the population
- Treatment-naïve GT-1a patients (n=12) carrying the IL28b CC genotype (rs12979860, GT-1a-CC) and GT-1b patients (n=20) carrying any IL28b genotype were treated with faldaprevir 120 mg QD + deleobuvir 600 mg BID
- No loading dose of deleobuvir was administered on Day 1 in SOUND-C3
- Baseline characteristics are shown in Table 1

Figure 4. SOUND-C3 trial design

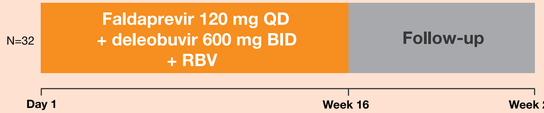


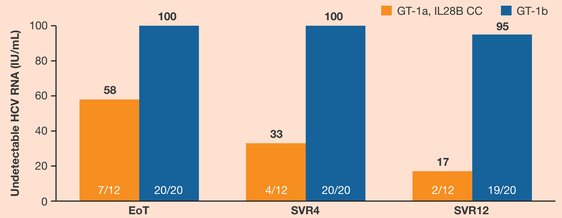
Table 1. Baseline characteristics

	GT-1a (n=12)	GT-1b (n=20)
Mean age, years (SD)	47 (5)	50 (15)
Male, n (%)	7 (58)	5 (25)
Caucasian, n (%)	12 (100)	20 (100)
Mean BMI, kg/m^2 (SD)	26 (4)	26 (4)
IL28B CC, n (%)	12 (100)	3 (15)
Liver cirrhosis, n (%)	0	4 (20)
Mean baseline HCV RNA, log$_{10}$ IU/mL (SD)	6.5 (0.7)	6.3 (0.7)
Baseline HCV RNA ≥800,000 IU/mL, n (%)	10 (83)	17 (85)

RESULTS

- The interferon-free combination of faldaprevir, deleobuvir and RBV for 16 weeks was highly efficacious in patients infected with HCV GT-1b with SVR12 rates of 95% (Figure 5)

Figure 5. Primary endpoint SVR 12 (ITT)



EoT, end of treatment; ITT, Intention-to-treat analysis.

- One GT-1b-infected patient discontinued treatment at Day 69 due to AEs, did not achieve SVR12, and subsequently relapsed
- Another GT-1b infected patient discontinued treatment early at Day 41 due to AEs but went on to achieve SVR12
- Eight GT-1a treatment-naïve patients experienced rebound or relapse, two patients were below the limit of detection (BLD) (~10 IU/mL) at SVR12 follow-up, and one patient discontinued while BLD and did not complete follow-up (Figure 6)
- Adverse events and worst on-treatment changes in laboratory values are shown in Tables 2 & 3

Table 2. Adverse event summary

AE, n (%)	N=32
Any AE	30 (94)
Serious AEs	1 (3)
Dehydration	1 (3)[a]
AEs leading to discontinuation	3 (9)
Dehydration	1 (3)[a]
Vomiting	1 (3)
Pruritus	1 (3)
Any AE Grade ≥2	15 (47)
AEs of interest of highest frequency	
Anemia	5 (16)
Fatigue	3 (9)
Vomiting	3 (9)
Nausea	3 (9)
Life threatening AEs	0

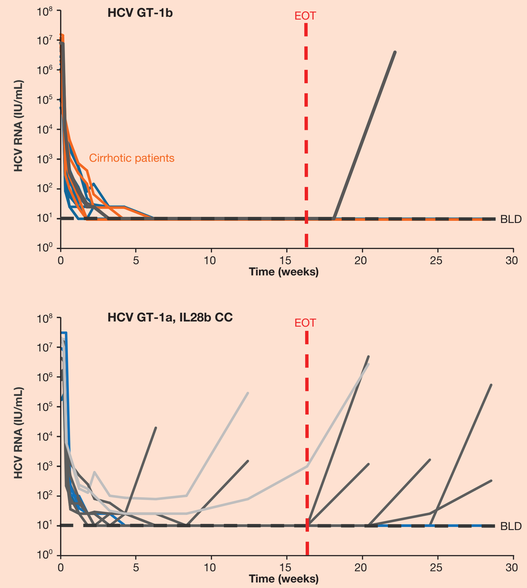
[a]Same patient

Table 3. Grade 3 and 4 changes in laboratory values

Grade 3 and 4 adverse events, n (%)		N=32
Hemoglobin	≤8.9 g/dL	4 (13)
White blood cell count	≤1499/mm^3	0
Lymphocytes	≤499/mm^3	0
Neutrophils	≤749/mm^3	1 (3)[a]
Platelets	≤49,999/mm^3	0
ALT	≥5.1 x ULN	0
Bilirubin (total)	≥2.6 x ULN	14 (44)

DAIDS Grade 3 and 4 laboratory changes shown. Three patients had Grade 4 bilirubin changes (>5 x ULN); all other events were Grade 3. [a]One patient had severe neutropenia and had received metamizole (dipyrone) for from Day 14 to Day 22. Neutropenia was seen at visits on Day 30, 44, and 58. Neutrophil levels returned to normal at the next visit (Day 90). ALT, alanine transaminase; DAIDS, division of AIDS.

Figure 6. Individual HCV RNA over time



EOT, end of treatment. Graph truncated at first measurement >1000 IU/mL after nadir. Last observation carried forward (LOCF) for missing time points. Lower panel: One patient discontinued at BLD and could not complete follow-up visits due to personal circumstances. LOCF for missing time points.

CONCLUSIONS

- The interferon-free combination of faldaprevir, deleobuvir, and RBV for 16 weeks was highly efficacious in patients infected with HCV GT-1b with SVR12 rates of 95%
- All four GT-1b-infected patients with cirrhosis achieved SVR12
- The combination of faldaprevir, deleobuvir, and RBV was well tolerated with few discontinuations due to AEs
- Virological response in GT-1a-infected patients was significantly lower

References: **1.** Zeuzem et al. J Hepatol. 2012;56(Suppl2):S45 (Abstract 101). **2.** Sabo et al. Hepatology. 2012;56:568A (Abstract 777). **3.** SOUND-C2, data on file.

Acknowledgments: This poster was originally presented at the The German Society for Digestive and Metabolic Diseases, September 11-14, 2013, Nürnberg, Germany. This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and were fully responsible for all content and editorial decisions, and were involved at all stages of poster development. The authors received no compensation related to the development of the poster, but are consultants for BIPI and did receive research grant support for this study. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Katharine Howe of Adelphi Communications Ltd. Editorial support and formatting assistance for this poster was provided by Adelphi Communications, which was contracted and compensated by BIPI for these services.

Disclosures: P Mantry has served as a speaker and received grant and research support from Abbott, Boehringer Ingelheim, Genentech, Merck, Salix, and Vertex. M Schuchmann has received medical writing assistance from Boehringer Ingelheim; served as a consultant for Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Norgine, and Roche; has received grants/grants pending from DFG; and has served on speakers' bureaus for Bristol-Myers Squibb, Boehringer Ingelheim, Falk, Gilead, Merck, MSD, and Roche. A Lohse has received grant/research support from Roche, MSD, Boehringer Ingelheim, Bristol-Myers Squibb, and Gilead and has served as a speaker/teacher for Roche, MSD, and Falk. K Arasteh has received grant/research support, medical writing assistance, and served as a board member, consultant, and on speakers' bureaus for Boehringer Ingelheim. M Manns has served as a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Janssen, Merck, Novartis, and Roche; has received grants/grants pending from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis, and Roche; and has served on speakers' bureaus for Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche. T Berg has served as a consultant for and has grants/grants pending from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, MSD, Novartis, Roche, and Vertex; and has served as a board member and on speakers' bureaus for AbbVie, Bristol-Myers Squibb, Gilead, MSD, Novartis, Roche, and Vertex. S Mauss has served as a speaker for Abbott, Bristol-Myers Squibb, Tibotec, and Roche; has served on advisory boards for Abbot, GlaxoSmithKline, Gilead, and Tibotec; and has received research funding from Abbott and Roche. M Geissler has nothing to disclose. Federic Mensa is an employee of Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT. WO Böcher is an employee of Boehringer Ingelheim Pharma, Biberach, Germany. S Zeuzem has served as a consultant for Abbot, Achillion, AstraZeneca, BMS, Boehringer Ingelheim, Gilead, Idenix, Janssen, Merck, Novartis, Presidio, Roche, Santaris, and Vertex; and has served on speakers' bureaus for Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, MSD, Roche and Janssen.