A POOLED ANALYSIS OF TWO RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIALS (STARTVerso1 AND 2) OF FALDAPREVIR PLUS PEGYLATED INTERFERON α-2a AND RIBAVIRIN IN TREATMENT-NAÏVE PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE-1 INFECTION

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BACKGROUND

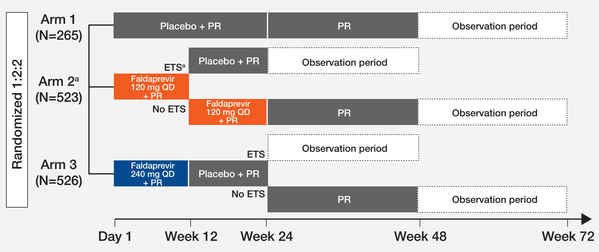
- Faldaprevir (FDV) is a potent inhibitor of HCV NS3/4A.[1]
- FDV has broad antiviral activity against HCV genotypes (GT) 1, 4, 5, and 6 in vitro.[1]
- FDV pharmacokinetics support oral, once-daily administration.[2]
- In Phase II studies, FDV plus pegylated interferon α-2a and ribavirin (PR) demonstrated:[3]
  - Significantly higher sustained virologic response (SVR) versus placebo
  - Favorable safety and tolerability profile.
- Three Phase III trials of FDV plus PR in HCV GT-1 are complete.
  - FDV is also being investigated in Phase III interferon-free trials.
- STARTVerso1 (Europe and Japan; NCT01343888) and STARTVerso2 (North America, South Korea, and Taiwan; NCT01297270) assessed the safety and efficacy of FDV plus PR in treatment-naïve patients with chronic HCV GT-1 infection.
- We present here the results of a pre-specified pooled analysis of the primary efficacy and safety results from these 2 studies.
  - Efficacy results across different patient subgroups in the pooled population are presented in Poster 1114.

METHODS

STUDY DESIGN

- Multicenter, randomized, double-blind, placebo-controlled Phase III studies (N=1314).
- Study design was similar for both studies (summarized in **Figure 1**).
- Adult, treatment-naïve patients with chronic GT-1 HCV infection were randomized 1:2:2 to receive 24 or 48 weeks of PR plus:
  - Placebo for 24 weeks (arm 1, N=265)
  - FDV 120 mg QD for 12 weeks or 24 weeks (arm 2, N=523)
    - In STARTVerso1, patients who achieved early treatment success (ETS, HCV RNA <25 IU/mL at week 4 and undetectable at week 8) stopped FDV at week 12
    - In STARTVerso2, all patients in this arm received FDV for 24 weeks
  - FDV 240 mg QD for 12 weeks (arm 3, N=526).
- In arms 2 and 3, patients achieving ETS stopped all treatment at week 24.
- The primary endpoint in both studies was SVR at 12 weeks after completion of treatment (SVR12).

FIGURE 1. Study design



Randomized/treated: STARTVerso1 N=656/652; STARTVerso2 N=658/657.
[a]In STARTVerso2, all patients in arm 2 received 24 weeks of faldaprevir, at which stage patients who achieved ETS could stop all treatment.
ETS, early treatment success, defined as HCV RNA <25 IU/mL at week 4 and undetectable at week 8 (Roche COBAS® Taqman HCV/HPS assay). PR, pegylated interferon α-2a 180 µg/week and weight-based ribavirin.

ANALYSES

- Efficacy analyses used the full analysis set (all randomized patients who received at least 1 dose of study treatment, intent-to-treat [ITT] population).
  - In a pre-planned pooled analysis, data from the 2 studies were combined to provide a larger sample size for integrated analyses of dose and duration.
  - Primary analysis compared each FDV plus PR regimen versus placebo plus PR using the Cochran–Mantel–Haenszel test, stratified by study (STARTVerso1 or 2), GT-1 subtype (1a, 1b, other GT-1), and race (black, Asian, other).
- The safety analysis set included all patients who received at least 1 dose of study medication regardless of randomization.
  - Safety was assessed by monitoring adverse events (AEs) and laboratory parameters throughout the trial and for 30 days after the end of treatment.
  - AEs were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.

RESULTS

PATIENTS

- Of 1314 randomized patients, 1309 received at least 1 dose of study medication (652 and 657 in STARTVerso1 and 2, respectively).
- Baseline patient demographics and disease characteristics were well balanced across the pooled treatment groups (**Table 1**).
  - Approximately 20% of patients were from Asia with 40% each from Europe and North America.
  - Approximately half of the patients were infected with HCV GT-1a.
  - Approximately 40% of patients had an IL28B (rs12979860) CC genotype across the treatment groups.
  - Approximately 10% of patients had cirrhosis.
  - Among patients from North America, 16% were black/African American, 68% had an IL28B non-CC genotype, and 74% were infected with HCV GT-1a.

TABLE 1. Baseline characteristics

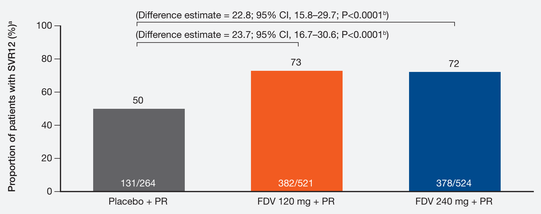
		Placebo + PR N=264	FDV 120 mg + PR N=521	FDV 240 mg + PR N=524
Male, n (%)		153 (58)	278 (53)	300 (57)
Race, n (%)	White	188 (71)	374 (72)	372 (71)
	Asian	53 (20)	104 (20)	102 (19)
	Black	19 (7)	36 (7)	39 (7)
Region, n (%)	Asia	47 (18)	99 (19)	97 (19)
	Europe	108 (41)	207 (40)	211 (40)
	N. America	109 (41)	215 (41)	216 (41)
Mean age, years (SD)		48.4 (10.9)	49.0 (10.8)	49.4 (10.8)
Mean BMI, kg/m² (SD)		26.2 (4.8)	26.2 (4.9)	26.2 (4.9)
HCV GT-1a subtype[a], n (%)		125 (47)	247 (47)	253 (48)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (SD)		6.4 (0.7)	6.4 (0.8)	6.3 (0.8)
Baseline HCV RNA ≥800,000 IU/mL, n (%)		209 (79)	418 (80)	397 (76)
IL28B (rs12979860), n (%)	CC	94 (36)	213 (41)	213 (41)
	CT	126 (48)	239 (46)	235 (45)
	TT	43 (16)	68 (13)	71 (14)
Fibrosis stage[b], n (%)	F0–F2	205 (78)	408 (78)	420 (80)
	F3/F4	57 (22)	109 (21)	97 (19)
Cirrhosis present[c], n (%)		30 (11)	45 (9)	40 (8)

[a]HCV GT-1 subtype analyses by sequencing of NS3. [b]If no Metavir, then Fibroscan result was used (<9.5 F0–F2, ≥9.5 F3/F4). If neither was available and patient was indicated to have cirrhosis, then F3/F4 was recorded. [c]Cirrhosis determined by investigator based on Fibroscan, biopsy, and/or other clinical parameters.
BMI, body mass index; GT, genotype; SD, standard deviation.

EFFICACY

- SVR12 rates in the pooled ITT population were significantly higher for patients treated with FDV 120 mg or 240 mg compared with placebo (**Figure 2a**).
  - SVR12 rates were comparable in FDV 120 mg and FDV 240 mg arms.
- ETS was achieved by 84% of patients treated with FDV (**Figure 2b**)
- Among patients with ETS:
  - 83% achieved SVR12 (**Figure 2c**)
  - SVR12 rates were comparable among those receiving 12 weeks and 24 weeks of FDV (**Figure 2d**).
- SVR12 rates were lower in patients from North America than in patients from Asia or Europe in all treatment groups (**Figure 3**).

FIGURE 2a. SVR12



[a]ITT analysis. SVR12 rates adjusted for trial, race, and GT-1 subtype.
[b]Cochran–Mantel–Haenszel test.

FIGURE 2b. ETS

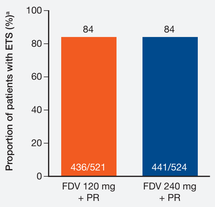
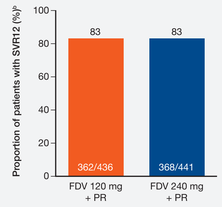
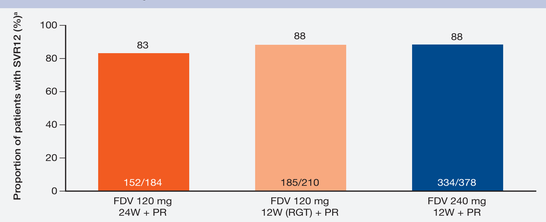


FIGURE 2c. SVR12 in patients who achieved ETS



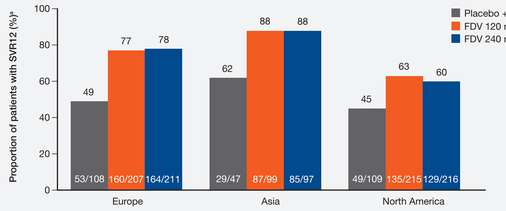
[a]ETS: HCV RNA <25 IU/mL (detected or undetected) at week 4 and <25 IU/mL (undetected) at week 8. ITT analysis.
[b]Denominator is number with ETS.

FIGURE 2d. ETS and SVR12 by duration of FDV



ETS: HCV RNA <25 IU/mL (detected or undetected) at week 4 and <25 IU/mL (undetected) at week 8. RGT, response guided therapy (STARTVerso1 only); W, weeks.
[a]Denominator: patients with ETS who completed planned duration of FDV and PR.

FIGURE 3. SVR12 by region

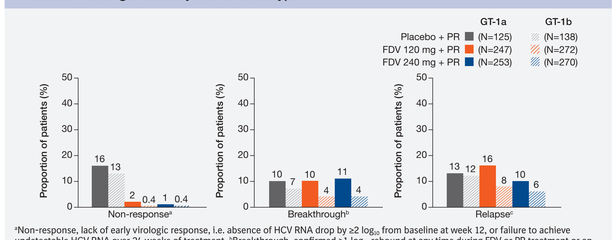


[a]ITT analysis.
Europe = Switzerland, Portugal, Austria, Belgium, Germany, Spain, Russian Federation, Romania, UK, France; Asia = Taiwan, South Korea, Japan; North America = USA, Canada.

VIROLOGIC FAILURE

- Among FDV-treated patients:
  - There were few non-responders (≤2%) (**Figure 4**)
  - Most cases of virologic failure resulted from on-treatment breakthrough or post-treatment relapse (**Figure 4**)
  - Breakthrough rates while taking FDV were low and comparable across the two dose groups.
- Among patients in the placebo arm the most frequent cause of virologic failure was non-response (**Figure 4**).

FIGURE 4. Virologic failure by HCV GT-1 subtype



[a]Non-response, lack of early virologic response, i.e. absence of HCV RNA drop by ≥2 $\log_{10}$ from baseline at week 12, or failure to achieve undetectable HCV RNA over 24 weeks of treatment. [b]Breakthrough, confirmed ≥1 $\log_{10}$ rebound at any time during FDV or PR treatment or an increase to HCV RNA >25 IU/mL after being <25 IU/mL (detected or undetected).
[c]Relapse, HCV RNA undetectable at end of treatment and virologic rebound in the post-treatment period.

BASELINE POLYMORPHISMS

- No common baseline NS3 polymorphism was associated with a reduction in SVR12, including the GT-1a Q80K polymorphism.
- Q80K was observed in 208/615 (33.8%) patients with HCV GT-1a infection.
  - SVR12 in 198/311 (64%) of FDV-treated patients with wild-type Q80.
  - SVR12 in 108/164 (66%) of FDV-treated patients with Q80K, K/Q (n=1), or K/R (n=3).
- NS3 R155 and D168 variants associated with resistance to FDV were observed in 8/1289 (0.6%) baseline sequences.
  - Three patients with GT-1a HCV: 2 with R155K and 1 with D168D/E.
  - Five patients with GT-1b HCV: 4 with D168D/E and 1 with D168D/E.
  - 6/6 (100%) FDV-treated patients with R155K, D168E, or D168D/E achieved SVR12.

SAFETY

- Similar incidence across all treatment groups for:
  - AEs, serious AEs, and AEs leading to discontinuation (**Table 2**)
  - Laboratory abnormalities, hemoglobin reduction, and anemia (**Table 2**, **Table 3** and **Figure 5**).
- Compared with placebo + PR, FDV + PR was associated with a greater frequency of gastrointestinal events, rash, and bilirubin elevations.
  - These events were infrequently severe or serious and infrequently led to discontinuation.
  - Bilirubin elevations were characterized by a predominance of unconjugated bilirubin, peaked around week 2 and rapidly returned to baseline levels in all patients after completion of FDV treatment.
  - In vitro studies suggest these increases are predominantly due to FDV-mediated inhibition of the bilirubin-conjugating enzyme UDP-glucuronosyltransferase-1A1 (UGT1A1).[4]

TABLE 2. Summary of adverse events (AEs)

	Placebo + PR N=264	FDV 120 mg + PR N=521	FDV 240 mg + PR N=524
Any AE, n (%)	255 (97)	511 (98)	514 (98)
AEs leading to discontinuation of all medication, n (%)	10 (4)	27 (5)	40 (8)
AEs leading to discontinuation of FDV or placebo only, n (%)	1 (<1)	6 (1)	14 (3)
Serious AEs, n (%)	16 (6)	39 (7)	43 (8)
AEs of at least moderate intensity (any)[a], n (%)	156 (59)	302 (58)	332 (63)
Rash	11 (4)	39 (7)	50 (10)
Photosensitivity	0	0	3 (1)
GI	19 (7)	58 (11)	96 (18)
Anemia	38 (14)	73 (14)	70 (13)
Bilirubin associated	2 (1)	18 (3)	47 (9)

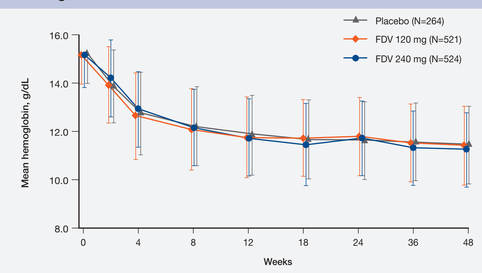
One patient with cirrhosis at baseline developed acute-on-chronic liver failure after 16 days of FDV (240 mg) and PR, discontinued all treatment, and died 12 days later. The event was considered not related to FDV but to pegylated interferon by investigator.
[a]DAIDS Grade 2 to 4; protocol-defined AEs of special interest.
DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; GI, gastrointestinal.

TABLE 3. Grade ≥3 laboratory abnormalities during the first 24 weeks of treatment

	Placebo + PR N=264	FDV 120 mg + PR N=521	FDV 240 mg + PR N=524
Platelets ≤50,000/mm³, n (%)	7 (3)	16 (3)	16 (3)
Neutrophils ≤750/mm³, n (%)	46 (17)	107 (21)	74 (14)
Lymphocytes ≤500/mm³, n (%)	28 (11)	94 (18)	93 (18)
ALT ≥5 x ULN, n (%)	8 (3)	12 (2)	9 (2)
Total bilirubin ≥2.5 x ULN, n (%)	1 (<1)	65 (12)	243 (46)

Laboratory value categories based on the DAIDS grading system; ULN, upper limit of normal.

FIGURE 5. Hemoglobin over time



SUMMARY

- FDV plus PR increased SVR12 compared with PR alone.
- SVR12 rates were lower in patients from North America than in patients from other regions.
  - Most differences in SVR in the STARTVerso1 and STARTVerso2 trials are explained by baseline characteristics:
    - Reasons for virologic failure are similar when adjusting for different factors impacting response (race, HCV genotype, IL28B genotype, HCV RNA level, GGT level, presence of cirrhosis)
    - However, there was a higher discontinuation rate for reasons other than virologic failure in North America, indicating different AE management and treatment discontinuation, which impacted the overall response.
- FDV efficacy was similar at 120 mg and 240 mg doses and with 12 or 24 weeks of treatment.
- Among FDV-treated patients, 84% achieved ETS and were eligible to stop all treatment at week 24.
- In patients with an ETS, SVR12 was achieved by:
  - 83% overall
  - 88% of patients who received 12 weeks of FDV (120 mg or 240 mg) and a total of 24 weeks of PR.
- FDV was well tolerated at both doses.
- At a dose of 120 mg FDV safety profile was comparable with that of placebo.

CONCLUSIONS

- The addition of FDV to PR was efficacious in treatment-naïve patients infected with HCV GT-1.
  - FDV plus PR showed increases in SVR regardless of GT1 sub-type, IL28B genotype, liver disease stage, and other factors associated with response to PR.
  - The treatment regimen has the potential to improve tolerability and convenience compared with first-generation protease inhibitors.

- FDV is also being investigated in interferon-free combinations:
  - In the SOUND-C3 study of FDV in combination with the non-nucleoside NS5B inhibitor deleobuvir (DBV) plus ribavirin, SVR12 rates of up to 95% were achieved in patients infected with HCV GT-1b (Poster 1102)
  - Early data from a Phase II study with FDV plus DBV and the NS5A inhibitor PPI-668 in difficult to treat HCV GT-1a patients showed a rapid virologic response in 97% of patients (Poster LB-22).

REFERENCES: 1. White PW, et al. *Antimicrob Agents Chemother* 2010;54:4611–4618. **2.** Manns MP, et al. *J Hepatol* 2011;54:1114–1122. **3.** Sulkowski MS, et al. *Hepatology* 2013;57:2143–2154. **4.** Sane R, et al. *J Hepatol* 2011; 54(Suppl. 1):S488.

DISCLOSURES

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