# HIGH RATE OF SUSTAINED VIROLOGIC RESPONSE IN PATIENTS WITH HCV GENOTYPE-1A INFECTION: A PHASE 2 TRIAL OF FALDAPREVIR, DELEOBUVIR AND PPI-668, WITH AND WITHOUT RIBAVIRIN

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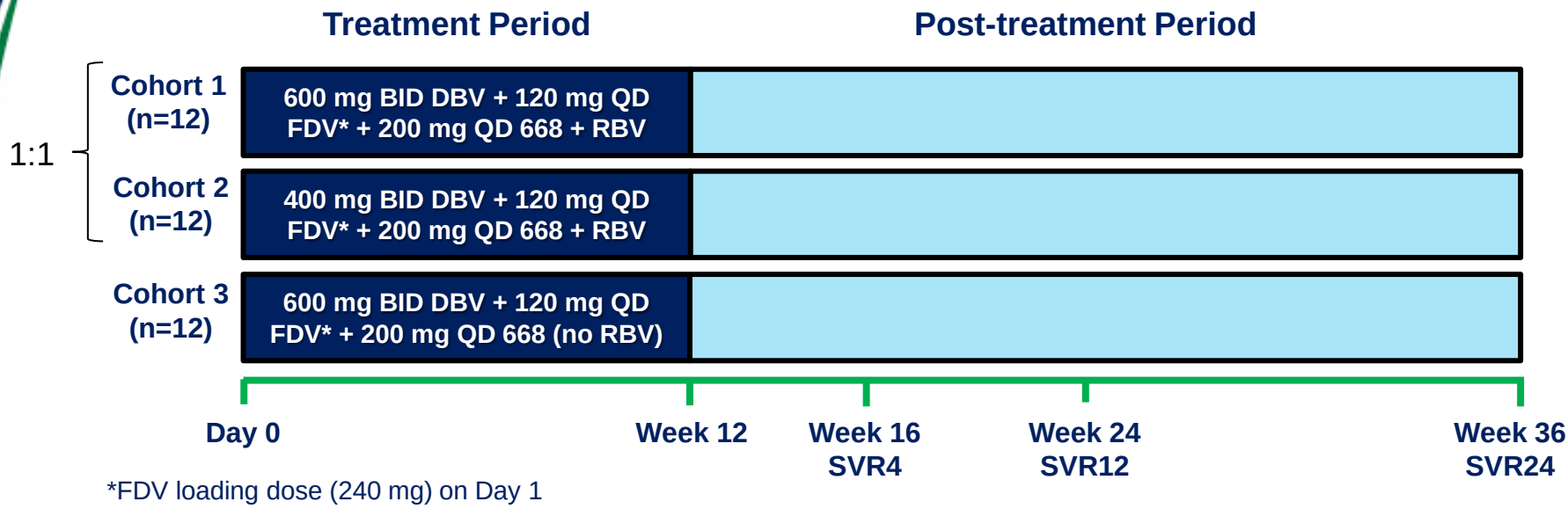
# Study Background

- This is a Phase 2a study evaluating 3 direct-acting antivirals (DAA) with and without ribavirin (RBV)
  - PPI-668 (Presidio; NS5A inhibitor)
  - Faldaprevir (FDV; B-I protease inhibitor)
  - Deleobuvir (DBV; B-I Non-nuc, thumb 1 inhibitor)
- Previous Phase 2 studies with FDV + DBV + RBV had <50% sustained virologic response (SVR) rates in GT-1a patients (Zeuzem S, et al. *N Engl J Med. 2013;369:630–689*)
- Primary objective: Assess the efficacy of 12 weeks treatment with the investigational regimen of PPI-668 plus FDV and DBV in patients with HCV GT-1a infection
  - With and without RBV
- Secondary objectives
  - Assess two dose levels of DBV (600 mg BID vs 400 mg BID)
  - Assess the safety/tolerability of each of the 3 treatment regimens
  - Evaluate the pharmacokinetics (PK) of all 3 drugs when administered together

# Entry Criteria

- Key entry criteria included:
  - Chronic HCV; genotype-1a
  - Treatment-naïve
  - Serum HCV RNA at screening >5 x $10^5$ IU/mL
  - The more favorable IL28B ‘CC’ genotype was restricted to only one-third of patients
  - No history of signs/symptoms of hepatic decompensation, no known cirrhosis; FibroTest score < 0.75 and APRI score < 2 at Screening

# Study Design and Methods




*FDV loading dose (240 mg) on Day 1

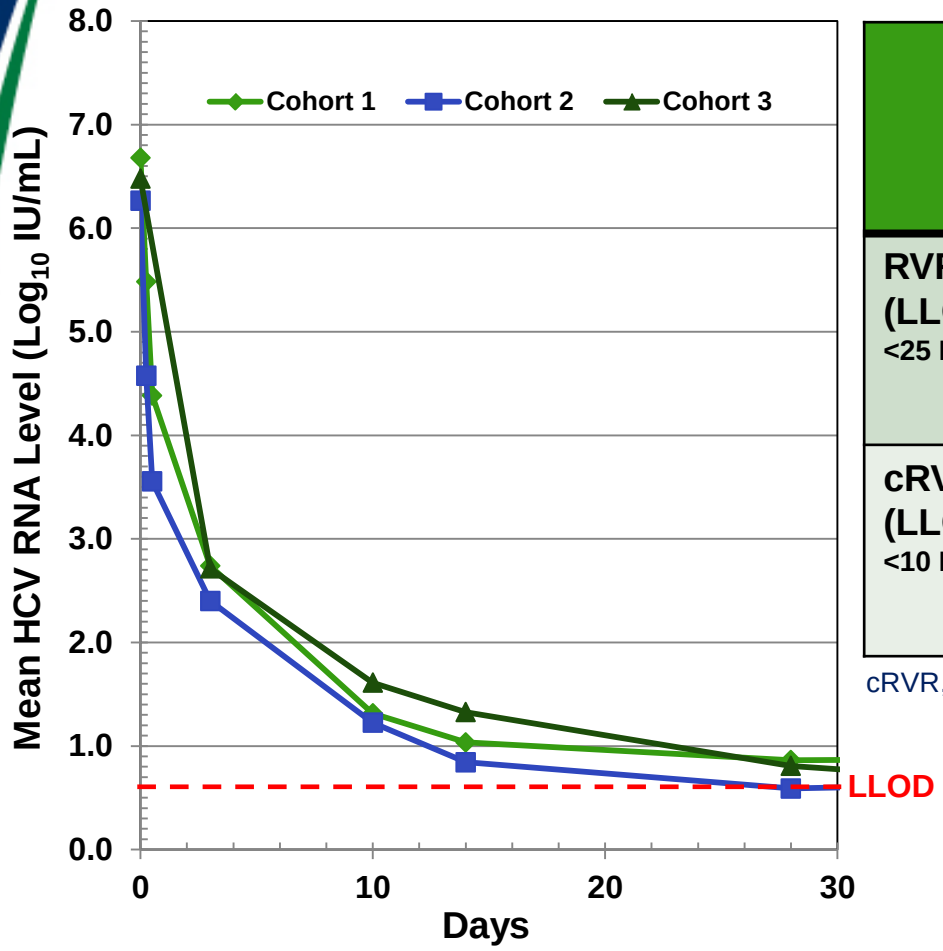
- All patients treated for 12 weeks, with 24 weeks of follow-up
- Primary efficacy endpoint: SVR12 (HCV RNA < LLOD using Roche TaqMan™ HCV 2.0)
- Initiation of RBV-free Cohort 3 required HCV RNA ≤LLOQ at Week 2 in >70% of first 12 patients from Cohorts 1 and 2, with satisfactory safety/tolerability
- Weight-based RBV used for Cohorts 1 and 2
- NS3, NS5A, and NS5B sequencing of all baseline samples and any virologic breakthroughs or relapses

# Baseline Characteristics

| Cohort | Median Age Years (Range) | Gender %M/%F | Median HCV RNA $Log_{10}$ IU/mL (Range) | IL28B Genotype Non-CC, % | Median ALT IU/L (Range) |
|---|---|---|---|---|---|
| 1 (n=12) | 57 (30–65) | 83/17 | 6.63 (6.09-7.89) | 67% | 84 (30–239) |
| 2 (n=12) | 55 (42–62) | 67/33 | 6.40 (4.72-7.17) | 67% | 64 (9–409) |
| 3 (n=12) | 54 (22–71) | 64/36 | 6.68 (5.60-7.43) | 58% | 80 (39–169) |
| All (n=36) | 55 (22–71) | 71/29 | 6.54 (4.72-7.89) | 64% | 78 (9–409) |

- All patients were HCV GT-1a
- Patient population was 78% Caucasian, 19% African American, and 3% Asian-Pacific Islander
- Treatment groups were pre-stratified for IL28B genotypes, with the favorable ‘CC’ genotype limited to approximately one-third of patients
  - Overall study population: 36% CC and 64% non-CC (56% CT, 8%TT)

# Week 4 RVR and cRVR Across Cohorts

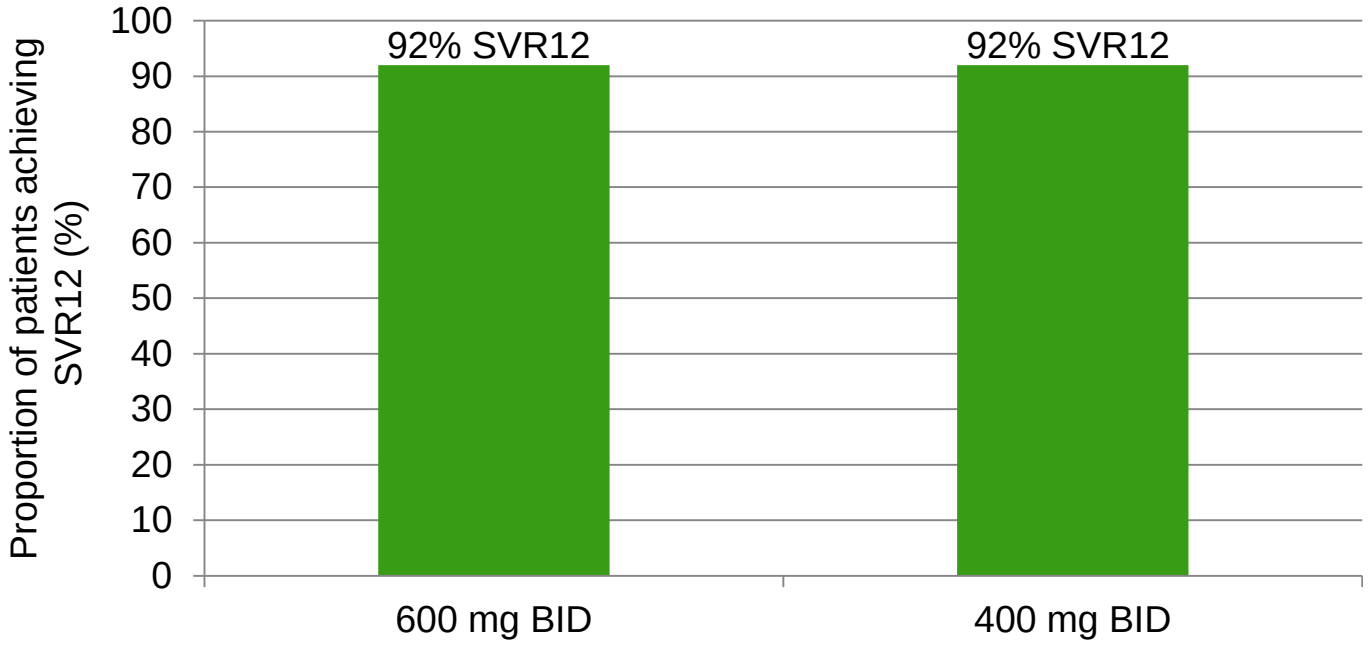



| | Cohort 1 600 mg DBV, (n/N) | Cohort 2 400 mg DBV, (n/N) | Cohort 3 (RBV-free), (n/N) | Total (n/N) |
|---|---|---|---|---|
| **RVR (LLOQ)** <25 IU/mL | 92% (11/12) | 100% (12/12) | 100% (12/12) | 97% (35/36) |
| **cRVR (LLOD)** <10 IU/mL | 75% (9/12) | 100% (12/12) | 75% (9/12) | 83% (30/36) |

cRVR, complete rapid virologic response; RVR, rapid virologic response

- cRVR achieved in 75–100% of patients, regardless of RBV or DBV dose

# SVR12 Results for Cohorts 1 and 2
## (DBV 600 mg BID vs. 400 mg BID)




- 92% (22/24) of patients achieved SVR12 in Cohorts 1 and 2, regardless of DBV dose; one efficacy failure in each cohort:
  - Cohort 1: A patient with virologic breakthrough at Week 5 had high-level linked pre-existing NS5A and NS5B resistance mutations in Baseline serum
  - Cohort 2: A patient relapsed at 4 weeks post-treatment
  - Of note, one Cohort 1 patient self-discontinued at Week 9 (due to side effects), but achieved SVR12 despite shorter treatment duration

# Results for Cohort 3 (RBV-free)

- 14 patients enrolled in Cohort 3 (2 replacements required)
  - One Cohort 3 patient was incarcerated after Day 10 visit (HCV RNA <LLOQ)
  - One patient had viral rebound due to non-compliance at Week 8
- Of the 12 remaining patients:
  - 8 patients achieved SVR12
  - 1 patient self discontinued treatment at Week 8, but has achieved SVR8 (patient continues to be followed)
  - 1 rebound at Week 12 associated with very low plasma concentrations for all three study DAAs
  - 2 patients relapsed at 4 weeks post-treatment
- 1 patient decompensated (variceal bleeding) between Screen and Baseline (seen at outlying hospital without informing study site). Patient achieved <LLOD at Week 2 and remained <LLOD through week 8, when he received a liver transplant. With only 8 weeks of pre-transplant study Rx, this patient exhibits SVR at 12 weeks post-transplant

# AEs Occurring in ≥5 Patients Overall, Regardless of Attribution to Study Drugs/RBV

| AE Term, n (%) | Cohort 1 600 mg DBV n=12 | Cohort 2 400 mg DBV n=12 | Cohort 3 RBV-free n=14* | TOTAL n=38 |
|---|---|---|---|---|
| Nausea | 9 (75) | 11 (92) | 7 (50) | 27 (71) |
| Fatigue | 4 (33) | 11 (92) | 8 (57) | 23 (61) |
| Diarrhea | 4 (33) | 4 (33) | 5 (36) | 13 (34) |
| Rash | 6 (50) | 1 (8) | 2 (14) | 9 (24) |
| Insomnia | 3 (25) | 5 (42) | 0 | 8 (21) |
| Anemia | 5 (42) | 1 (8) | 1 (7) | 7 (18) |
| Paresthesia | 1 (8) | 4 (33) | 2 (14) | 7 (18) |
| Photosensitivity reaction | 0 | 3 (25) | 4 (29) | 7 (18) |
| Vomiting | 2 (17) | 3 (25) | 2 (14) | 7 (18) |
| Abdominal pain upper | 2 (17) | 2 (17) | 1 (7) | 5 (13) |
| Flatulence | 1 (8) | 2 (17) | 2 (14) | 5 (13) |
| Pruritus | 3 (25) | 1 (8) | 1 (7) | 5 (13) |
| Tremor | 2 (17) | 3 (25) | 0 | 5 (13) |

*** ITT safety analysis: 2 patients were replaced (1 due to incarceration and 1 due to non-compliance). Both stayed in the ITT safety population**

# Safety Summary

- Clinical AEs were similar to those seen in prior studies of FDV and DBV (gastrointestinal [GI] side effects and skin rashes, mild to moderate in intensity)
- The RBV-free cohort exhibited predominantly (60%) mild AEs compared with predominantly grade-2 AEs for RBV-containing regimens (8–42% grade 1, 58–75% grade 2 and, 17% grade 3)
- One patient self-discontinued due to AE's (Cohort 1) at Week 9, for persistent GI side effects and fatigue; this patient achieved SVR12
- One serious AE (onset pre-treatment, not attributed to study treatment)
  - Liver transplant patient described on previous slide (patient received 8 weeks of treatment prior to transplant; has since achieved SVR 12 post-transplant)
- Grade ≥1 bilirubin elevations were common
  - 83–92% of Cohort 1 and 2 patients, less common in RBV-free Cohort 3 (50%)
  - Predominantly indirect bilirubin elevations, consistent with known FDV inhibition of hepatic UDP-glucuronosyltransferase-1A1 (UGT1A1)
  - No evidence for hepatotoxicity – no ALT spikes or liver function changes
- ALT normalized in 100% of patients with elevated ALT at Baseline

# Baseline Polymorphisms and Resistance

- 17 patients with wild-type HCV, with no detectable resistance-associated variants (RAVs) in the NS3, NS5A, and NS5B genes detected by population sequencing of pre-treatment (Baseline) sera
- 19 patients had resistance associated variants at Baseline
  - NS3 protease
    - 13 patients with Q80K polymorphism substitution, that can reduce the susceptibility to some HCV PIs *in vitro* and *in vivo*
  - NS5A protein
    - 3 patients with M28V resistance substitution
    - 3 patients with H58P secondary resistance substitution
    - 1 patient with linked M28A + Q30L ± H58P resistance substitutions
    - 1 patient with linked Q30L + Y93H resistance substitutions
  - NS5B polymerase
    - 10 patients with A421V polymorphism substitution, that can reduce the susceptibility to some NNucs *in vitro* and *in vivo*

# Viral Resistance Observations

- 89% (17/19) of patients with detectable Baseline resistance substitutions or polymorphisms and 82% (14/17) of patients WT at Baseline, achieved SVR12
- Cohort 1 - One Virologic Breakthrough at Week 5
  - High-level NS5A Linked Q30L + Y93H, and NS5B A421V substitutions at Baseline
  - Breakthrough associated with newly emerging L31V (NS5A), R155K (NS3) and P495L (NS5B) resistance substitutions between Day 3 and Day 28
- Cohort 2 – One Virologic Relapse at Week 16
  - NS3 Q80K polymorphism at Baseline
  - < LLOD from Week 2; no new substitutions at time of relapse
- Cohort 3
  - 1 patient WT at Baseline experienced a virologic breakthrough at Week 12
    - Virologic rebound associated with Q30E (NS5A), R155K (NS3), and A421V (NS5B) substitutions
    - Patient had decreasing plasma levels of the NNuc and PI during treatment
  - 1 patient WT at Baseline experienced a virologic relapse at Week 16
    - Relapse associated with M28T + Q30H/R (NS5A) and R155K (NS3) substitutions
    - Patient had decreasing plasma levels of NNuc during treatment
  - 1 patient WT at Baseline experienced a virologic relapse at Week 16
    - Genotype of relapsing virus could not be determined due to low concentration of virus

# Study Summary

- In a difficult-to-treat patient population (HCV GT-1a, IL28B CT/TT) the regimen of PPI-668 + FDV + DBV consistently produced high RVR and SVR12 response rates, with or without the inclusion of RBV
- 97% of patients (35/36) achieved <LLOQ by Week 4, with 83% achieving <LLOD
- In the two RBV-containing cohorts, 92% of patients achieved SVR12
- In the RBV-free cohort, 8 patients achieved SVR12, including one decompensated patient who received only 8 weeks of treatment and a subsequent liver transplant
  - Another patient in the RBV-free cohort self-discontinued at Week 8 but has achieved SVR8
- 3/3 patients achieved SVR despite only 8–9 weeks of treatment
- Despite potential resistance-associated substitutions and polymorphisms in 19 patients at Baseline, only 2 of these patients developed viral breakthrough
- Mild-moderate GI side effects and rashes were common, but usually manageable; side effects were milder in the RBV-free cohort

# Acknowledgement

We would like to thank the patients and their families, as well as Quest study coordinators and staff