Retreatment of Hepatitis C Infection in Patients Who Failed Glecaprevir/Pibrentasvir

David Wyles,[1] Ola Weiland,[2] Betty Yao,[3] Frank Weilert,[4] Stuart Gordon,[5] Fred Poordad,[6] Albrecht Stoehr,[7] Ashley St. John Mark Brown,[8] Stefan Mauss,[9] Suvajit Samanta,[3] Tami Pilot-Matias,[3] Lino Rodrigues Jr.,[3] Roger Trinh[3]

[1]Denver Health Medical Center, Denver, Colorado, USA; [2]Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]AbbVie Inc., North Chicago, Illinois, USA; [4]Waikato Hospital, Hamilton, New Zealand; [5]Henry Ford Hospital, Detroit, Michigan, USA; [6]Texas Liver Institute, UT Health, San Antonio, Texas, USA; [7]IFI Studien und Projekte Gmbh, Hamburg, Germany; [8]Imperial College Healthcare NHS Trust, London, United Kingdom; [9]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany

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abbvie

Background

Glecaprevir
pangenotypic NS3/4A protease inhibitor

Pibrentasvir
pangenotypic NS5A inhibitor

Co-formulated: G/P (300 mg/120 mg QD)

G/P is a next-generation direct-acting antiviral (DAA) for the treatment of hepatitis C virus (HCV) infection

- Overall SVR12 rate of 98% across GT1–6 in more than 2200 patients[1]
- Favorable safety profile[2]
- High barrier to resistance[3]
- The 8-week regimen is approved for treatment-naive patients who are non-cirrhotic[4]
- The 12-week regimen is approved for treatment-naive patients with compensated cirrhosis[4]
- The 16-week regimen is approved for difficult-to-treat populations[4*]

*Including IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN GT3 patients and NS5A inhibitor-experienced GT1 patients.
G/P is dosed once daily as three pills for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

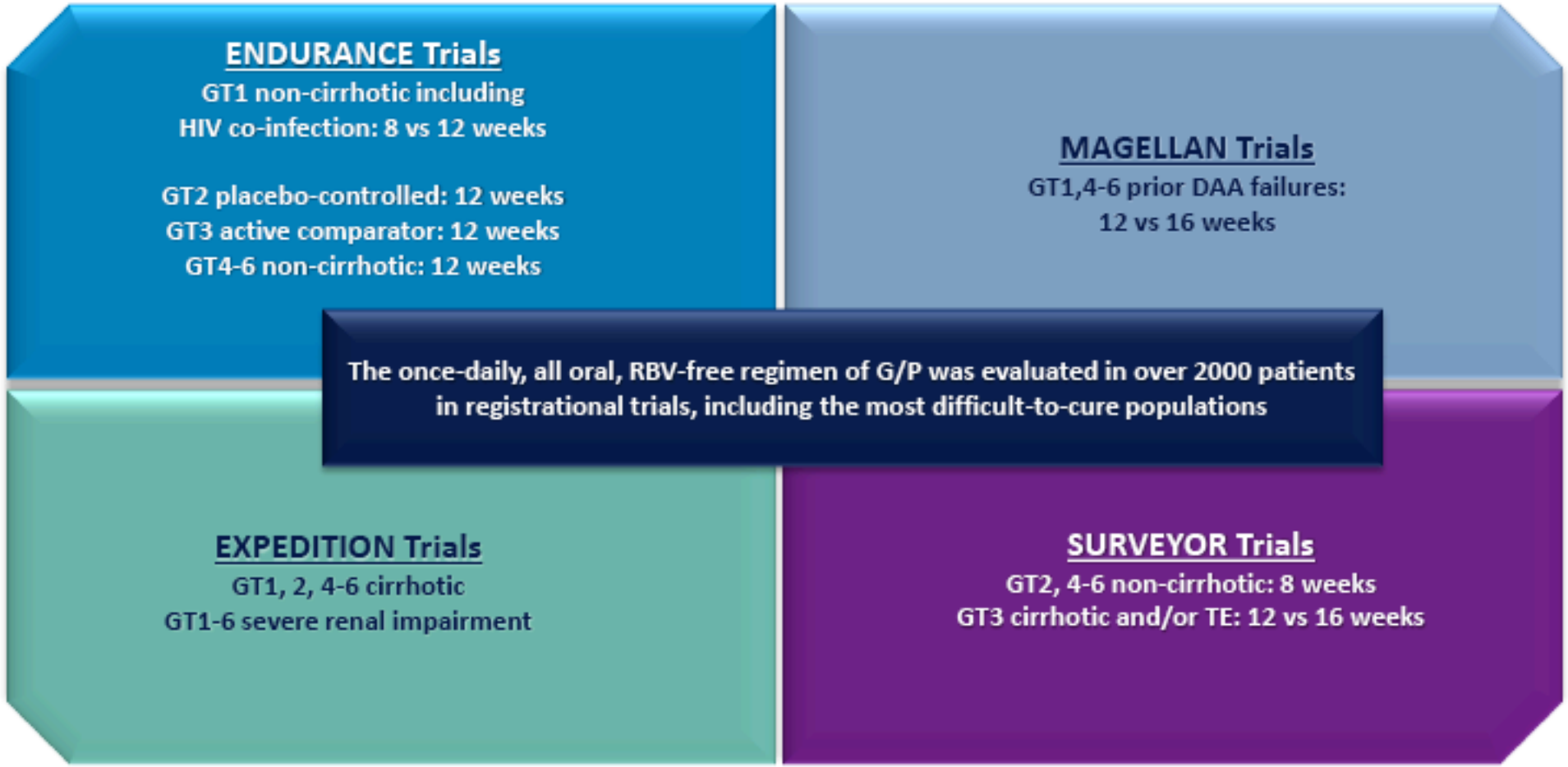
1. Grebely et al, INHSU, 08 Sept 2017;
2. Dufour J-F, et al. *J Hepatol* 2017; 66:S515;
3. Ng TI, et al. *Antimicrob Agents Chemother* 2017; 61:e02558–16;
4. Glecaprevir and pibrentasvir fixed-dose combination [US package insert]. AbbVie. 2018.

Background

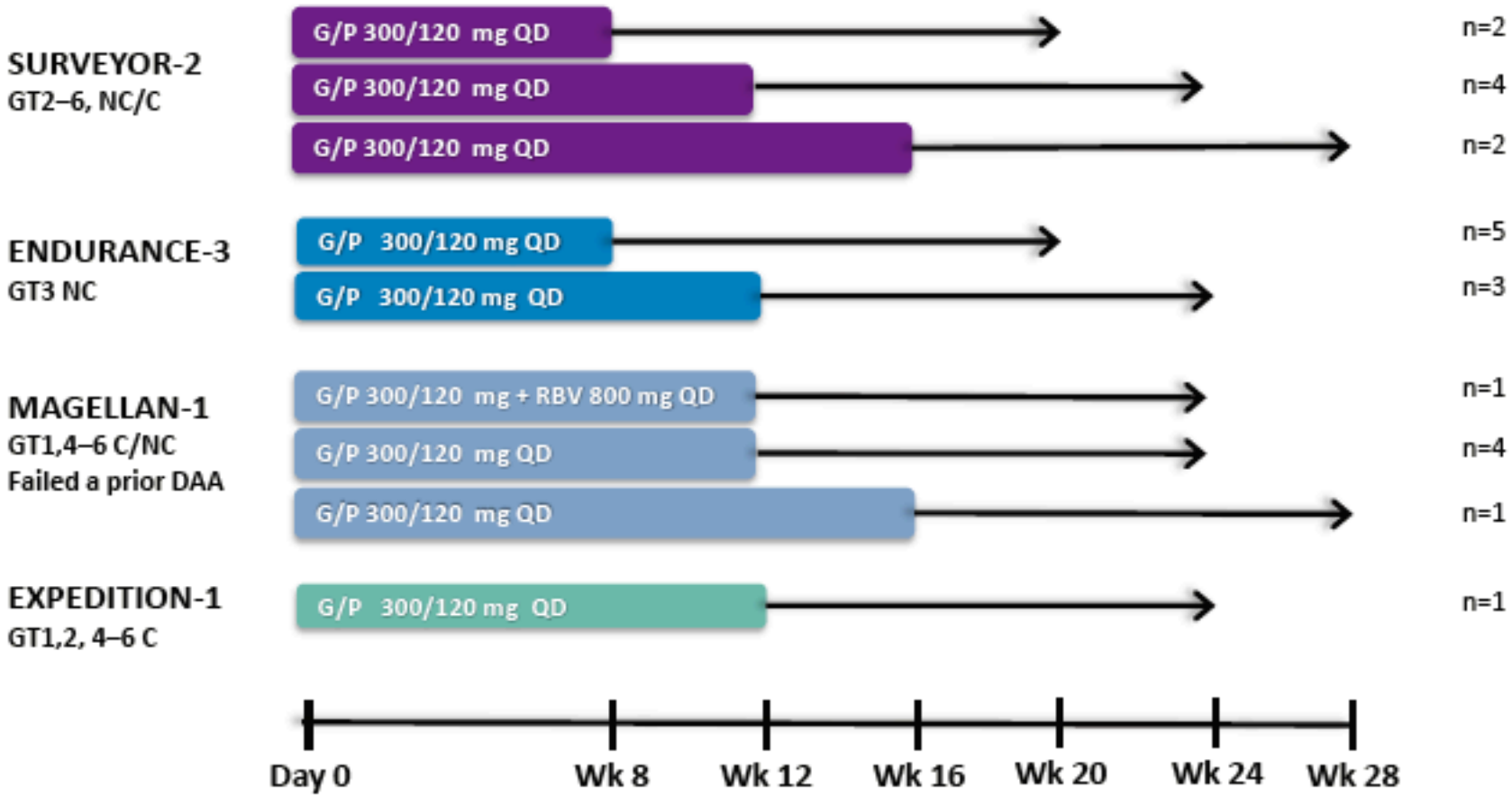
- Due to G/P's high overall SVR12 rate, retreatment data for those who experience virologic failure (VF) are scarce
  - This is the first presentation of data on the retreatment of patients who experienced VF following G/P treatment
- Data show that the administration of drugs with different MOAs in a combination retreatment regimen can increase the probability of achieving a sustained virologic response (SVR) in HCV-infected patients[1]
- Patients from AbbVie's registrational clinical trials who experienced VF with G/P were enrolled in this study designed to evaluate the safety and efficacy of G/P in combination with sofosbuvir (SOF) and ribavirin (RBV) as a retreatment regimen
- This study is ongoing and patients who experienced VF from selected phase 3b trials are eligible for participation

1. Ahmed A & Felmlee DJ. *Viruses*. 2015; 7(12):6716-29.

AbbVie Parent Registrational Studies



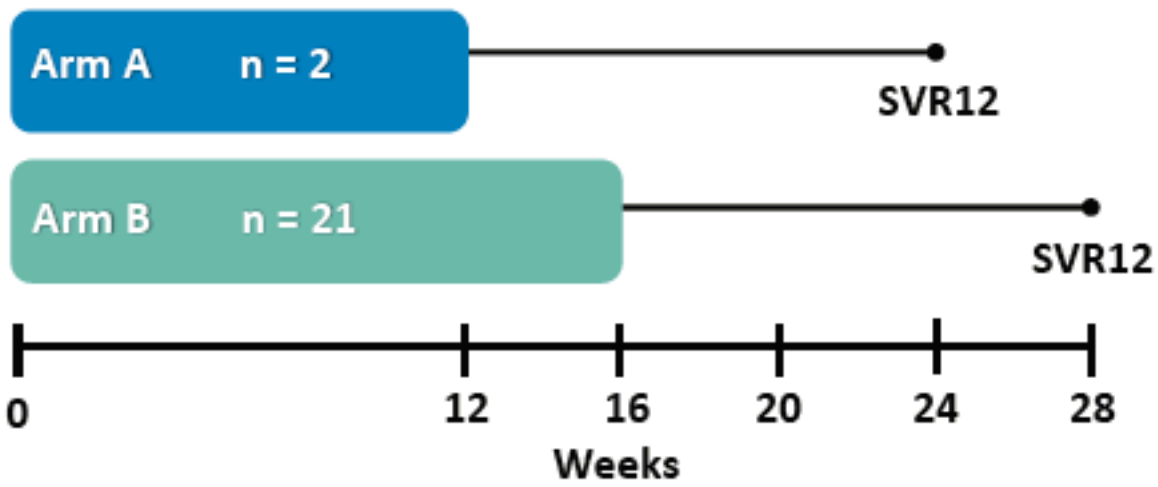
Enrollment from AbbVie Parent Registrational Studies



MAGELLAN-3: Study Design

Objective: Evaluate the efficacy and safety of 12- or 16-weeks of open-label G/P + SOF + RBV regimen in patients who had virologic failure following G/P treatment

Treatment: G/P (300 mg/120 mg QD) + SOF (400 mg QD) +RBV (1000–1200 mg BID)



HCV resistance testing was not a criteria for patient treatment duration assignment

Genotype	Cirrhotic Status	Prior NS5Ai and/or PI*	Treatment Arm
1, 2, 4, 5, 6	NC	No	A
3	Any	Any	B
Any	C	Any	B
Any	Any	Yes	B

C, cirrhotic; NC, non-cirrhotic.

* Either treatment or combination received **before** treatment with G/P.

BID, twice-daily; NS5Ai, NS5A inhibitor; PI, protease inhibitor; QD, once-daily; SOF, sofosbuvir; RBV, ribavirin; VF, virologic failure.

Key Patient Eligibility Criteria

- Age ≥18 years
- HCV GT1–6, without or with HIV-1 co-infection (ART-naïve or on stable ART)
- Experienced virologic failure during or after treatment with G/P in an Abbvie clinical study
- G/P treatment was completed or discontinued ≥1 month prior to screening
- Absence of co-infection with hepatitis B virus
- Absence of decompensated cirrhosis (Child-Pugh B/C)

Assessments

- **Patients who received ≥1 dose of study drug were analyzed for primary efficacy in the intent-to-treat population (ITT):**
  - Proportion of patients with HCV RNA below LLoQ 12 weeks post-treatment (Sustained virologic response at post-treatment week 12 [SVR12] rate)
- **Additional assessments:**
  - Rates of on-treatment virologic failure and post-treatment virologic relapse
  - SVR12 rate in the modified ITT (mITT) population, which excludes non-virologic failures
  - Resistance-associated substitutions (RASs) at baseline and at time of failure
  - Adverse events and laboratory abnormalities

LLoQ, lower limit of quantification.

Baseline Demographics and Clinical Characteristics

Characteristic	Arm A 12 weeks n = 2	Arm B 16 weeks n = 21	Total N = 23*
Male, n (%)	1 (50.0)	17 (81.0)	18 (78.3)
White race, n (%)	2 (100)	18 (85.7)	20 (87.0)
Age, mean years (SD)	56.0 (0)	54.9 (7.9)	55.0 (7.6)
BMI, mean kg/m^2 (SD)	35.1 (7.7)	27.5 (4.8)	28.2 (5.3)
HCV Genotype, n (%)			
1	0	7 (33.3)	7 (30.4)
2	2 (100)	0	2 (8.7)
3	0	14 (66.7)	14 (60.9)
Compensated Cirrhosis, n (%)	0	7 (33.3)	7 (30.4)
NS5Ai experienced prior to G/P	0	6 (28.6)	6 (26.1)

BMI, body mass index; NS5Ai, NS5A inhibitor; PI, protease inhibitor; VF virologic failure.
*A total of 24 enrolled patients who experience VF in the parent studies were included in the analysis. One patient in Arm A who failed ombitasvir/paritaprevir/r + dasabuvir was excluded.

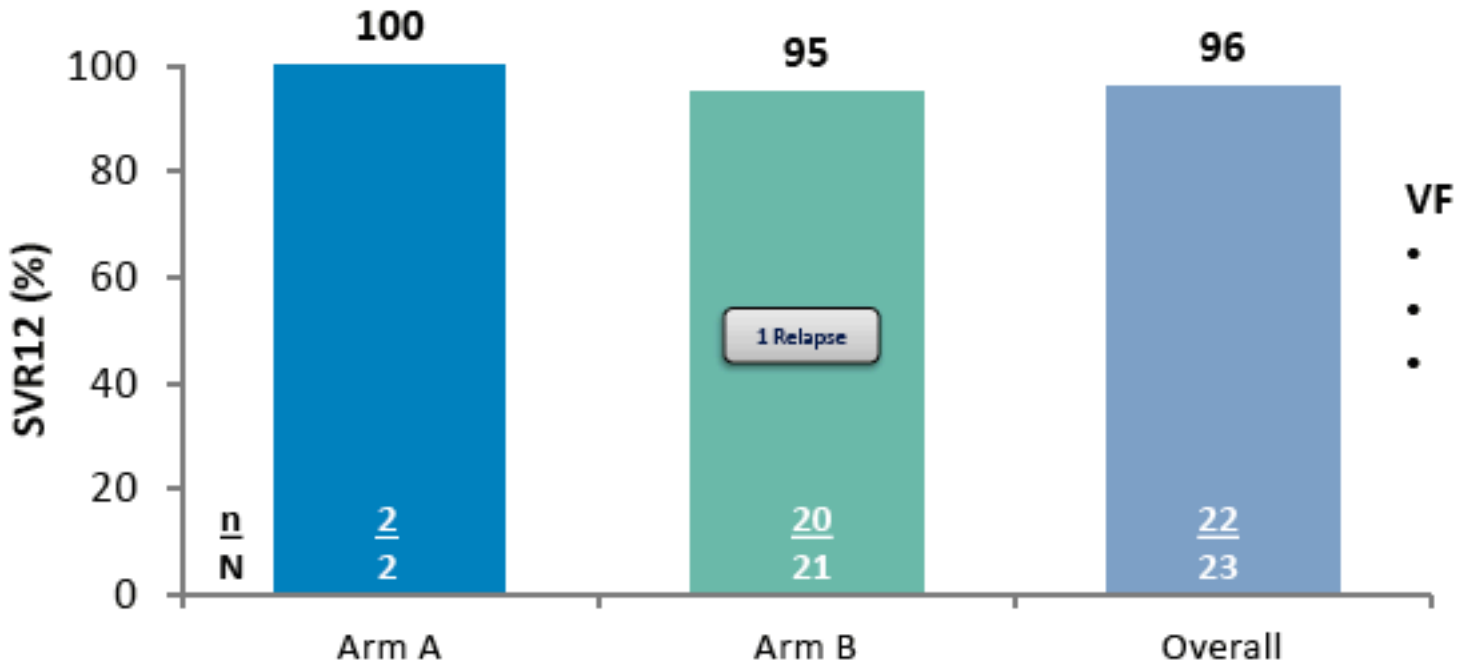
Baseline Polymorphisms

Baseline Polymorphisms,* n (%)	Arm A 12 weeks n = 2	Arm B 16 weeks n = 21	Total N = 23
NS3 alone	0	0	0
NS5A alone	2 (100)	16 (76.2)	18 (78.3)
Both NS3 and NS5A	0	5 (23.8)	5 (21.7)
None	0	0	0

* The detection threshold was 15%. NS3 resistance-associated substitution (RAS) positions included in this analysis were 155, 156 and 168. NS5A RAS positions included in this analysis were 24, 28, 30, 31, 32, 58, 92, and 93.

Efficacy: SVR12 by Intent-to-treat (ITT)

High SVR12 rates are achieved in the retreatment of G/P failures.



VF Patient

- GT1a
- Compensated cirrhosis
- Failed SOF/LDV prior to G/P

Summary of Adverse Events (AE)

Adverse event, n (%)	Total N = 23
Any AE	19 (82.6)
Serious AE	1 (4.3)[§]
DAA-related serious AE[*]	0
AE leading to drug discontinuation	0
Any Serious AE (Grade 3 or more)*	0
AEs in ≥10% of all patients	
Headache	6 (26.1)
Pruritus	5 (21.7)
Dizziness	4 (17.4)
Irritability	4 (17.4)
Fatigue	3 (13.0)
Insomnia	3 (13.0)
Upper respiratory-tract infection	3 (13.0)

* As determined by the investigator.
§ AE of cholelithiasis, assessed as not related to study drugs, in a subject with previous episodes of cholelithiasis

Laboratory Abnormalities

Adverse event, n (%)	Total N = 23
ALT, Grade ≥3 (>5 × ULN)	1 (4.3)
AST, Grade ≥3 (>5 × ULN)	0
Total Bilirubin, Grade ≥3 (>3 × ULN)	0
Decreases in Hemoglobin, Grade ≥3	0
RBV dose reductions due to toxicity	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBV, Ribavirin ULN, upper limit of normal.

Conclusions

- Preliminary data from this study show that HCV-infected patients who experienced VF following G/P treatment can achieve high SVR12 rates with G/P + SOF + RBV
- G/P + SOF + RBV was well tolerated