ZIRCON: Pharmacokinetics, Safety, and Efficacy of Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir ± Ribavirin in Adolescents With Genotype 1 or 4 Hepatitis C Virus Infection

THU-251

Daniel H Leung[1], Betty B Yao[2], Rolando M Viani[2], Regino P Gonzalez-Peralta[3], Maureen M Jonas[4], Steven J Lobritto[5], Michael R Narkewicz[6], Etienne Sokal[7], Clàudia Fortuny[8], Evelyn K Hsu[9], Stefan Wirth[10], Antonio Del Valle-Segarra[11], Jiuhong Zha[2], Lois Larsen[2], Li Liu[2], Diana L Shuster[2], Daniel E Cohen[2], Philip Rosenthal[12]

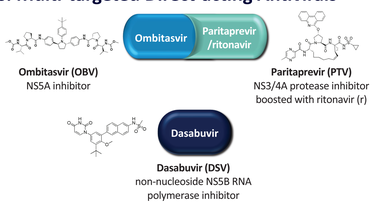
[1]Division of Gastroenterology, Hepatology, and Nutrition, Texas Children's Hospital and Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States; [2]AbbVie Inc., North Chicago, Illinois, United States; [3]Department of Pediatrics, University of Florida College of Medicine and Shands Children's Hospital, Gainesville, Florida, United States; [4]Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, United States; [5]New York—Presbyterian Morgan Stanley Children's Hospital and Department of Pediatrics, Columbia University Medical Center, New York, New York, United States; [6]Digestive Health Institute, Children's Hospital Colorado and Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado, United States; [7]Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium; [8]Servei de Pediatria, Hospital Sant Joan de Déu y Universitat de Barcelona, Barcelona, Spain; [9]Seattle Children's Hospital and Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, United States; [10]HELIOS Medical Center Wuppertal, Department of Pediatrics, Witten/Herdecke University, Wuppertal, Germany; [11]San Jorge Children's Hospital and University Pediatric Hospital, San Juan, Puerto Rico; [12]Department of Pediatrics, University of California, San Francisco, California, United States

Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver, 19–23 April 2017, Amsterdam, the Netherlands

BACKGROUND

- In adults, treatment of hepatitis C virus (HCV) genotype 1 (GT1) and GT4 with ombitasvir, paritaprevir, ritonavir ± dasabuvir (OBV/PTV/r ± DSV) ± ribavirin (RBV) results in high rates of sustained virologic response (SVR)[1–6]
- However, these direct-acting antivirals (DAAs) have not been studied in children or adolescents
- ZIRCON is an ongoing, global, open-label, 3-part study to evaluate the pharmacokinetics (PK), safety, and efficacy of OBV/PTV/r ± DSV ± RBV for pediatric and adolescent patients infected with HCV GT1 or GT4 (NCT02486406)
- Data for patients aged ≥12–17 years enrolled in Parts 1 and 2 are presented here

Study Drugs: Multi-targeted Direct-acting Antivirals



Ombitasvir (OBV)
NS5A inhibitor

Paritaprevir (PTV)
NS3/4A protease inhibitor boosted with ritonavir (r)

Dasabuvir (DSV)
non-nucleoside NS5B RNA polymerase inhibitor

Paritaprevir identified by AbbVie and Enanta. Ritonavir has no activity against HCV.

OBJECTIVES

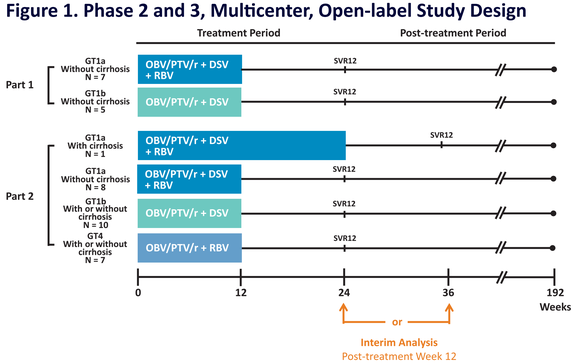
- To assess the PK of OBV/PTV/r + DSV ± RBV in HCV GT1-infected adolescents in Part 1
- To assess the efficacy and safety of OBV/PTV/r ± DSV ± RBV for 12 or 24 weeks in HCV GT1- or GT4-infected adolescents in Parts 1 and 2

METHODS

STUDY DESIGN

- Part 1 is a Phase 2 study enrolling treatment-naïve, non-cirrhotic, HCV GT1-infected patients who received treatment for 12 weeks **(Figure 1)**
- Part 2 is a Phase 3 study enrolling treatment-naïve or -experienced HCV GT1- or GT4-infected patients with or without compensated cirrhosis who received treatment for 12 or 24 weeks depending on their GT subtype and cirrhosis status **(Figure 1)**
  - Enrollment in Part 2 began as soon as dosing recommendations for the study drugs were available based on PK and clinical data from Part 1
- Treatment was OBV/PTV/r 25 mg/150 mg/100 mg once daily ± DSV 250 mg twice daily ± weight-based RBV 1000 mg or 1200 mg divided twice daily
- Blood samples were collected for intensive PK sampling in Part 1 at treatment Week 2 (at 2, 4, 8, 12, and 24 hours post dose)
- Blood samples were collected for measurement of HCV RNA in Parts 1 and 2 at treatment Day 1 and at Weeks 2, 4, 8, and 12 for patients who received the 12-week regimen, as well as Weeks 16, 20, and 24 for patients who received the 24-week regimen
- SVR was assessed at post-treatment Week 12 (SVR12)

Figure 1. Phase 2 and 3, Multicenter, Open-label Study Design



DSV, dasabuvir; GT, genotype; OBV/PTV/r, ombitasvir, paritaprevir, ritonavir; RBV, ribavirin; SVR12, sustained virologic response at post-treatment Week 12.

PATIENT SELECTION

Key Inclusion Criteria

- Patients aged ≥12–17 years with a body weight of ≥45 kg
- HCV infection (GT1 in Parts 1 and 2; GT4 in Part 2), defined as positive anti-HCV antibody and HCV RNA level >1000 IU/mL at screening
- Previous HCV therapy
  - Part 1: Treatment naïve
  - Part 2: Treatment naïve or interferon (IFN) experienced; IFN-based therapy must have been completed ≥6 months before enrollment

Key Exclusion Criteria

- Coinfection with hepatitis B virus or human immunodeficiency virus
- Current or past clinical evidence of Child-Pugh B or C (Child-Pugh score ≥7) or clinical history of liver decompensation
- Radiographically confirmed hepatocellular carcinoma
- Previous or current use of any investigational or commercially available anti-HCV drug other than IFN, pegylated IFN, or RBV
- History of solid organ transplantation
- Albumin <2.8 g/dL, hemoglobin <10 g/dL, platelets <25 000 cells/mm^3, or total bilirubin >3.0 mg/dL

ENDPOINTS

- In Part 1 of the study, PK endpoints for each study drug were:
  - Maximum plasma concentration (C_{max}) after dosing at Week 2
  - Area under the plasma concentration–time curve (AUC) at 0–12 hours (for DSV and RBV) or 0–24 hours (for OBV, PTV, and ritonavir) after dosing at Week 2
  - Trough concentration (C_{trough}) after dosing at Week 2
- In Parts 1 and 2, the primary efficacy endpoint was the percentage of patients who achieved SVR12 (HCV RNA <15 IU/mL at post-treatment Week 12)
- Results of the interim analysis performed at post-treatment Week 12 are reported here
- Adverse events (AEs) were recorded throughout the study

STATISTICAL ANALYSES

- The percentages of patients who achieved SVR12 in Parts 1 and 2 were calculated for the intention-to-treat (ITT) population, which comprised all patients who received at least 1 dose of the study drugs

RESULTS

PATIENTS

- 38 adolescents aged ≥12–17 years were enrolled at 18 sites in 5 countries (Belgium, Germany, Puerto Rico, Spain, and United States; **Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics (ITT Population)

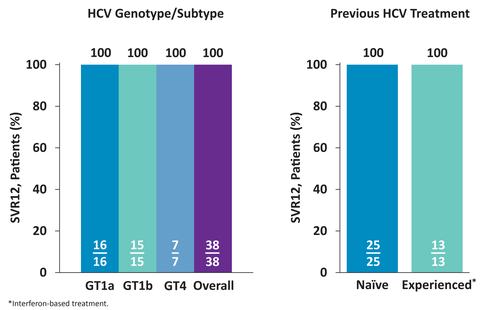
Characteristic	Patients N = 38
Male	13 (34)
Age, years, median (range)	15 (12–17)
Race	
White	29 (76)
Black or African American	5 (13)
Asian	3 (8)
Multiple	1 (3)
Ethnicity	
Hispanic or Latino	3 (8)
Weight, kg, median (range)	66.4 (48.5–118.7)
BMI ≥30 kg/m^2	6 (16)
HCV genotype/subtype	
GT1a	16 (42)
GT1b	15 (40)
GT4	7 (18)
HCV RNA ≥800 000 IU/mL	23 (61)
IL28B genotype, non-CC	29 (76)
Previous HCV treatment	
Naïve	25 (66)
Experienced	13 (34)
Cirrhotic status	
Non-cirrhotic	37 (97)

Data are n (%) unless stated otherwise.
BMI, body mass index; GT, genotype; HCV, hepatitis C virus; *IL28B*, interleukin 28B.

EFFICACY

- All 38 patients had undetectable HCV RNA levels at post-treatment Week 12 (100% SVR12; **Figure 2**)

Figure 2. SVR Rates by HCV Genotype/Subtype and Previous HCV Treatment (ITT Population)



*Interferon-based treatment.

SAFETY

- No AEs led to discontinuation of study drugs **(Table 2)**
  - The most common AEs occurring in ≥10% of patients were headache, fatigue, nasopharyngitis, pruritus, and upper respiratory tract infection
- No serious AEs (SAEs) occurred during treatment
- No confirmed Grade 3 or 4 laboratory abnormalities were reported **(Table 3)**

Table 2. Summary of Adverse Events

Adverse Event, n (%)	Patients N = 38
Any AE	32 (84)
Any AE possibly related to DAAs*	15 (39)
Any AE possibly related to RBV*	14 (37)
Any AE leading to discontinuation of study drug	0
AEs in ≥10% of all patients	
Headache	8 (21)
Fatigue	7 (18)
Nasopharyngitis	5 (13)
Pruritus	5 (13)
Upper respiratory tract infection	4 (11)

AE, adverse event; DAA, direct-acting antiviral; RBV, ribavirin.
*As assessed by investigator.

Table 3. Laboratory Abnormalities

Parameter, n (%)	Patients N = 38
Hemoglobin <10 g/dL	1 (3)
>1.5 × ULN elevation in alkaline phosphatase	1 (3)
≥2 × ULN elevation in total bilirubin	1 (3)
Post-baseline increase in ALT	
>5 × ULN and increased from previous measurement	0
>20 × ULN	0
CrCl <50 mL/min in patients with baseline >50 mL/min	0

ALT, alanine aminotransferase; CrCl, creatinine clearance; ULN, upper limit of normal.

PHARMACOKINETICS

- PK results from Part 1 showed that DAA exposures in adolescents (N = 12) were comparable to exposures seen in adults **(Table 4)**

Table 4. Preliminary Geometric Mean (CV%) of Pharmacokinetic Parameters From Adolescents in Study Part 1 vs Historical Geometric Mean Range in Adults

Drug	Adolescents (N = 12)*			Adults (Historical)†		
	C_{max} (ng/mL)	AUC (ng-h/mL)	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC (ng-h/mL)	C_{trough} (ng/mL)
Ombitasvir	75.4 (31)	918 (23)‡	19.0 (18)	81.9–143	1050–1600	22–34
Paritaprevir	738 (70)	4880 (52)‡	19.4 (64)	686–3040	3760–16 500	13.9–42.9
Dasabuvir	646 (49)	4460 (45)§	158 (43)	666–798	4460–5630	119–164

AUC, area under the plasma concentration–time curve; C_{max}, maximum concentration; C_{trough}, trough concentration.
*N = 11 for AUC and C_{trough} of ombitasvir and paritaprevir.
†Geometric mean range from 3 studies in HCV-infected adults that had intensive pharmacokinetic data (AbbVie Data on File).
‡$AUC_{0–24h}$.
§$AUC_{0–12h}$.

CONCLUSIONS

- In adolescent patients with HCV GT1 or GT4 infection, treatment with OBV/PTV/r ± DSV ± RBV resulted in 100% SVR12
- OBV/PTV/r ± DSV ± RBV was well tolerated in this population, and no Grade 3 or 4 laboratory abnormalities or treatment emergent SAEs were reported
- The exposures in adolescent patients were comparable to those observed in adults, suggesting that this regimen is suitable for treating adolescents without dosage adjustment
- Dosing in ≥9–11 and ≥3–8 year old pediatric patients is ongoing
- Long-term follow-up (approximately 3.5 years) of OBV/PTV/r ± DSV ± RBV in these patients will be investigated in Part 3 of ZIRCON

REFERENCES

1. Feld JJ, et al. *N Engl J Med*. 2014;370:1594–603.
2. Zeuzem S, et al. *N Engl J Med*. 2014;370:1604–14.
3. Andreone P, et al. *Gastroenterology*. 2014;147:359–65.
4. Ferenci P, et al. *N Engl J Med*. 2014;370:1983–92.
5. Poordad F, et al. *N Engl J Med*. 2014;370:1973–82.
6. Hézode C, et al. *Lancet*. 2015;385:2502–9.

ACKNOWLEDGMENTS

Medical writing support was provided by Deborah Eng, MS, ELS, of AbbVie and Paul MacCallum, PhD, of Fishawack Facilitate, and funded by AbbVie.

DISCLOSURES

AbbVie sponsored the study (NCT02486406); contributed to the design and data collection, analysis, and interpretation; and participated in the writing, review, and approval of this poster. All authors had access to all relevant data and participated in the writing, review, and approval of this poster.

DH Leung: Grant/research support from Gilead, AbbVie, BMS, and Roche/Genentech; served on the medical advisory boards of Gilead and Vertex Pharmaceuticals. **RP Gonzalez-Peralta:** Grant/research support from AbbVie, Gilead, and Sucampo; advisor/consultant for Genentech, Shire, Retrophin, and Albireo. **MM Jonas:** Consultant and grant support from Gilead and AbbVie; grant support from BMS, Echosens, and Roche. **SJ Lobritto:** Grant/research support from AbbVie. **MR Narkewicz:** Grant/research support from AbbVie and Gilead; consultant for Vertex and AbbVie. **E Sokal:** Grant/research support from AbbVie. **C Fortuny:** Grant/research support from AbbVie. **EK Hsu:** Grant/research support from AbbVie. **S Wirth:** Grant/research support from AbbVie. **A Del Valle-Segarra:** Grant/research support from AbbVie. **P Rosenthal:** Grant/research support Roche, Gilead, BMS, Vertex, and AbbVie; consultant for Merck. **BB Yao, RM Viani, J Zha, L Larsen, L Liu, DL Shuster, DE Cohen:** Employees of AbbVie and may hold stock or options.

abbvie