Safety and Efficacy of Bulevirtide Monotherapy and in Combination with Peginterferon alfa-2a in Patients with Chronic Hepatitis Delta: 24-week Interim Data of MYR204 Phase 2b Study

Asselah Tarik[1]; Arama Sorin Stefan[2]; Bogomolov Pavel[3]; Bourliere Marc[4]; Fontaine Hélène[5]; Gherlan George Sebastian[6,7]; Gorodin Vladimir[8]; Hilleret Marie-Noëlle[9]; Lazar Stefan[10]; Mamonova Nina[11]; Morozov Viacheslav[12]; Pantea Victor[13]; Placinta Gheorghe[13]; Gournay Jérôme[14]; RAFFI Francois[14]; Ratziu Vlad[15]; Stern Christiane[15]; Sagalova Olga[16]; Samuel Didier[17]; Stepanova Tatyana[18]; Syutkin Vladimir[19]; Streinu-Cercel Adrian[2]; Zoulim Fabien[20]; Roulot Dominique[21]

[1]Hôpital Beaujon APHP, Université de Paris, INSERM, Clichy, France; [2]Matei Bals National Institute of Infectious Diseases, Bucharest, Romania; [3]Moscow Regional Research-Clinical Institute, Moscow, Russian Federation; [4]Hôpital Saint Joseph Marseille, Marseille, France; [5]Hôpital Cochin - Unité d'Hépatologie 'Pavillon Achard, Paris, France; [6]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [7]Dr. Victor Babes Foundation, Bucharest, Romania; [8]State Budgetary Institution of Health Care "Specialized Clinical Infectious Diseases Hospital," Krasnodar, Russian Federation; [9]Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; [10]Dr. Victor Babes Foundation - Infectious and Tropical Diseases Hospital, Bucharest, Romania; [11]National Research Medical Centre for Phthisiopulmonology and Infectious Diseases, Moscow, Russian Federation; [12]LLC Medical Company "Hepatolog," Samara, Russian Federation; [13]Infectious Clinical Hospital "T. Ciorba" - Medical University Department of Infectious Diseases, Chisinau, Moldova; [14]Nantes University Hospital (CHU de Nantes Hôtel-Dieu), Nantes, France; [15]CH Pitié-Salpétrière, Paris, France; [16]Southern Ural State Medical University, Chelyabinsk, Russian Federation; [17]Centre Hépato-Biliaire - Hôpital Paul Brousse, Université Paris Saclay, Villejuif, France; [18]LLC "Clinic of Modern Medicine," Moscow, Russian Federation; [19]Institute of Emergency Medicine n.a. NV Sklifosovsky, Liver Surgery and Transplantation, Moscow, Russian Federation; [20]Hospital Croix Rousee, Service Hepatologie, Lyon, France; [21]Hôpital Avicenne, APHP, Université Sorbonne Paris Nord, Bobigny, France; [22]Gilead Sciences, Hong Kong, China

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Background

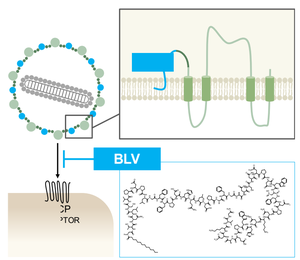
Hepatitis Delta Virus (HDV) Background

- HDV is a satellite virus of HBV and requires HBV envelope proteins to infect hepatocytes[1]
- Approximately 12 million people infected with HDV worldwide[2]
- HDV is the most severe form of chronic viral hepatitis,[3] with 2–3-fold increased risk of mortality compared to HBV monoinfection[4,5]
- An undetectable HDV RNA or a 2-log_{10} decline with ALT normalization is an acceptable chronic on-therapy surrogate endpoint[6] (FDA draft guidance for development of HDV treatment)
- Achieving HDV viral control or cure is warranted[7]

ALT, alanine aminotransferase; HBV, hepatitis B virus

Bulevirtide (BLV)

- First-in-class entry inhibitor for treatment of chronic HDV infection
- Linear 47-amino acid chemically synthesized lipopeptide
- Specifically binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[8]
- Favorable safety and tolerability
- Conditionally approved in Europe for treatment of chronic HDV[9]
- Interim Week 24 data from ongoing Phase 3 MYR301 study is presented as Poster 2730 at ILC 2021

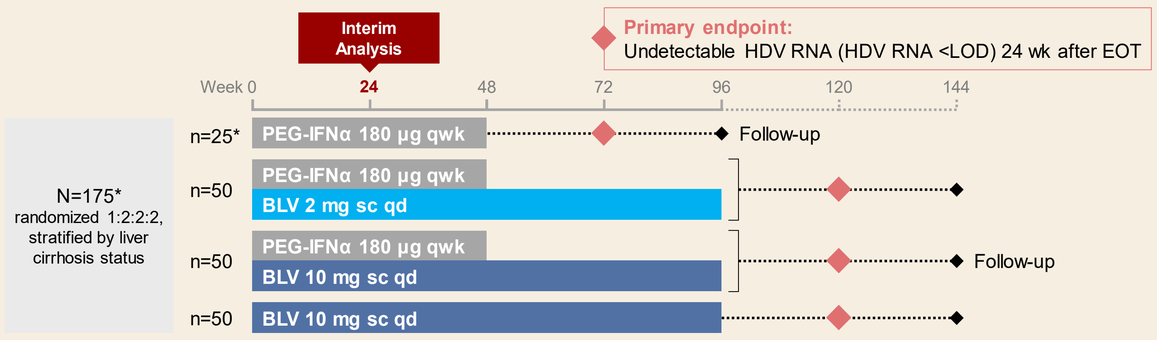


HBsAg, hepatitis B surface antigen; NTCP, sodium taurocholate cotransporting polypeptide.

MYR204 Study Objectives

- To evaluate the safety and efficacy of BLV administered subcutaneously at a dose of 2 or 10 mg qd in combination with pegylated interferon alfa-2a (PEG-IFNα) qwk relative to BLV 10 mg monotherapy: Interim week 24 analysis

MYR204 Study Design



*1 patient withdrew before dosing; †ClinicalTrials.gov NCT03852433; ‡RoboGene HDV RNA Quantification Kit 2.0, Analytik Jena, Leipzig Germany; LOD (limit of detection) 6 IU/mL.

- Multicenter, open-label, randomized Phase 2b study† in patients with chronic HDV conducted in 4 countries (France, Russia, Romania, Moldova)
- Key inclusion criteria:
  - Chronic HDV infection with or without cirrhosis and compensated liver disease (CTP ≤6)
  - ALT >1x ULN and <10x ULN
- Key secondary endpoints:
  - Undetectable and/or ≥2-log IU/mL decline in HDV RNA‡
  - ALT normalization (based on central laboratories reference ranges)
  - Combined response (undetectable HDV RNA or decrease by ≥2 log_{10} IU/mL from BL and ALT normalization)

Baseline Characteristics

	PEG-IFNα n=24	PEG-IFNα + BLV 2 mg n=50	PEG-IFNα + BLV 10 mg n=50	BLV 10 mg n=50
Mean age, y (SD)	40.6 (8.4)	40.9 (9.3)	41.5 (8.6)	40.4 (8.5)
Male sex, n (%)	18 (75)	33 (66)	35 (70)	38 (76)
Race, n (%)				
Caucasian	20 (83)	44 (88)	43 (86)	44 (88)
Asian	4 (17)	3 (6)	4 (8)	4 (8)
Black or African American	0	3 (6)	2 (4)	2 (4)
Other	0	0	1 (2)	0
Compensated Cirrhosis, n (%)	8 (33)	17 (34)	18 (36)	17 (34)
Mean liver stiffness, kPa (SD)	15.83 (11.57)	12.79 (6.43)	12.51 (7.60)	12.68 (6.65)
Patients with >20 kPa, n (%)	6 (25)	9 (18)	7 (14)	6 (12)
Mean ALT, U/L (SD)	121.5 (95.9)	107.5 (77)	112.6 (98.6)	118.4 (108.1)
Median HDV RNA, log_{10} IU/mL (range)	5.2 (2.3–7.3)	5.6 (0.0–7.1)	5.5 (0.0–6.7)	5.6 (2.8–7.1)
HBV genotype A / D / E, n (%)	3 (13) / 9 (38) / 0	3 (6) / 21 (42) / 0	5 (10) / 19 (38) / 1 (2)	4 (8) / 18 (36) / 0
HDV genotype, n (%)				
1	24 (100)	48 (96)	47 (94)	49 (98)
5 / 6 / ND	0 / 0 / 0	1 (2) / 1 (2) / 0	2 (4) / 0 / 1 (2)	1 (2) / 0 / 0

ND, not determined; SD, standard deviation.

Results

Overall Safety Summary: Interim Week 24 Analysis

	n (%)	PEG-IFNα n=24	PEG-IFNα + BLV 2 mg n=50	PEG-IFNα + BLV 10 mg n=50	BLV 10 mg n=50
AEs	Any AE*	21 (88)	48 (96)	49 (98)	33 (66)
	Grade ≥3 AE	11 (46)	24 (48)	27 (54)	6 (12)
	Any serious AE	2 (8)†	2 (4)‡	1 (2)§	1 (2)¶
	Any AE leading to D/C of BLV	0	0	0	0
	Any AE leading to D/C of PEG-IFNα	0	2 (4)	2 (4)	0
	Death	0	1 (2)*	0	0
AEs of special interest	Injection site reactions	0	7 (14)	8 (16)	4 (8)
	Liver related events	0	0	1 (2)‡	0

All adverse events (AEs) reported in table considered treatment emergent; only symptomatic and clinically significant total bile salt elevations were collected
†Appendicitis, pyrexia
‡Astrocytoma, chronic sinusitis, neither related to BLV§Drug-induced liver injury and cholestasis, assessed as possibly related to PEG-IFNα but not related to BLV, and resolved
¶Urinary tract infection, not related to BLV
D/C, discontinuation

- BLV monotherapy or combination with Peg-IFN was generally safe and well tolerated
  - There were no serious AEs related to BLV or AEs leading to D/C of BLV
  - Injection-site reactions were rare and mostly mild in grade
  - Elevations in total bile salts across all BLV arms were asymptomatic

References

1. Rizzetto M, et al. J Infect Dis 1980;141:590-602; 2. Stockdale AJ, et al. J Hepatol 2020;73:523-32; 3. Wedemeyer H, et al. Nat Rev Gastroenterol Hepatol 2010;7:31-40; 4. Fattovich G, et al. Gut 2000;46:420-6; 5. Romeo R, et al. Gastroenterology 2009;136:1629-38; 6. Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance November 2019. 7. Asselah et al. Liver International, 2020;40 S1:54-60; 8. Ni Y, et al. Gastroenterology 2014;146:1070-83; 9. Hepcludex [SmPC]. Bad Homburg, Germany: Myr GmbH; 7/20

Acknowledgments & Disclosures:

We extend our thanks to the patients, their families, and all participating investigators. This study was funded by MYR GmbH.
Employee of Paris Public University Hospitals (AP-HP, Beaujon's Hospital) and University of Paris
Principal investigator for research grants: Funds paid to Hospital (AP-HP)
Consultant, expert and speaker for: Gilead, Abbvie, Bristol-Myers Squibb, Eiger BioPharmaceuticals, Janssen, Merck Sharp Dohme, MYR Pharmaceuticals, Roche
Grants from: ANR, CNRS, INSERM, University of Paris, ANRS

Results (cont'd)

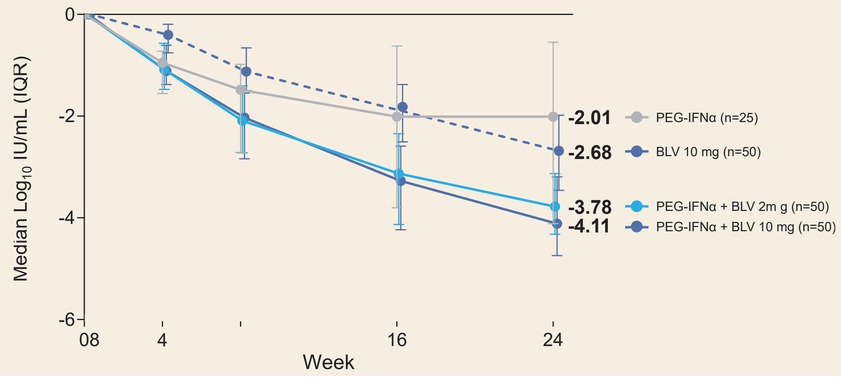
HBV markers: Interim 24 Week Analysis

	PEG-IFNα n=24	PEG-IFNα + BLV 2 mg n=50	PEG-IFNα + BLV 10 mg n=50	BLV 10 mg
HBsAg decrease >1 log_{10} IU/mL from baseline, n (%)	1 (4)	6 (12)	4 (8)	0
HBsAg loss with/without seroconversion, n	0	0	0	0
Mean HBV DNA* change from baseline, log_{10} IU/mL, (SD)	0.074 (0.763)	-0.626 (1.321)	-0.324 (1.298)	-0.791 (1.367)

* At baseline 55% of patients were on HBV oral nucleos(t)ide treatment per guidelines

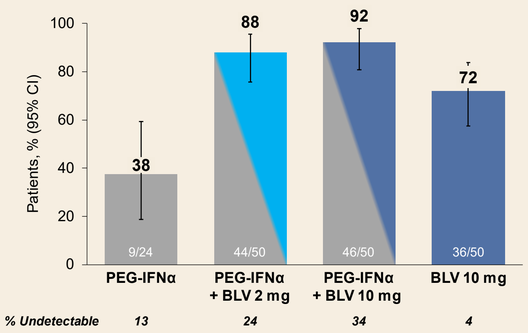
- Trends for HBsAg declines were observed in BLV combination with PEG-IFNα
- Modest declines in HBV DNA were observed in BLV containing arms compared to PEG-IFNα alone

Efficacy: Decline in HDV RNA Over Time



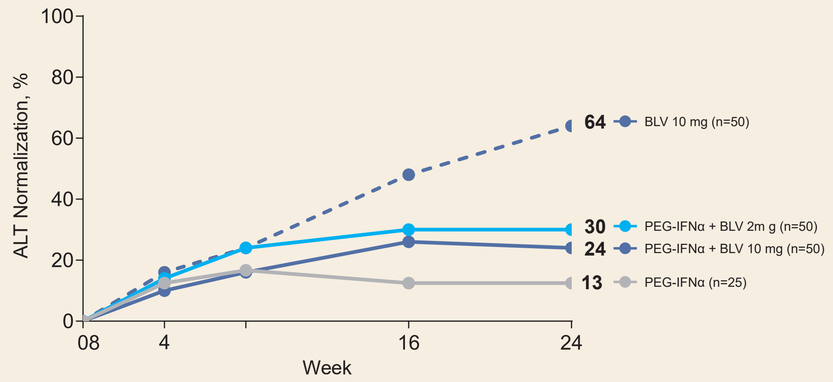
- Combination of BLV with PEG-IFNα resulted in greater declines of HDV RNA levels when compared to either therapy as monotherapy

Efficacy: Virological Response at Interim Week 24 Analysis
Undetectable HDV RNA or ≥ 2-log_{10} IU/mL Decline



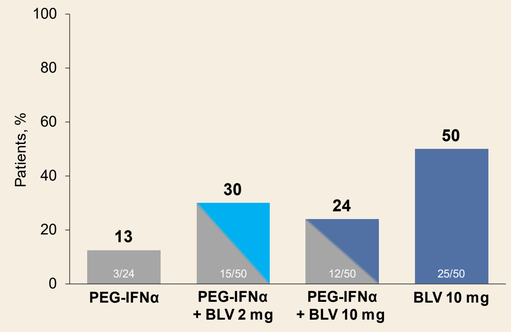
- 24 weeks treatment with BLV as monotherapy or in combination with PEG-IFNα led to a higher virological response compared with PEG-IFNα monotherapy

Efficacy: ALT Normalization Over Time



- ALT normalization rates were higher in patients treated with BLV, especially as a monotherapy

Efficacy: Combined Response at Interim Week 24 Analysis
Undetectable HDV RNA or ≥2 log_{10} IU/mL decline from BL and ALT Normalization



- The rates of patients reaching a combined response after 24 weeks of treatment were higher in patients treated with BLV, especially in the monotherapy arm

Conclusions

- In this Interim week 24 analysis from MYR 204 study:
  - Bulevirtide monotherapy or combination with PEG-IFNα-2a was safe and well tolerated through 24 weeks of therapy
  - BLV combination therapy with PEG-IFNα resulted in higher rates of HDV viral decline while ALT normalization was higher with BLV monotherapy
  - Combined response rates (2-log_{10} decline or undetectable HDV RNA with ALT normalization) were higher in BLV treated arms compared to Peg-IFN alone with the highest biochemical response seen in BLV monotherapy arm
- The primary endpoint analysis including viral and biochemical response will be performed 24 weeks post treatment
- 2 mg BLV monotherapy is conditionally approved in Europe, with availability in several countries