Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D (CHD): results from an interim analysis of a phase 3 randomized study

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Hepatitis Delta Virus

- Hepatitis delta virus (HDV) is a satellite virus that requires the envelope protein from hepatitis B virus (HBV) to infect hepatocytes and propagate[1]
- Between 9-19 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis,[3,4] with 2–3-fold increased risk of mortality compared to HBV mono-infection[5,6]
- Pegylated interferon-alfa (PegIFNα) is recommended by treatment guidelines; however, PegIFNα therapy only benefits a small subset of patients and is often poorly tolerated[7]

- **Achieving HDV viral control or cure of CHD is an unmet medical need**

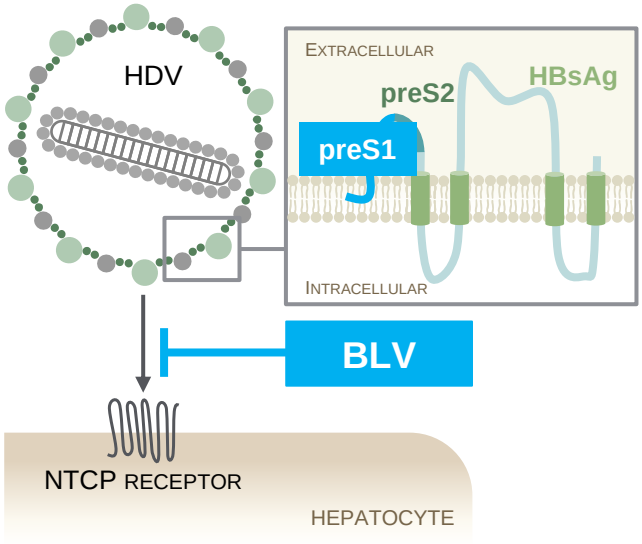
CHD, chronic hepatitis delta; HBV, hepatitis B virus; HDV, hepatitis delta virus; Pegylated interferon-alfa PegIFNα

1. Rizzetto M, et al. J Infect Dis 1980;141:590-602; 2. Stockdale AJ, et al. J Hepatol 2020;73:523-32; 3. Alfaiate D, et al. J Hepatol. 2020 Sep;73(3):533-539; 4. Rizzetto M, et al. J Hepatol 2021;74(5):1200-1211; 5. Fattovich G, et al. Gut 2000;46:420-6; 6. Romeo R, et al. Gastroenterology 2009;136:1629-38;.7. Sandmann L, et al. Liver International 2022;00:1-11.

Background

Bulevirtide (BLV)

- First-in-class entry inhibitor for treatment of CHD
- Linear 47-amino acid chemically synthesized lipopeptide
- Binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[1]
- Conditionally approved in Europe in 2020 for treatment of CHD in patients with compensated liver disease[2,3]
- **MYR301 week 48 data** demonstrated that[3]:
  - Monotherapy with BLV (2 mg/d or 10 mg/d) was superior to no anti-HDV treatment based on the combined viral and biochemical response
  - HDV RNA responses were similar at the 2 dose levels
  - BLV was generally safe and well tolerated



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

1. Ni Y, et al. Gastroenterology 2014;146:1070-83; 2. Lampertico P, et al. J Hepatol 2022;77 (5):1422-30; 3. Wedemeyer H, et al. NEJM 2023; June 22. DOI: 10.1056/NEJMoa2213429

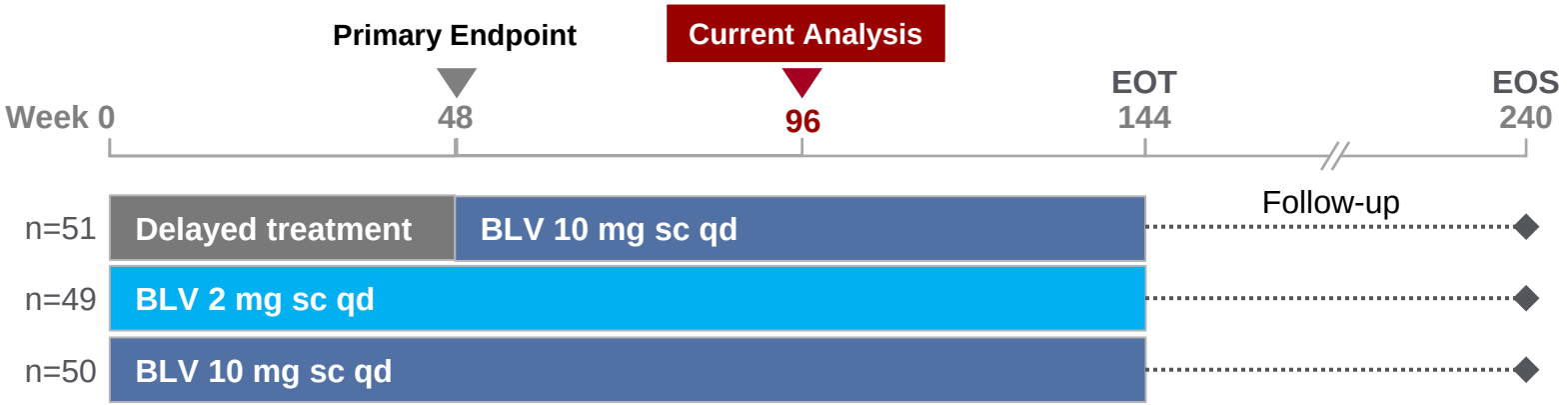
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

H. Wedemeyer, S. Aleman, M.R. Brunetto, A. Blank, P. Andreone, P. Bogomolov, V. Chulanov, N. Mamonova, N. Geyvandova, V. Morozov, O. Sagalova, T. Stepanova, A. Berger, D. Manuilov, V. Suri, Q. An, B. Da, J. Flaherty, A. Osinusi, Y. Liu, U. Merle, J.S.. Wiesch, S. Zeuzem, S. Ciesek, M. Cornberg, and P. Lampertico, for the MYR 301 Study Group*

Study Design



- Multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 16 sites across 4 countries (Germany, Italy, Russian Federation, and Sweden)
- **Key Inclusion Criteria:**
  - CHD without or with cirrhosis and CPT ≤7
  - ALT >1X to <10X ULN
  - Platelets ≥60,000 cells/mm^3
  - Controlled HIV coinfection allowed

ALT, alanine transaminase; BLV, bulevirtide; CHD, chronic hepatitis delta; CPT, Child-Pugh-Turcotte; EOS, end of study; EOT, end of treatment; ULN, upper limit of normal; sc, subcutaneous; qd, once daily.

Study Endpoints

Primary Study Endpoint:

The proportion of patients achieving combined response at Week 48:

- HDV RNA undetectable *or* decrease of ≥ 2 $\log_{10}$ IU/mL from baseline and
- ALT normalization[1]

Week 96 Analysis Endpoints:

The proportion of patients with:

- HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL or undetectable HDV RNA
- Undetectable HDV RNA
- ALT normalization
- Change in liver stiffness (transient elastography)
- Adverse events (AEs)

ALT, alanine transaminase. HDV RNA was manual extracted and viral load quantified by RoboGene® 2.0, LLOQ 50 IU/mL.

1. As recommended by: Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance November 2019.

Demographic and Disease Characteristics

		Delayed Treatment/ BLV 10 mg n=51	BLV 2 mg n=49	BLV 10 mg n=50
Mean age, years (SD)		41 (8)	44 (9)	41 (9)
Male sex, n (%)		26 (51)	30 (61)	30 (60)
Race[#], n (%)	White	40 (78)	41 (84)	43 (86)
	Asian	11 (22)	8 (16)	6 (12)
Cirrhosis, n (%)		24 (47)	23 (47)	24 (48)
Mean platelets, $X10^3$ cells/mm^3 (SD)		158 (57)	153 (53)	160 (53)
Mean liver stiffness, kPa (SD)		15.3 (9.0)	14.0 (8.2)	14.8 (9.3)
Mean ALT, U/L (SD)		102 (62)	108 (63)	123 (81)
Mean HDV RNA, log_{10} IU/mL (SD)		5.08 (1.36)	5.10 (1.20)	4.96 (1.46)
HDV genotype 1, n (%)*		51 (100)	49 (100)	48 (96)
Mean HBsAg, log_{10} IU/mL (SD)		3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
HBV DNA >10 IU/mL, positive, n (%)		13 (26)	14 (29)	11 (22)
Mean HBV DNA, log_{10} IU/mL (SD)		0.89 (0.99)	1.30 (1.29)	1.08 (1.26)
HBeAg positive, n (%)		4 (8)	4 (8)	7 (14)
HBV genotype, n (%)	A	4 (8)	2 (4)	3 (6)
	D	39 (77)	44 (90)	43 (86)
	Other^/Missing	8 (16)	3 (6)	4 (8)
Previous IFN therapy, n (%)		29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)		32 (63)	32 (65)	27 (54)

[#]BLV 10-mg group: n=1 Black; *BLV 10-mg group: n=1 HDV GT 5, n=1 missing HDV GT; ^BLV 10-mg group: n=1 HBV GT E. HBeAg, hepatitis B e antigen; IFN, interferon; IQR, interquartile range; NUC, nucleos(t)ide; GT: genotype.

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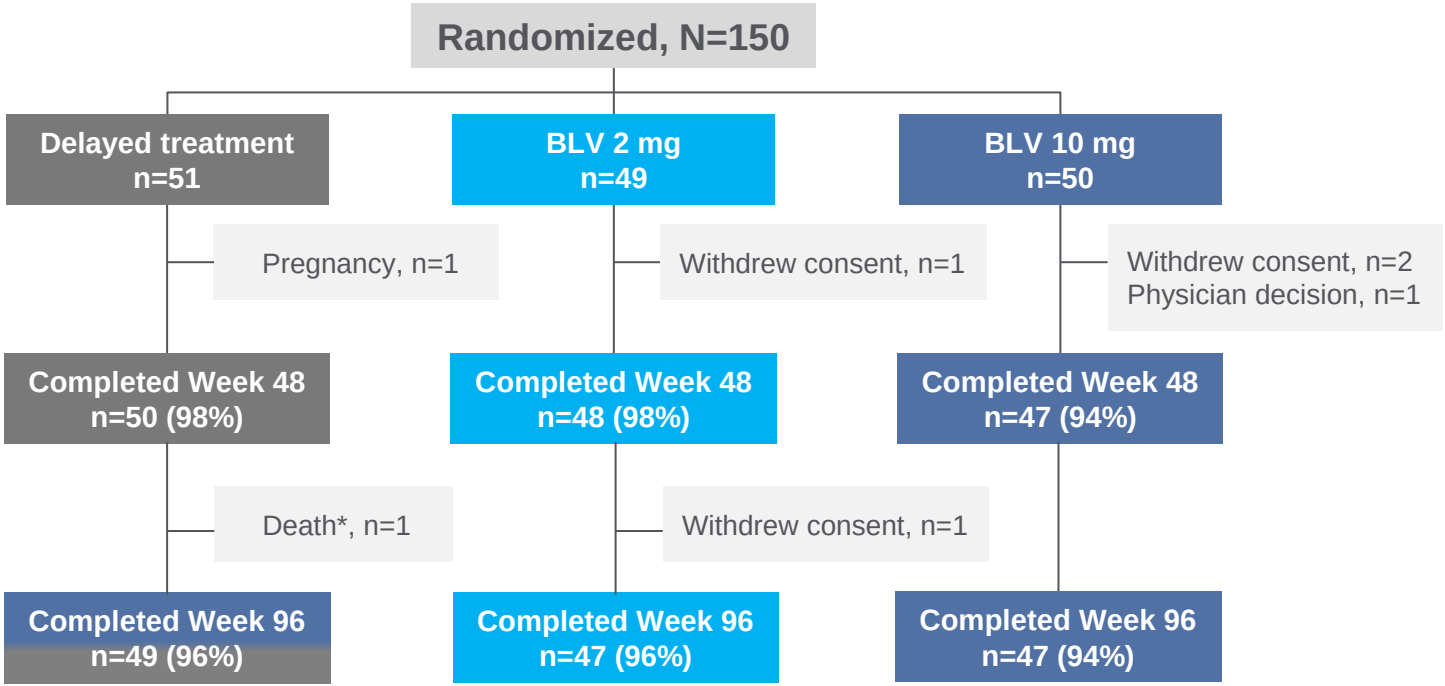
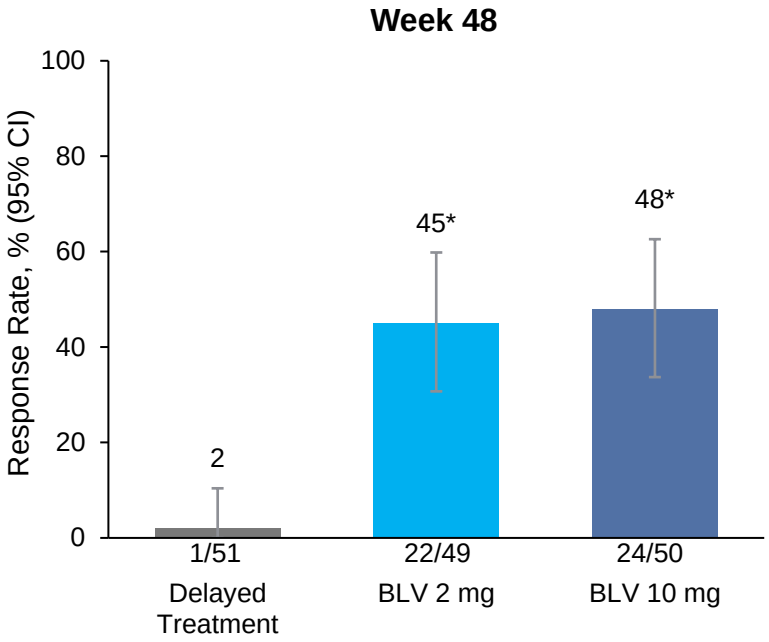
Patient Disposition



− 2 patients did not complete week 96, none related to study treatment

BLV, bulevirtide. *One death due to plasma cell myeloma.

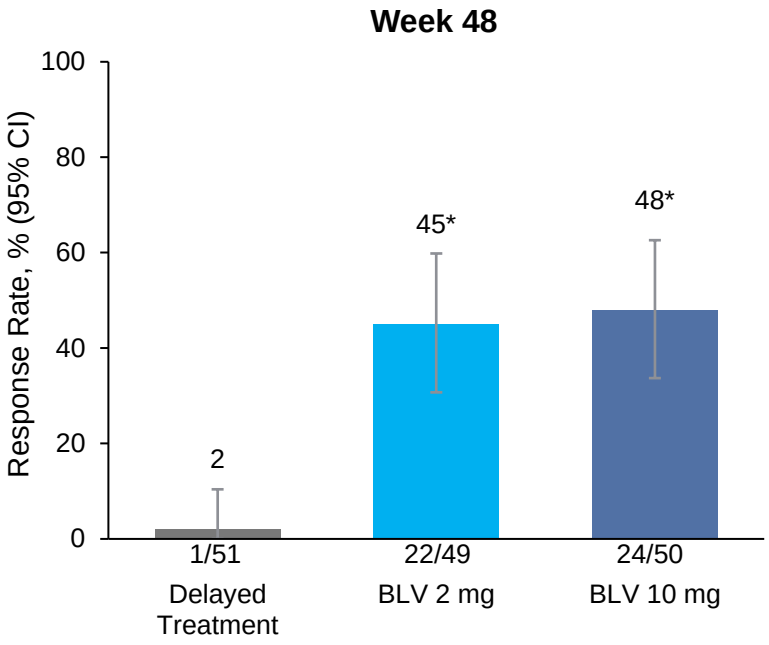
Results: Combined Response

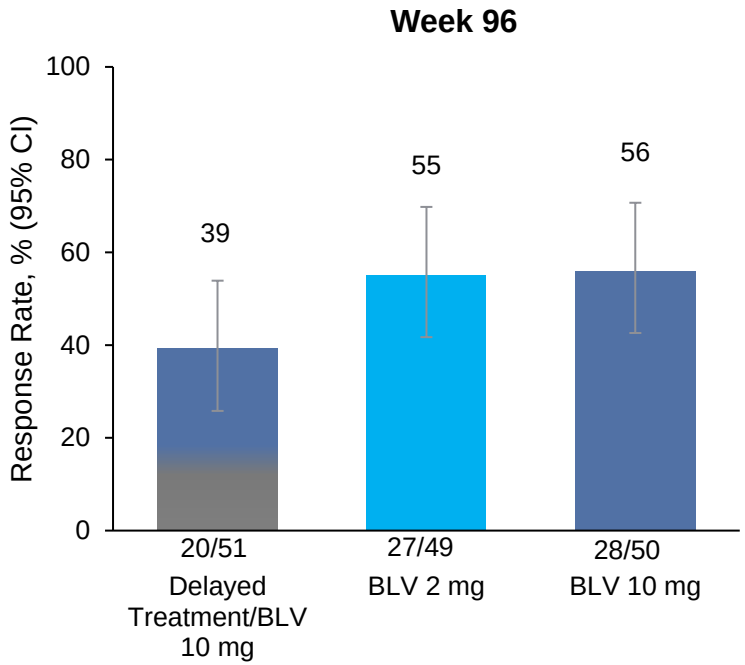


- **Combined response:** HDV RNA undetectable or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization

*p<0.0001 vs Delayed treatment arm. Combined response defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL and ALT Normalization; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). BLV, bulevirtide.

Results: Combined Response

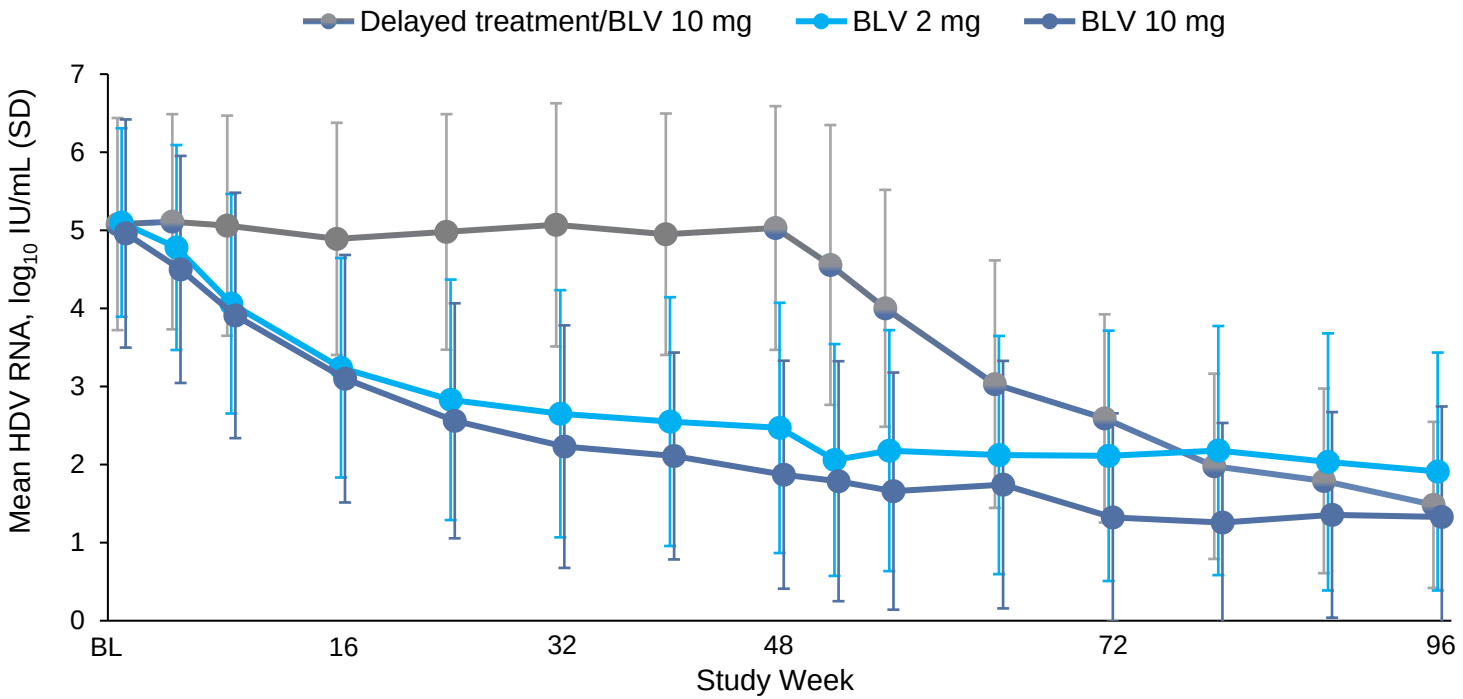




- Combined response rates were increased at Week 96 in all arms; similar response between BLV 2-mg and 10-mg doses

*p<0.0001 vs Delayed treatment arm. Combined response defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL and ALT Normalization; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). BLV, bulevirtide.

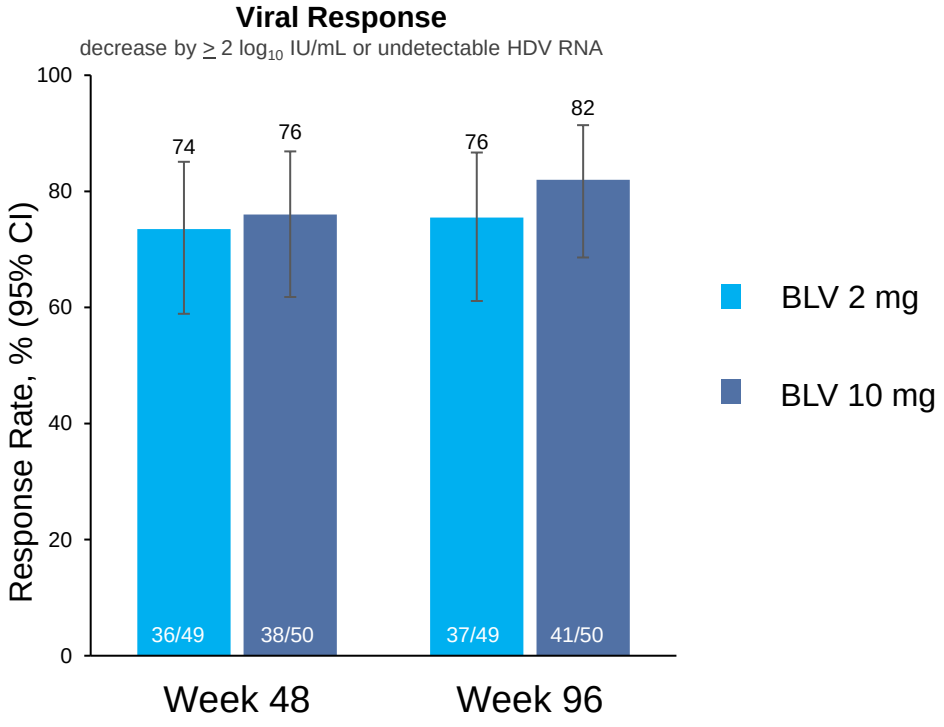
Results: HDV RNA Decline Over 96 Weeks

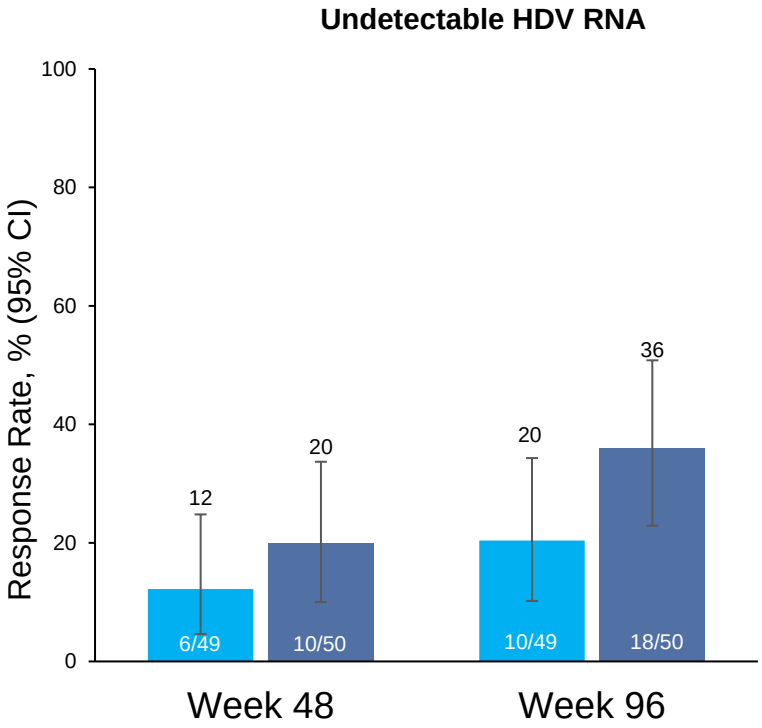


– Similar mean HDV RNA declines were seen over 96 weeks with BLV 2 mg and 10 mg

BL, baseline; BLV bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus.

Results: Virologic Endpoints

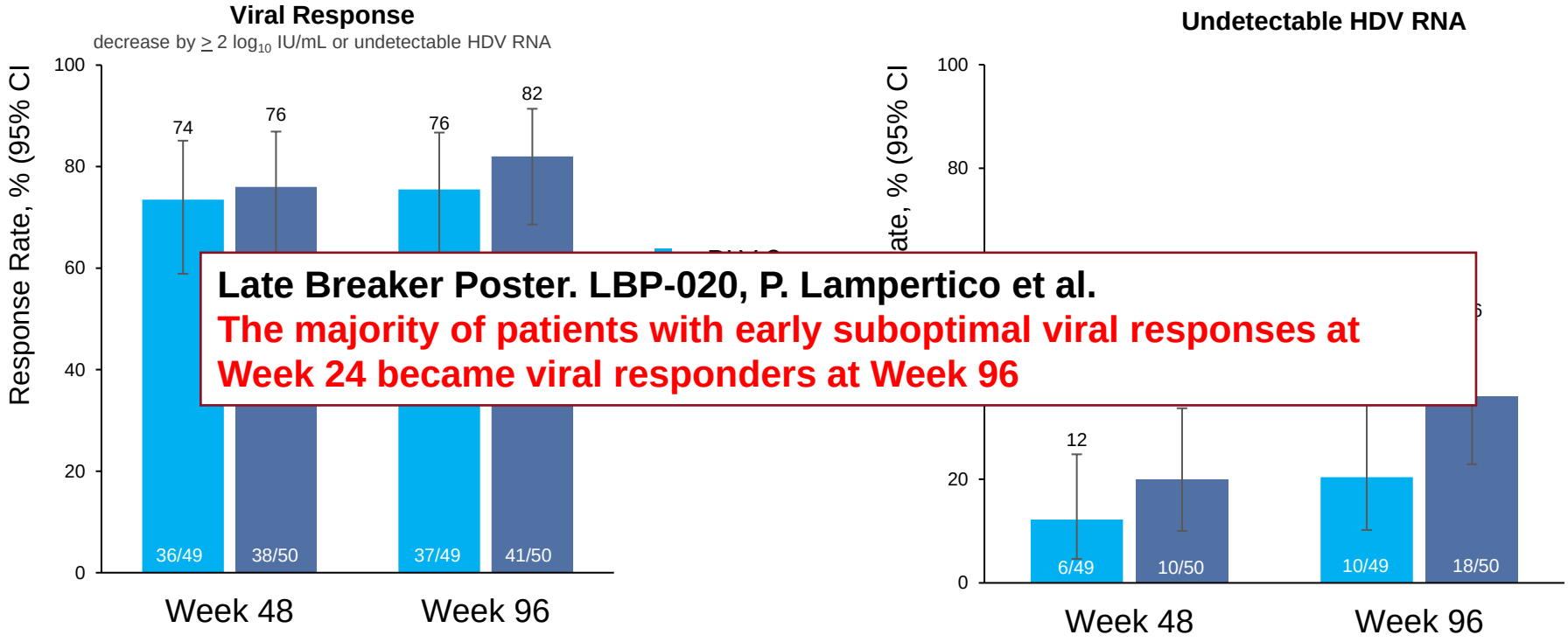




− Rates of virological response in BLV arms increased over time

Viral response defined as HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). BLV: bulevirtide; HDV, hepatitis delta virus.

Results: Virologic Endpoints



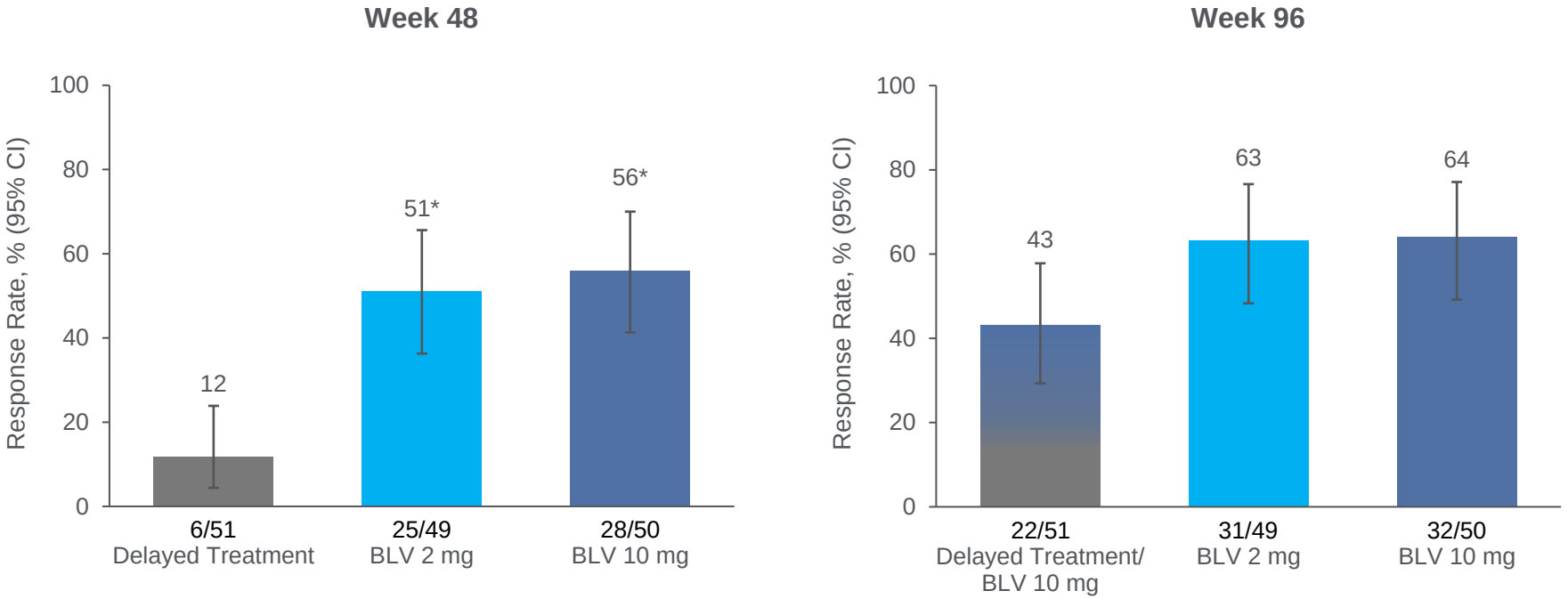
Late Breaker Poster. LBP-020, P. Lampertico et al.

The majority of patients with early suboptimal viral responses at Week 24 became viral responders at Week 96

- Rates of virological response in BLV arms increased over time

Viral response defined as HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). BLV: bulevirtide; HDV, hepatitis delta virus.

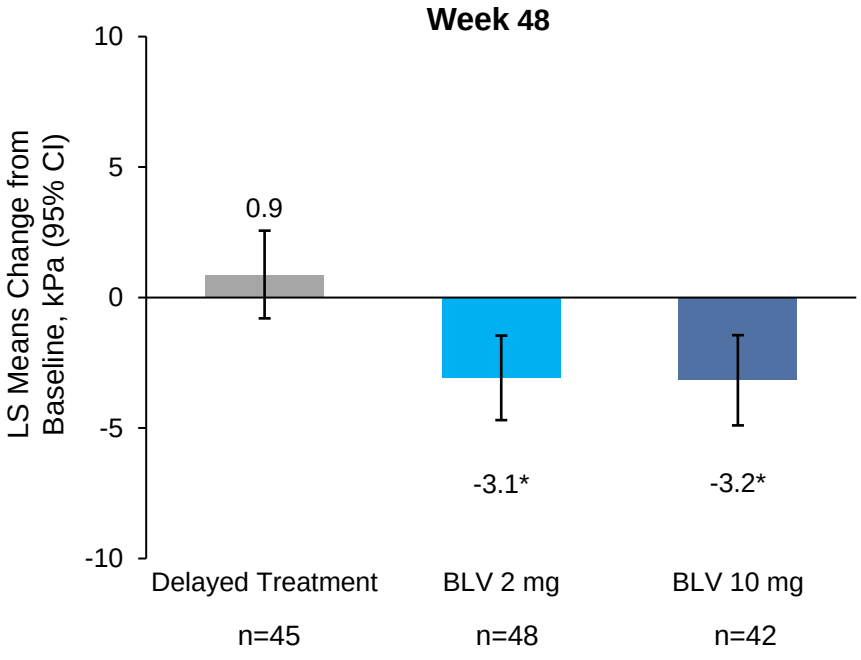
Results: ALT Normalization

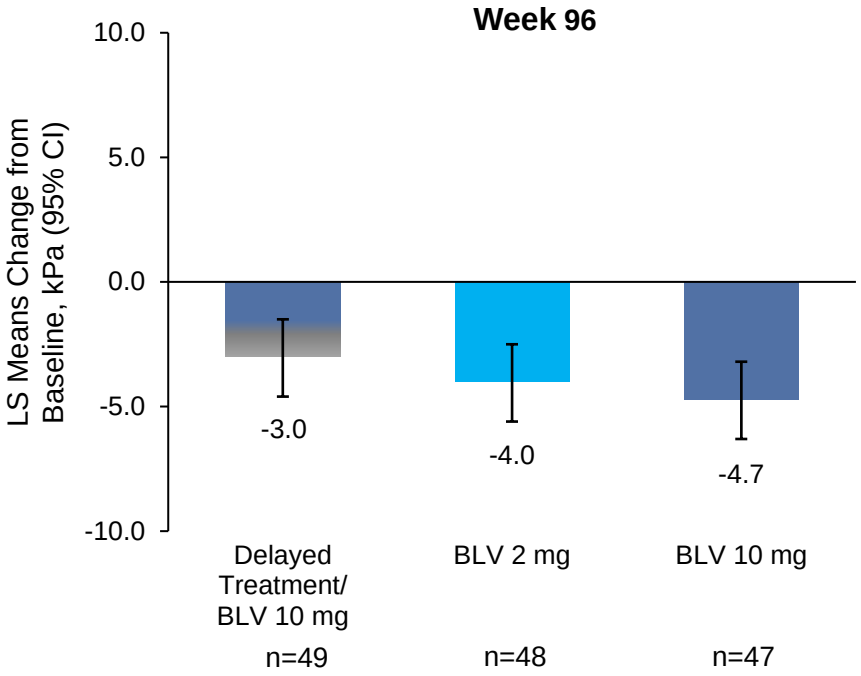


- Rates of biochemical response improved over time and were similar between doses

*p<0.0001 vs Delayed treatment arm. ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). ALT, alanine transaminase; BLV, bulevirtide.

Results: Change in Liver Stiffness at Weeks 48 and 96





- BLV was associated with continued reductions in liver stiffness by transient elastography

*p=0.0010 vs Delayed treatment arm. BLV, bulevirtide; LS, least-squares.

Results: HBV Efficacy Endpoints at Week 96

		Delayed Treatment/BLV 10 mg n=51	BLV 2 mg n=49	BLV 10 mg n=50
HBsAg	HBsAg loss, n (%)	0	0	0
	HBsAg response: >1 $\log_{10}$ IU/mL decrease, n (%)	1 (2)	0	1 (2)
	LS mean change in HBsAg, $\log_{10}$ IU/mL (95% CI)	-0.152 (-0.277, -0.026)	-0.240 (-0.370, -0.110)	-0.139 (-0.271, -0.007)

- No events of HBsAg loss were observed and changes in HBsAg levels were minimal

BLV, bulevirtide; HBsAg, hepatitis B s antigen HBV, hepatitis B virus; LS, least-squares.

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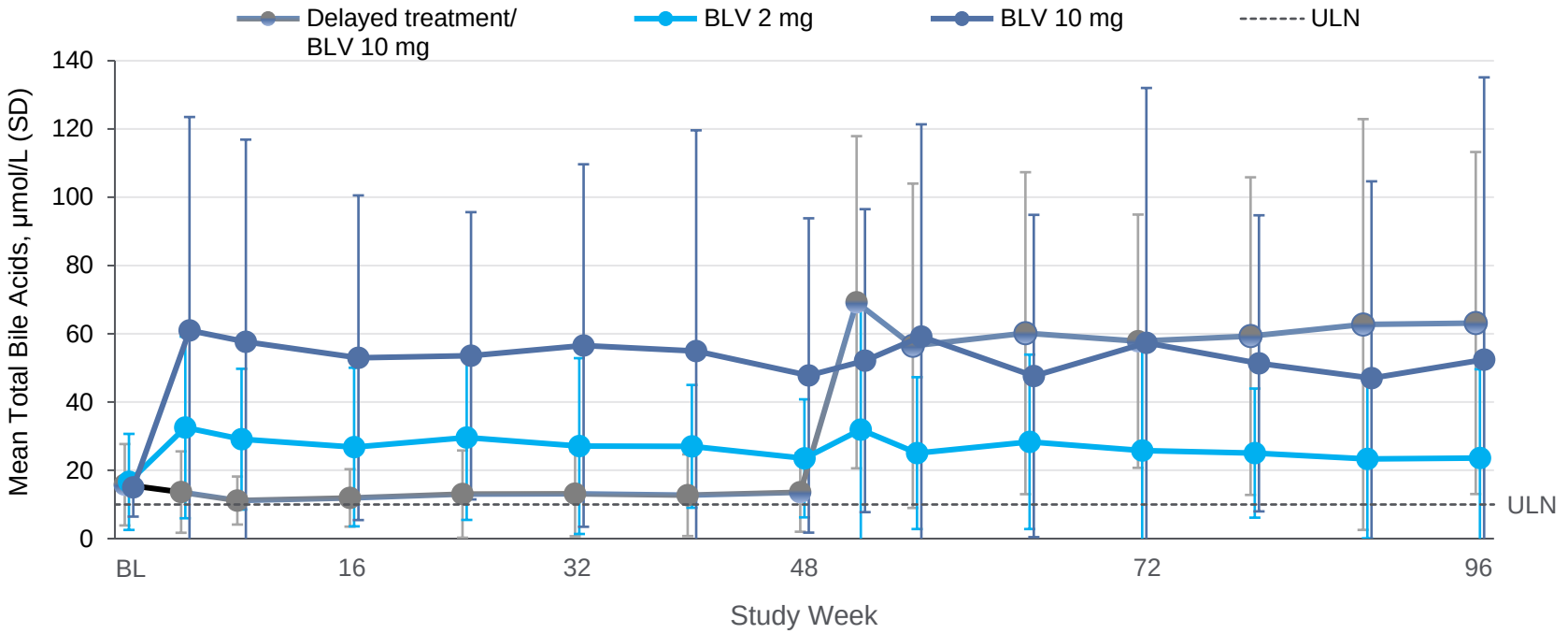
HBV DNA	Mean change from BL in HBV DNA, $\log_{10}$ IU/mL (SD)	-0.363 (0.889)	-0.583 (1.305)	-0.599 (1.073)

- No events of HBsAg loss were observed and changes in HBsAg levels were minimal
- Small declines in HBV DNA levels were observed with BLV treatment in patients not on NUC treatment

BLV, bulevirtide; HBsAg, hepatitis B s antigen HBV, hepatitis B virus; LS, least-squares.

Results: Total Bile Acids Levels Over 96 Weeks



- Dose-dependent asymptomatic elevations in total bile acids were observed with BLV treatment which were less pronounced in the 2 mg dose group

Safety analysis set. BLV, bulevirtide; ULN, upper limit of normal.

Safety: Overall Summary

Patients With, n (%)		Delayed Treatment/ BLV 10 mg (n=51)		BLV 2 mg (n=49)		BLV 10 mg (n=50)	
		Week 48	Week 48-96*	Week 48	Week 96	Week 48	Week 96
Any AE		39 (77)	42 (84)	41 (84)	47 (96)	44 (88)	48 (96)
Any Grade 3–4 AE		4 (8)	3 (6)	5 (10)	9 (18)	4 (8)	8 (16)
Any SAE		1 (2)	2 (4)	2 (4)	2 (4)	1 (2)	4 (8)
Any AE leading to withdrawal of BLV		0	0	0	0	0	0
Any AE related to BLV		0	22 (44)	24 (49)	25 (51)	36 (72)	36 (72)
Death		0	1 (2)[1]	0	0	0	0
AEs of interest[§]	Headache	0	7 (14)	9 (18)	9 (18)	10 (20)	12 (24)
	Dizziness	0	1 (2)	2 (4)	2 (4)	3 (6)	4 (8)
	Nausea	2 (4)	1 (2)	3 (6)	3 (6)	4 (8)	6 (12)
	Pruritis	0	0	6 (12)	6 (12)	8 (16)	9 (18)
	Fatigue	1 (2)	2 (4)	5 (10)	7 (14)	7 (14)	9 (18)
	Injection site reactions[¶]	0	3 (6)	9 (18)	10 (20)	15 (30)	15 (30)

- No SAEs or AEs leading to discontinuation of study drug were related to BLV
- Injection site reactions were mild to moderate in severity and occurred at a higher frequency with BLV 10 mg

All AEs were treatment emergent over 96 weeks. *n=50; [§]AEs with higher frequencies in BLV groups compared to delayed treatment; [¶]Grouped term including injection site (reaction, erythema, pruritus, swelling, pain, haematoma, rash, abscess, dermatitis, irritation). AE, adverse event; BLV, bulevirtide; SAE, serious adverse event.

[1] 1 death due to plasma cell myeloma not related to study treatment.

Safety: Grade 3 or 4 AE#s & Laboratory Abnormalities

Patients with, n (%) (>1 Patient per arm)		Delayed Treatment/ BLV 10 mg (n=51)		BLV 2 mg (n=49)		BLV 10 mg (n=50)	
		Week 48	Week 48-96	Week 48	Week 96	Week 48	Week 96
Grade ≥3 AEs*	**Any Grade ≥3 AE**	4 (8)	3 (6)	5 (10)	9 (18)	4 (8)	8 (16)
	Thrombocytopenia	3 (6)	0	1 (2)	1 (2)	2 (4)	2 (4)
	Neutropenia	2 (4)	0	0	1 (2)	2 (4)	2 (4)
Grade ≥3 Laboratory Abnormalities	**Any Grade ≥3**	6 (12)	7 (14)	6 (12)	9 (18)	5 (10)	9 (18)
	Neutrophils decreased	2 (4)	3 (6)	1 (2)	2 (4)	2 (2)	4 (8)
	Platelets decreased	2 (4)	2 (4)	2 (4)	2 (4)	4 (8)	7 (14)
	Hypokalemia	1 (2)	0	0	2 (4)	0	0

- No case of Grade 3 or 4 elevation in total bile salts or eosinophils were observed through 96 weeks

#All treatment-emergent adverse events; *Grade ≥3 AEs, 1 participant each: BLV 10 mg: COVID-19, Leukopenia, Coronavirus pneumonia, Headache, Neutrophil count decrease, Osteoarthritis, Lumbar vertebral fracture; Activated partial thromboplastin time prolonged; BLV 2 mg: Foot fracture, Neutrophil count decreased, Osteopenia, Depression, Headache, Blood chloride decreased, Blood sodium decreased, Lipase increased; Delayed treatment/BLV 10 mg: Leukopenia, Urinary tract infections, Neutrophil count decreased.

Summary/Conclusions

— In patients with chronic HDV, treatment with BLV for 96 weeks demonstrated:

- Improved combined response with BLV at week 96 vs week 48
- Similar combined response between BLV 2 mg and 10 mg doses
- Increased proportion with undetectable HDV RNA at week 96 in both BLV 2 mg and 10 mg arms compared to week 48
- Continued improvement in liver stiffness through week 96 with BLV treatment at both 2 mg and 10 mg doses
- No relevant effect of BLV monotherapy on HBsAg or HBV DNA in either study arm
- BLV remained safe and well tolerated with no discontinuation for adverse events

Treatment with BLV for 96 weeks is safe and efficacious

BLV, bulevirtide; HDV, hepatitis delta virus.

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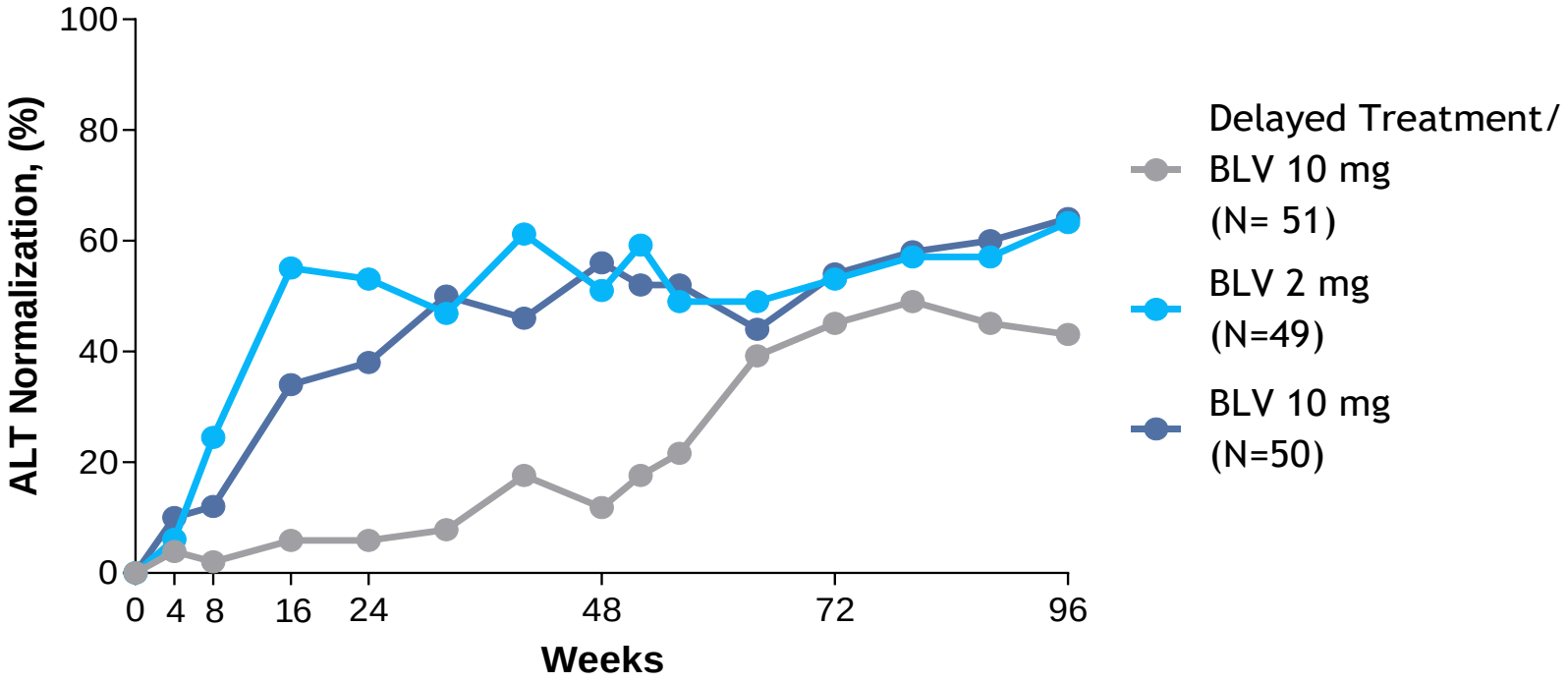
Back-up Slides

ALT Normalization Over Time



- Rates of biochemical response increased over time and were similar between doses

ALT: Alanine transaminase; BLV : bulevirtide; PegIFNα: pegylated interferon alpha

Safety: Serious Adverse Events

Patients With, n (%)	Delayed Treatment/ BLV 10 mg (n=51)		BLV 2 mg (n=49)		BLV 10 mg (n=50)	
	Week 48	Week 48-96*	Week 48	Week 96	Week 48	Week 96
Any SAE	1 (2)	2 (4)	2 (4)	2 (4)	1 (2)	4 (8)
Cholelithiasis	1					
Covid-19	1					
Covid-19 pneumonia					1	1
Coronavirus pneumonia						1
Urinary tract infection		1				
Foot Fracture			1			
Lumbar vertebral fracture						1
Plasma cell myeloma		1				
Headache			1			
Hemiparesis			1			
Depression			1			

All AEs were treatment emergent over 96 weeks. *n=50; §AEs with higher frequencies in BLV groups compared to delayed treatment; ¶Grouped term including injection site (reaction, erythema, pruritus, swelling, pain, haematoma, rash, abscess, dermatitis, irritation). AE, adverse event; BLV, bulevirtide; SAE, serious adverse event; ISR, injection site reactions.

[1] 1 death due to plasma cell myeloma not related to study treatment.