NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

Starhotels E.c.ho. Milano

UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Università degli Studi della Campania *Luigi Vanvitelli*

Conference

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Hepatitis delta: a curable disease

Nicola Coppola

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Infectious Diseases Unit, AOU Vanvitelli
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In questa slide il Docente dovrà dichiarare l'eventuale conflitto d'interessi ed indicare:

Il sottoscritto **Nicola Coppola**
in qualità di (moderatore, relatore, formatore, tutor, docente)

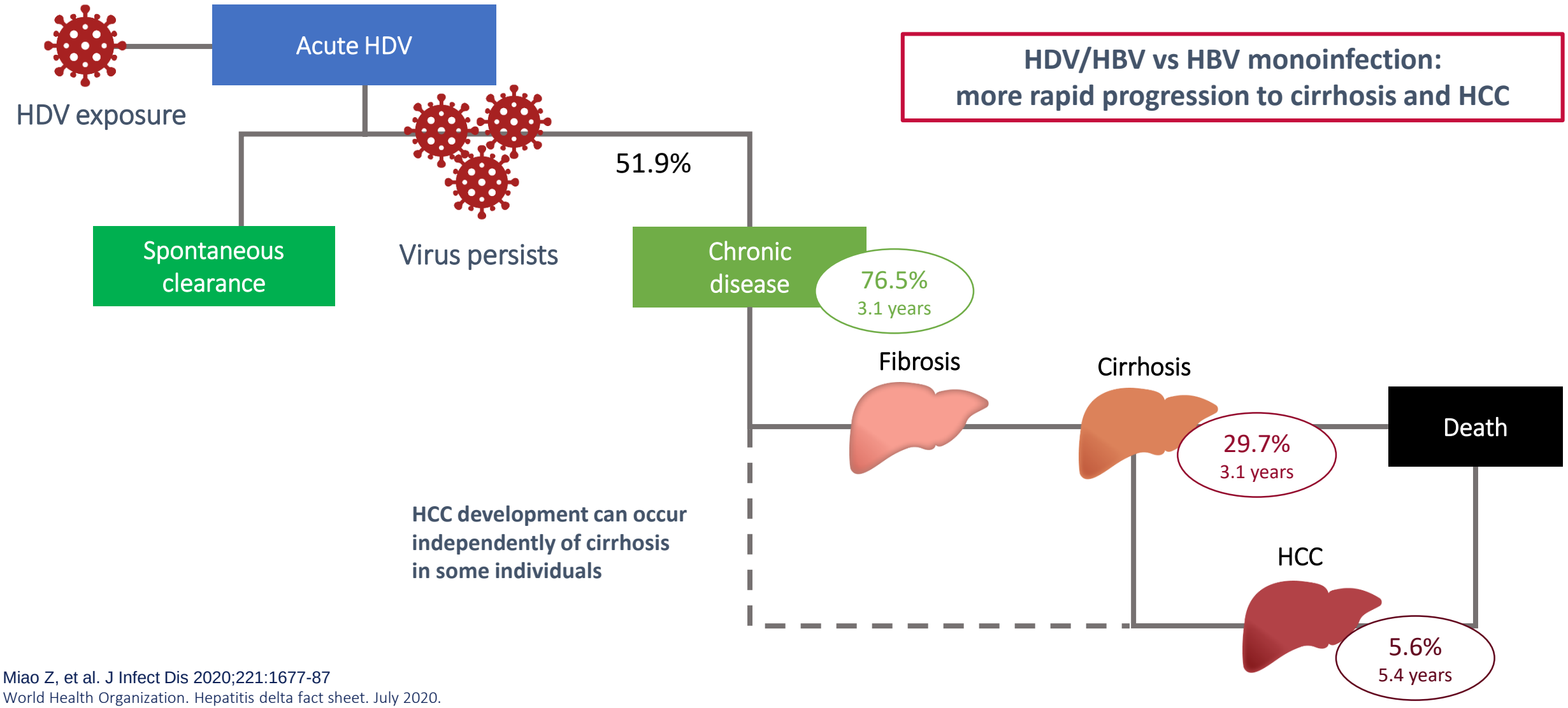
-ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

-- grants from ViiV Healthcare, Janssen-Cilag and Gilead Science
- personal fees from Gilead Sciences, Abbvie, Bristol-Myers Squibb, Correvio, Merk-Sharp & Dohme, Angelini, Shionogi

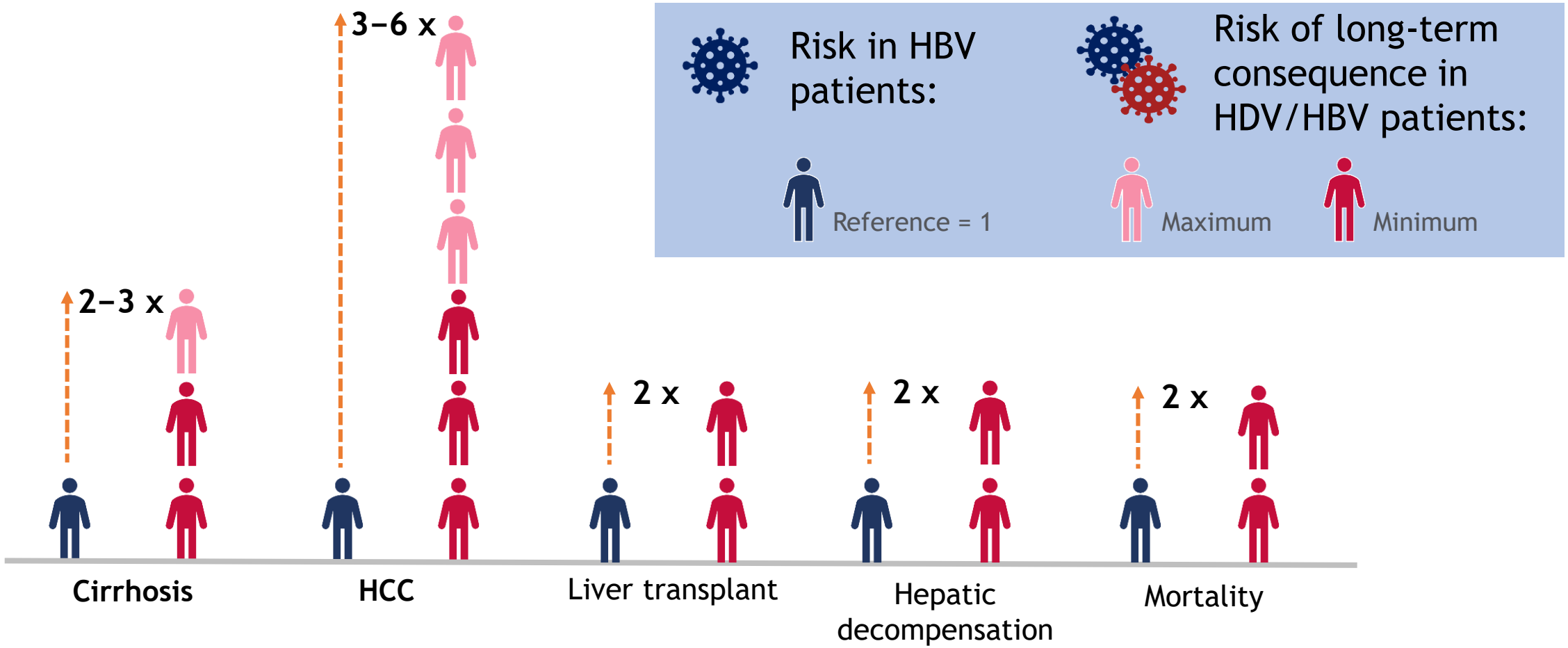
Clinical course of hepatitis delta



Miao Z, et al. J Infect Dis 2020;221:1677-87
World Health Organization. Hepatitis delta fact sheet. July 2020.
https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. Accessed March 2021.

HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

Increased risk of long-term consequences of viral hepatitis in HBV/HDV patients versus HBV monoinfection



Disease progression in chronic hepatitis B is not linear and HCC can develop in the absence of cirrhosis.
HBV: hepatitis B virus;
HCC: hepatocellular carcinoma; HDV: hepatitis delta virus

Da BL, et al. Gastroenterol Rep 2019;7:231-45.

Adjusted HDV Prevalence in 21 Countries/Territories

Prevalence of HDV among HBsAg+ Populations Based on Literature Review and Expert Validation							
Region	Country/Territory	2023 HBsAg+ (n)	Unadjusted*		Adjusted‡		
			Anti-HDV+** (%)	HDV RNA+† (%)	Anti-HDV+** (%)	RNA+ HDV Prevalence (%)	RNA+ HDV Cases**§ (n)
Asia	Mainland China	78,548,000	1.2	66.6	1.2	0.8	627,800
	Taiwan	1,864,000	3.3	60.0	0.9	0.5	10,100
	Republic of Korea	1,360,000	0.3	54.0	0.3	0.2	2,200
	Japan	926,000	8.5	40.8	0.5	0.2	1,900
	Hong Kong	332,000	0.2	60.0	0.2	0.1	300
Europe	England	418,400	2.9	50.0	1.0	0.5	2,100
	France	142,000	1.8	75.0	3.5	2.7	3,800
	Germany	215,000	5.5	60.0	3.0	1.8	3,900
	Spain	208,000	5.2	72.9	2.3	1.7	3,500
	Italy	301,600	8.3	60.5	3.4	2.0	6,200
	Portugal	110,000	12.6	72.9	1.5	1.1	1,200
	Sweden	31,000	3.8	75.0	2.0	1.6	500
	Romania	568,000	23.1	80.0	2.9	2.3	13,200
Middle East	Israel	129,000	6.5	60.0	6.8	4.1	5,300
	Saudi Arabia	570,000	8.6	60.0	4.0	2.4	13,700
	Turkey	1,962,000	2.8	68.0	2.8	1.9	37,300
North America	USA	1,650,000	6.0	66.0	3.0	2.0	32,700
	Mexico	116,000	2.4	69.9	0.2	0.2	200
	Canada	214,000	1.6	64.8	4.4	2.9	6,100
South America	Brazil	1,025,000	3.2	75.3	1.7	1.3	13,100
	Colombia	302,000	5.2	69.9	1.0	0.7	2,100

Adjusted prevalence figures provide an updated picture of HDV burden globally

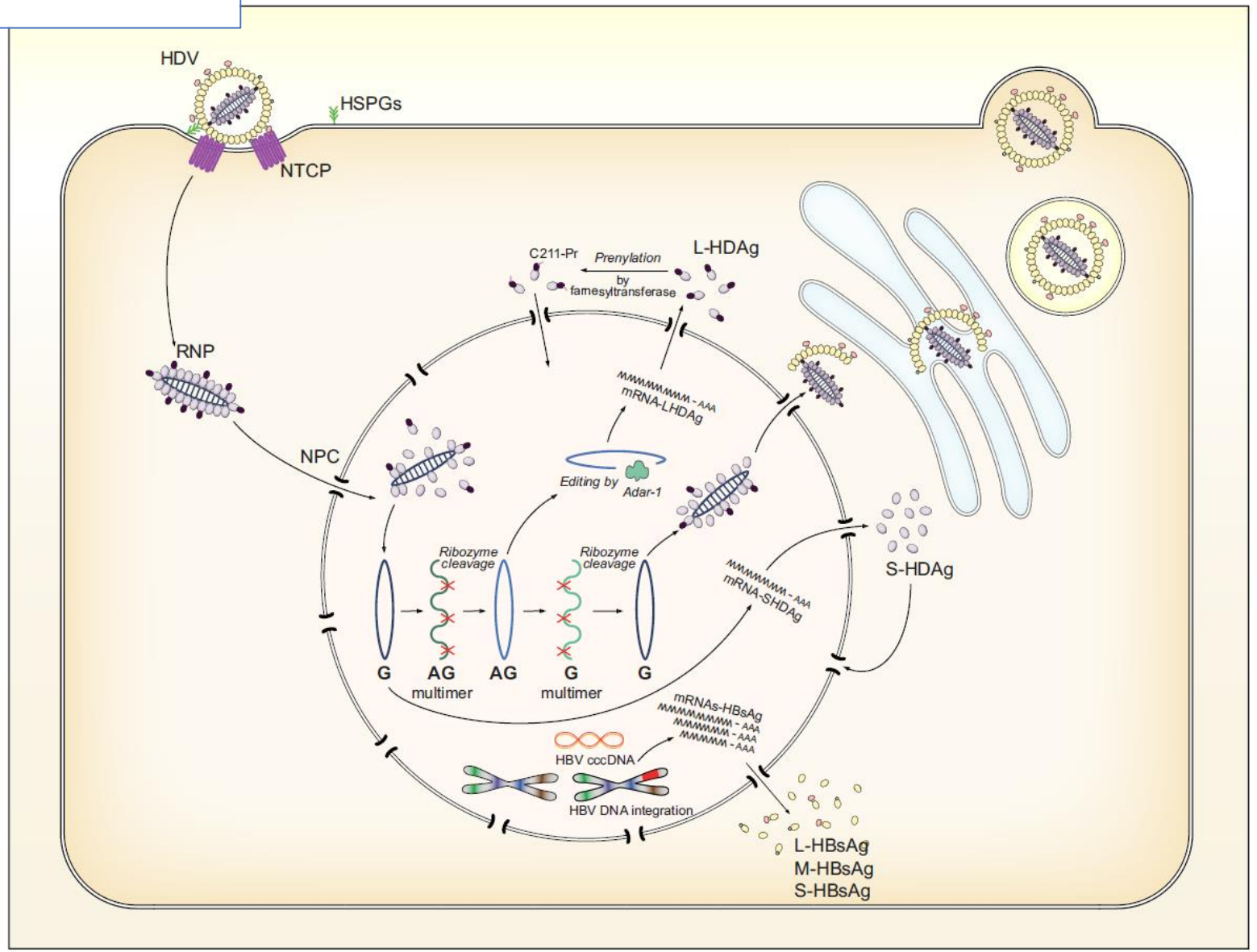
*Unadjusted based on literature; **Among the HBsAg+ population; †Among the anti-HDV+ population; ‡Adjusted for geographical distribution, disease stage and special populations; §Adjusted for HDV RNA positivity.
Razavi-Shearer D, et al. EASL 2023. FRI-116

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis delta virus☆

European Association for the Study of the Liver*



EASL Clinical practice HDV guidelines, J Hepatol 2023

Treatment of HDV infection

- **Interferon**
- **Lonafarnib**
- **Bulevirtide**
- **Future options**

The NEW ENGLAND JOURNAL of MEDICINE

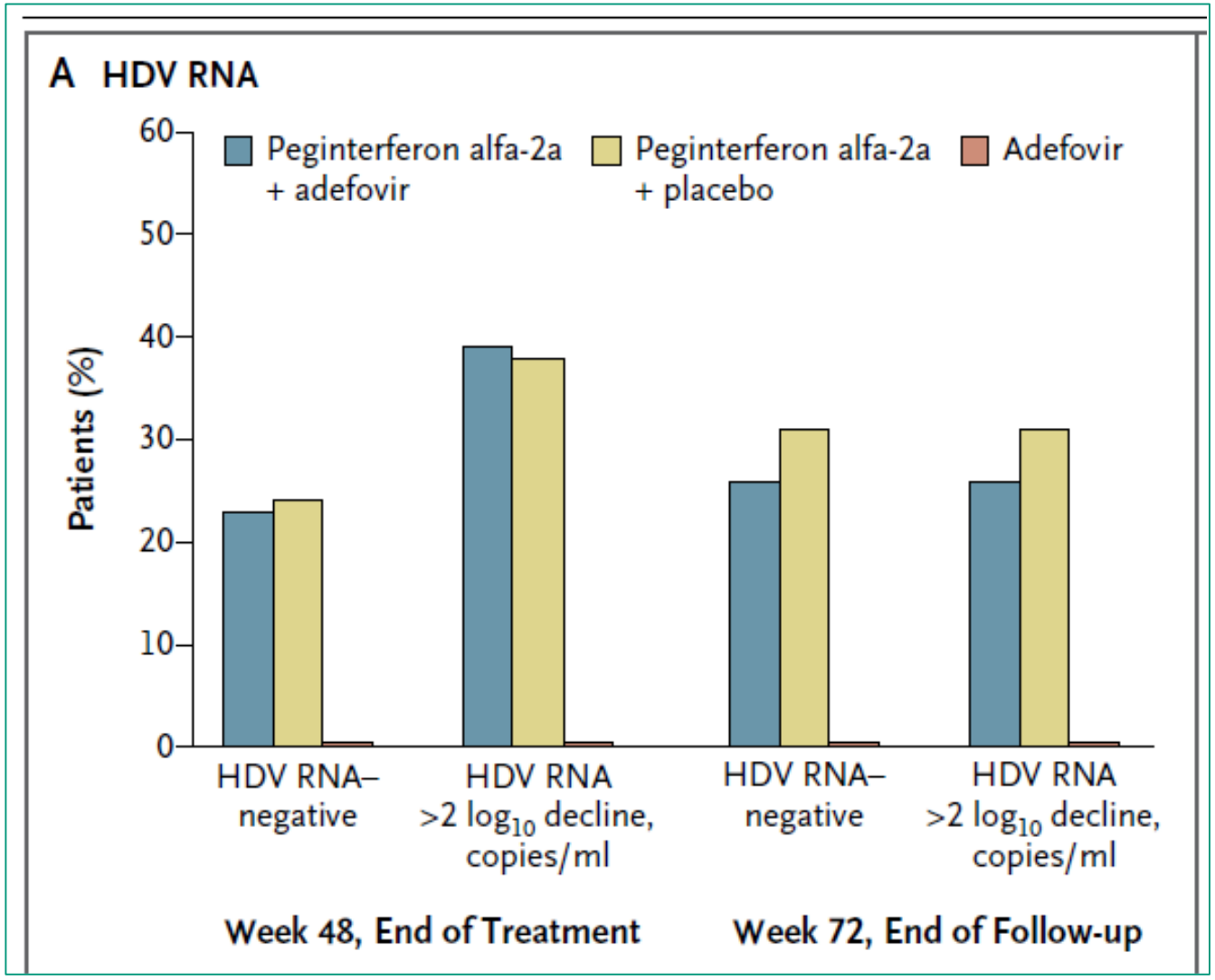
ORIGINAL ARTICLE

Peginterferon plus Adefovir versus Either Drug Alone for Hepatitis Delta

Heiner Wedemeyer, M.D., Cihan Yurdaydìn, M.D., George N. Dalekos, M.D., Andreas Erhardt, M.D., Yilmaz Çakaloğlu, M.D., Halil Değertekin, M.D., Selim Gürel, M.D., Stefan Zeuzem, M.D., Kalliopi Zachou, M.D., Hakan Bozkaya, M.D., Armin Koch, M.D., Thomas Bock, M.D., Hans Peter Dienes, M.D., and Michael P. Manns, M.D., for the HIDIT Study Group*

A randomized trial (HIDIT-I) in which 60 HDV patients were treated for 48 weeks

- **31 with Peg-IFN plus adefovir**



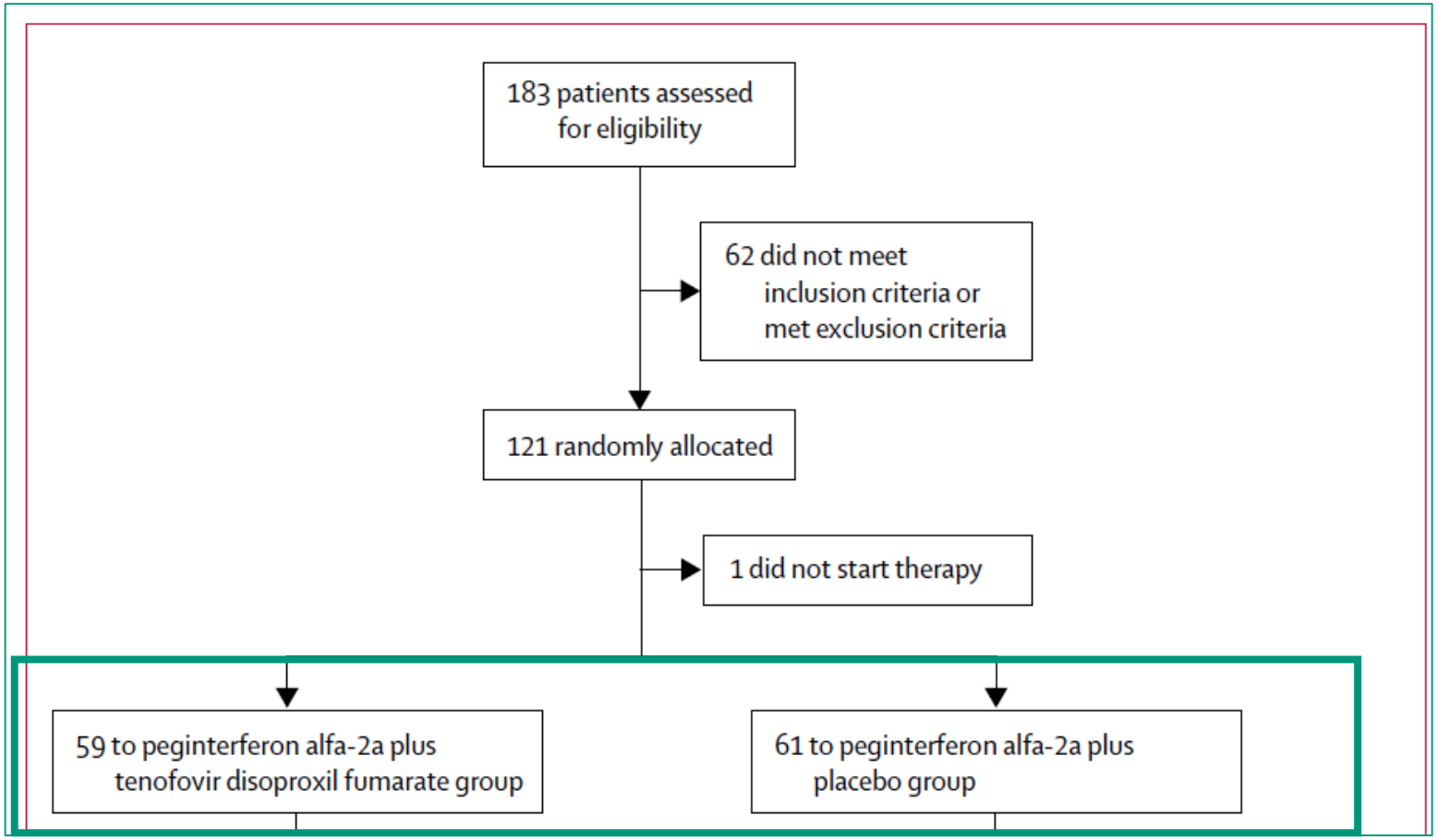
NEJM 2011

Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial

Heiner Wedemeyer, Cihan Yurdaydin*, Svenja Hardtke, Florin Alexandru Caruntu, Manuela G Curescu, Kendal Yalcin, Ulus S Akarca, Selim Gürel, Stefan Zeuzem, Andreas Erhardt, Stefan Lüth, George V Papatheodoridis, Onur Keskin, Kerstin Port, Monica Radu, Mustafa K Celen, Ramazan Idilman, Kristina Weber, Judith Stift, Ulrike Wittkop, Benjamin Heidrich, Ingmar Mederacke, Heiko von der Leyen, Hans Peter Dienes, Markus Cornberg, Armin Koch, Michael P Manns, for the HIDIT-II study team†*

A double blinding randomized trial (HIDIT-II) in which 120 HDV patients were treated for 96 weeks
- **59 with Peg-IFN plus Tenofovir**
- **61 with Peg-IFN and placebo**

End point: undetectable HDV RNA at the end of treatment assessed by intention to treat



Lancet Infect Dis 2019

Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis D (HIDIT-II): a randomised, placebo controlled, phase 2 trial

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A double blinding randomized trial in which 120 HDV patients were treated for 96 weeks

- **31 with Peg-IFN plus Tenofovir**
- **29 with Peg-IFN and placebo**

	Baseline	Week 12	Week 24	Week 48	Week 72	Week 96	Week 120
HDV RNA negative							
Peginterferon alfa-2a plus TDF (n=59)	1 (2%)	14 (24%)	21 (36%)	25 (42%)	23 (39%)	28 (48%)	18 (31%)
Peginterferon alfa-2a plus placebo (n=61)	1 (2%)	9 (15%)	18 (30%)	21 (34%)	19 (31%)	20 (33%)	14 (23%)
OR (95% CI), p value	..	1·71 (0·67–4·41), 0·26	1·32 (0·60–2·89), 0·49	1·60 (0·73–3·48), 0·24	1·66 (0·74–3·71), 0·22	1·84 (0.86–3·91), 0·1154	1·46 (0·64–3·31), 0·37
HBsAg decline ≥0·5% from baseline							
Peginterferon alfa-2a plus TDF (n=59)	..	4 (6·8%)	10 (16·9%)	14 (23·7%)	11 (18·6%)	17 (28·8%)	12 (20·3%)
Peginterferon alfa-2a plus placebo (n=61)	..	4 (6·6)	18 (29·5)	15 (24·6)	9 (14·8)	12 (19·7)	14 (23·0%)
OR (95% CI), p value	..	0·90 (0·21–3·90), 0·89	0·40 (0·15–1·03), 0·057	1·08 (0·41–2·86), 0·88	1·60 (0·54–4·67), 0·40	1·74 (0·67–4·51), 0·25	0·85 (0·32–2·26), 0·75
Normal ALT values							
Peginterferon alfa-2a plus TDF (n=59)	8 (14%)	12 (20%)	12 (20%)	18 (31%)	21 (36%)	26 (44%)	27 (46%)
Peginterferon alfa-2a plus placebo (n=61)	3 (5%)	10 (16%)	15 (25%)	16 (26%)	23 (38%)	23 (38%)	16 (26%)
OR (95% CI), p value	3·18 (0·79–12·82), 0·10	1·30 (0·51–3·34), 0·58	0·76 (0·30–1·94), 0·56	1·44 (0·61–3·37), 0·40	1·12 (0·49–2·57), 0·79	1·58 (0·72–3·48), 0·26	3·42 (1·38–8·47), 0·008

HDV=hepatitis D virus. TDF=tenofovir disoproxil fumarate. OR=odds ratio. ALT=alanine aminotransferase.

Table 2: Virological and biochemical treatment response

Lancet Infect Dis 2019

Treatment of HDV infection

- **Interferon=** **20-30% of HDV-RNA negativity at 24wks after the stop of IFN (with or without NUC)**
- **Lonafarnib**
- **Bulevirtide**
- **Future options**

Treatment of chronic hepatitis D with peginterferon lambda—the phase 2 *LIMT-1* clinical trial

Ohad Etzion[1,2] | Saeed Hamid[3] | Yoav Lurie[4] | Edward J. Gane[5]
David Yardeni[1,2] | Sarah Duehren[6] | Nimrah Bader[3] |
Anat Nevo-Shor[1,2] | Saleh Muhammad Channa[7] | Scott J. Cotler[6]
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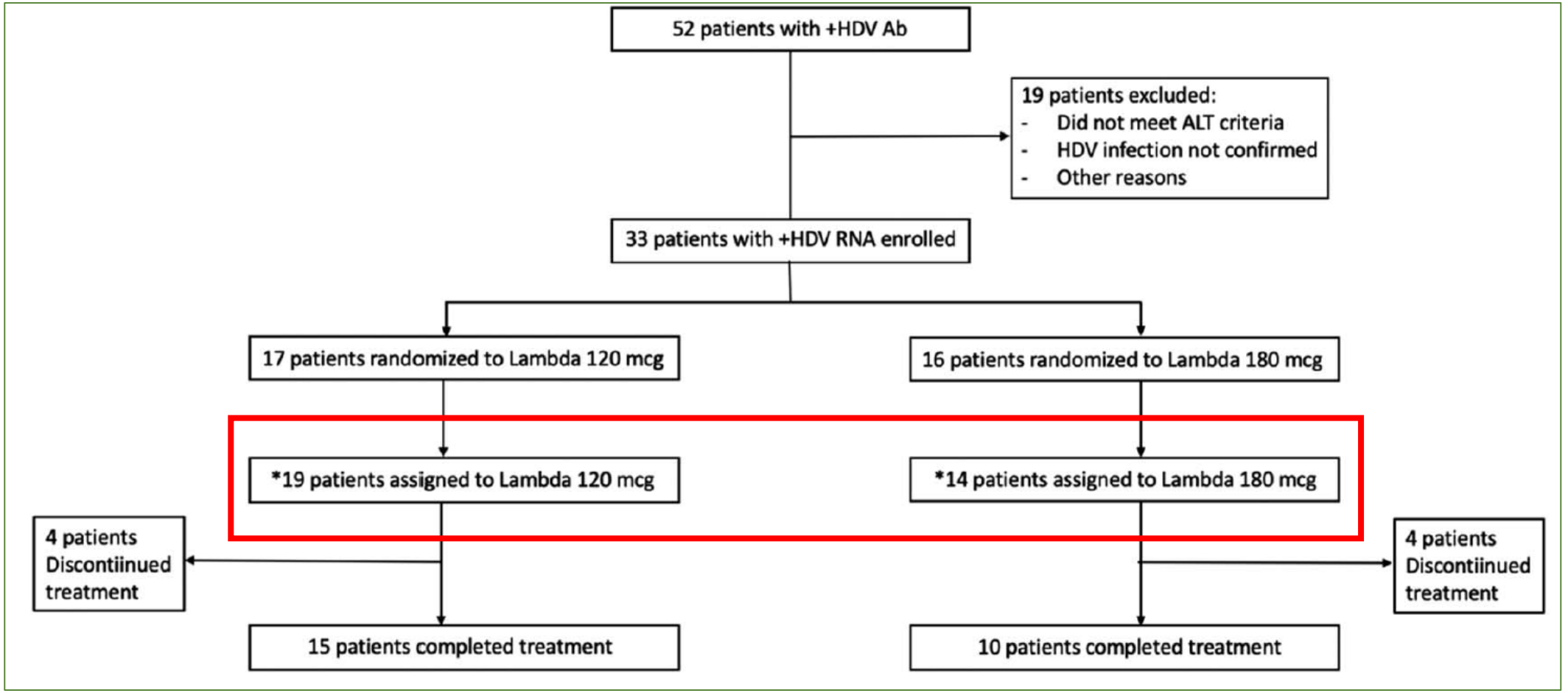
Jeffrey S. Glenn[9]

An open-label study of Lambda Interferon 120 or 180 mcg, administered once weekly by subcutaneous injections for 48 weeks, followed by 24 weeks of post-treatment follow-up



Hepatology 2023

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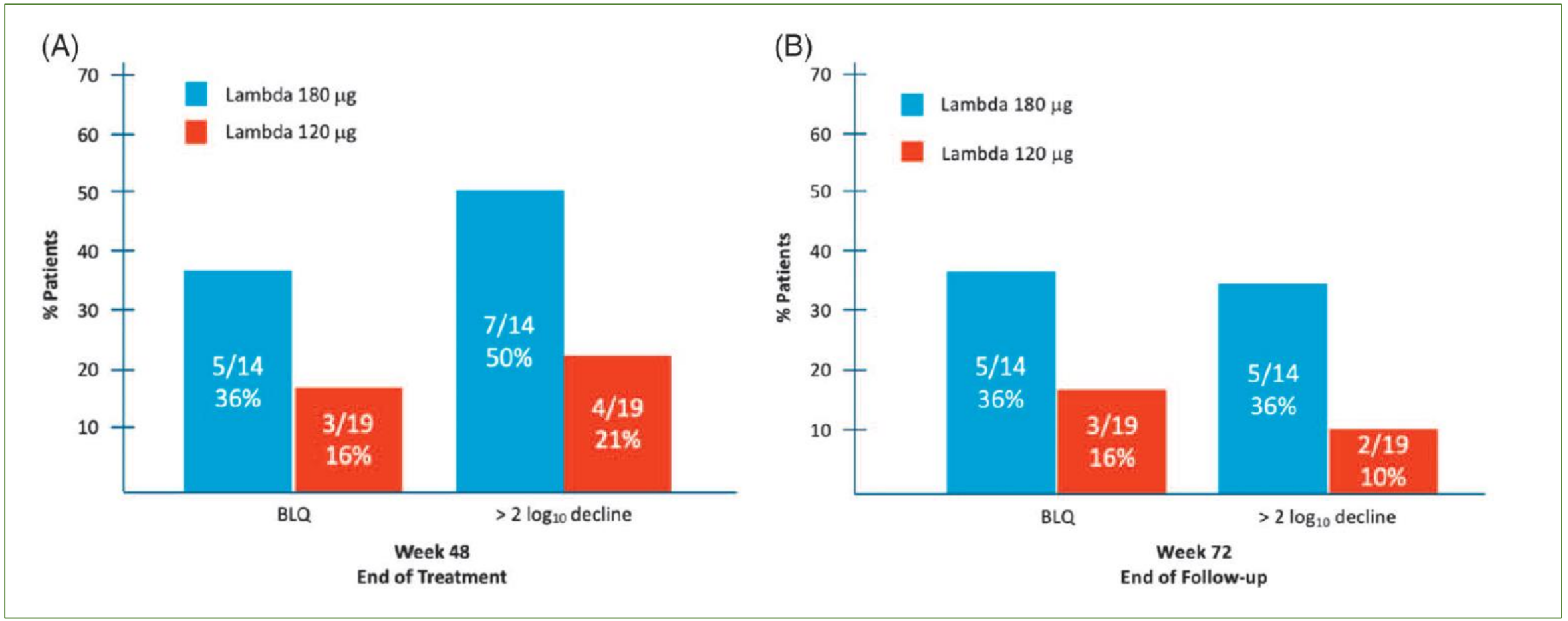

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Eight (24%) cases of hyperbilirubinemia with or without liver enzyme elevation, leading to drug discontinuation, were mainly observed in the Pakistani cohort

TABLE 2 Treatment emergent adverse events of special interest

Classification and preferred term	Number of patients experiencing adverse event: 120 mcg (n = 19), n (%)	180 mcg (n = 14), n (%)	Total (N = 33), n (%)
Flu-like	13 (68.4)	9 (64.3)	22 (66.7)
Pyrexia	8 (42.1)	7 (50.0)	15 (45.5)
Chills	5 (26.3)	3 (21.4)	8 (24.2)
Arthralgia	8 (42.1)	7 (50.0)	15 (45.5)
Myalgia	5 (26.3)	7 (50.0)	12 (36.4)
Musculoskeletal	10 (52.6)	10 (71.4)	20 (60.6)
Arthralgia	8 (42.1)	7 (50.0)	15 (45.5)
Myalgia	5 (26.3)	7 (50.0)	12 (36.4)
Back pain	6 (31.6)	3 (21.4)	9 (27.3)
Constitutional	4 (21.1)	9 (64.3)	13 (39.4)
Fatigue	3 (15.8)	8 (57.1)	11 (33.3)
Asthenia	1 (5.3)	3 (21.4)	4 (12.1)
Neurological	9 (47.4)	12 (85.7)	21 (63.6)
Headache	9 (47.4)	12 (85.7)	21 (63.6)
Dizziness	1 (5.3)	4 (28.6)	5 (15.2)
Psychiatric	0	1 (7.1)	1 (3.0)
Depression	0	1 (7.1)	1 (3.0)
Irritability	0	0	0
Insomnia	0	0	0

Hepatology 2023

Treatment of HDV infection

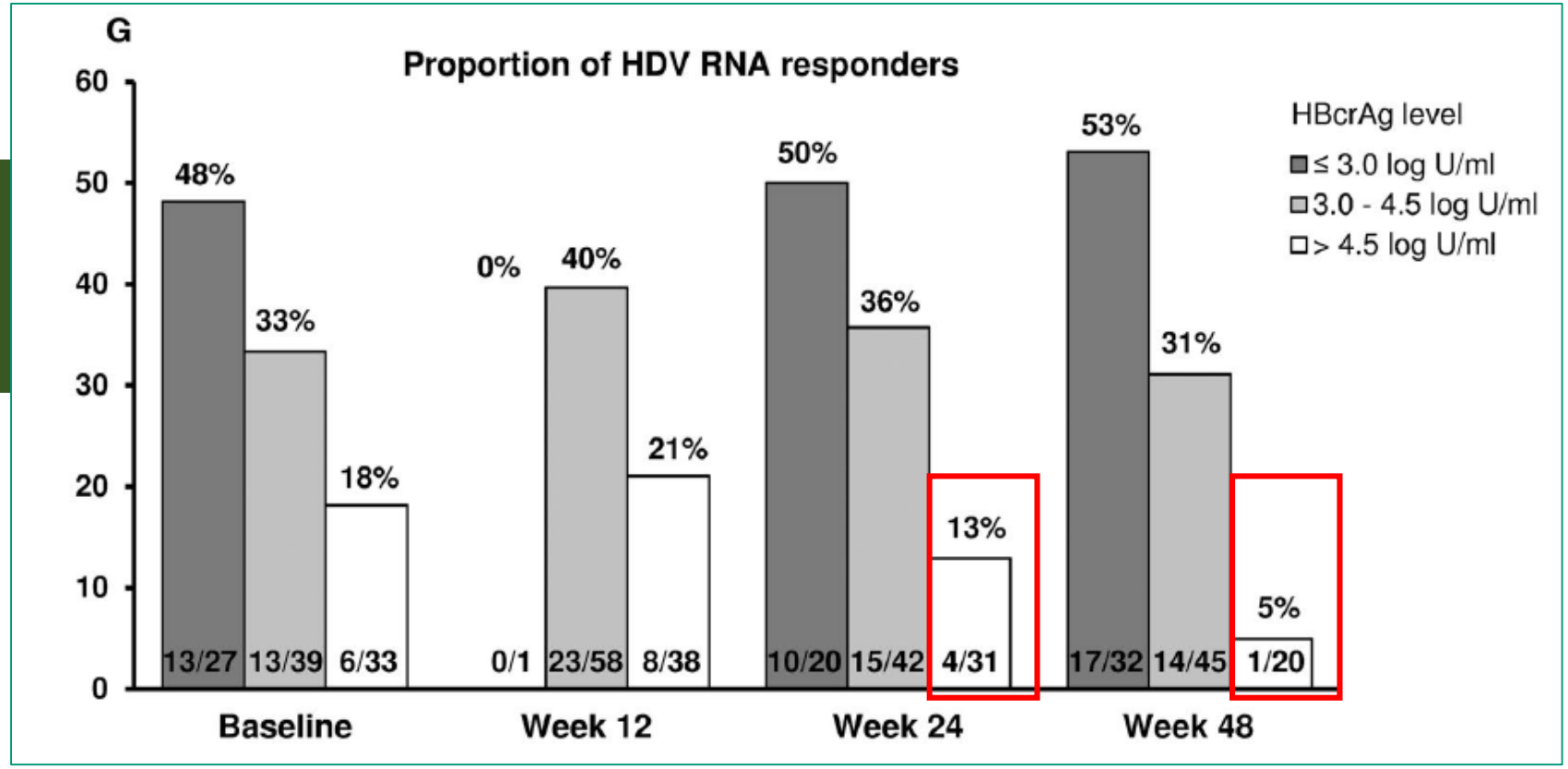
- **Interferon**
  - **Predictive factors to sustained response**
  - **Long-term follow-up**
  - **Long-term IFN treatment**
- Lonafarnib
- Bulevirtide
- Future options

HBcrAg Levels Are Associated With Virological Response to Treatment With Interferon in Patients With Hepatitis Delta

Lisa Sandmann,[1] Cihan Yurdaydin,[2,3] Katja Deterding,[1] Benjamin Heidrich,[1] Svenja Hardtke,[1,4] Patrick Lehmann,[1] Birgit Bremer,[1] Michael P. Manns,[1,6] Markus Cornberg,[1,4-6] Heiner Wedemeyer,[1,4,5*] and Benjamin Maasoumy[1,5,6*], for the HIDIT-II Study Group

NPV of HBcrAg>4.5log at baseline, at week 24 and week 48: 81.8%, 87.1%, 95%, respsctively

The role of HBcrAg to predict HDV response was analyzed in 120 patients with HBV/HDV co-infection undergoing peg-IFNα in **HIDIT-II** Trial

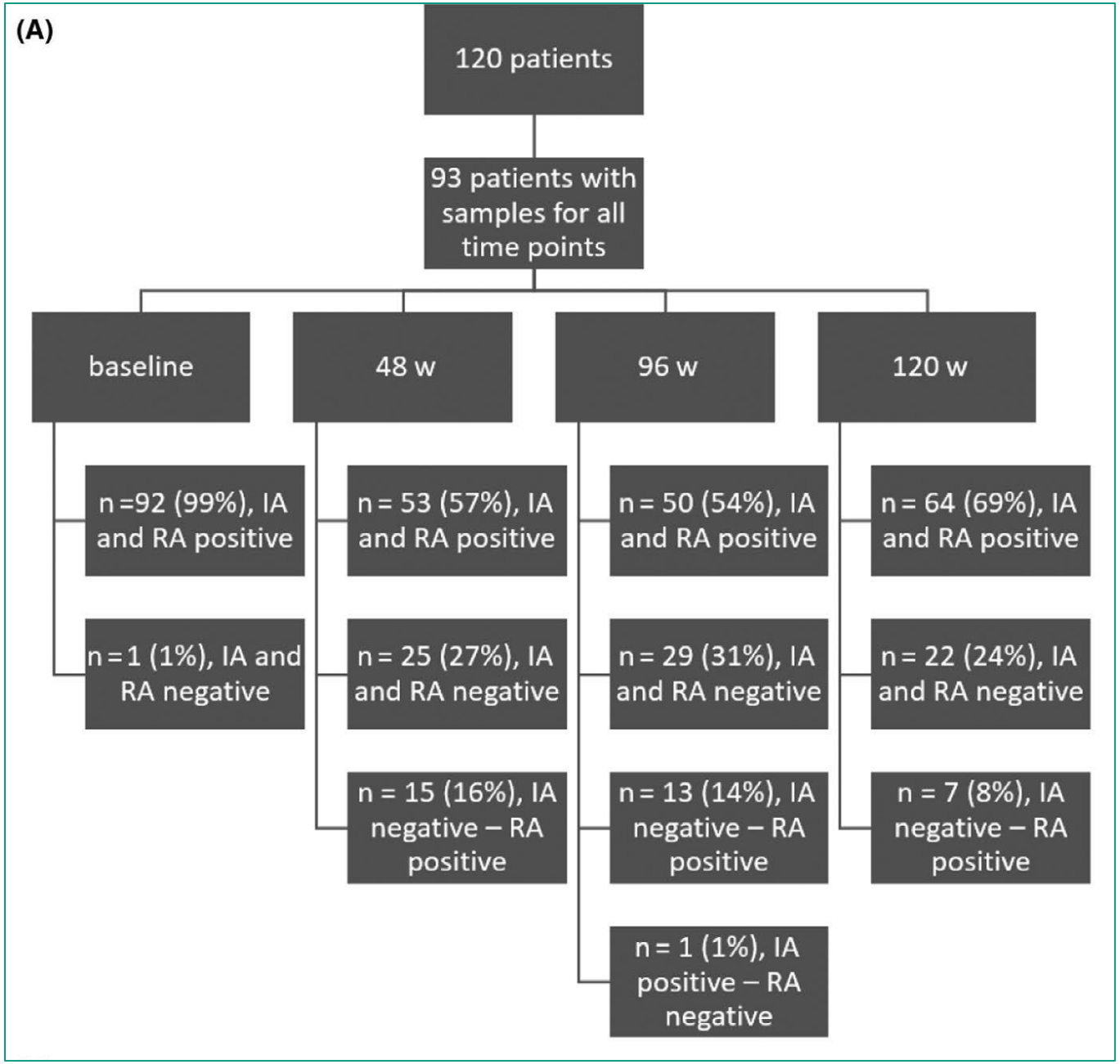


Hepatol Com 2022

Residual low HDV viraemia is associated HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis delta: Results from the HIDIT-II study

Birgit Bremer[1] | Olympia E. Anastasiou[2] | Svenja Hardtke[3,14] | Florin Alexandru Caruntu[4] | Manuela G. Curescu[5] | Kendal Yalcin[6] | Ulus S. Akarca[7] | Selim Gürel[8] | Stefan Zeuzem[9] | Andreas Erhardt[10] | Stefan Lüth[11] | George V. Papatheodoridis[12] | Monica Radu[4] | Ramazan Idilman[13] | Michael P. Manns[1,14] | Markus Cornberg[1,14] | Cihan Yurdaydin[13,15] | Heiner Wedemeyer[1,14,16]

A re-analysis of HDV RNA in 372 samples collected in the HIDIT-2 trial with the Robogene assay (RA; Jena Analytics). Data were compared with the previously reported in-house assay (IA).



Liver Intern 2021

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HDV-RNA was detected in one-third of samples previously classified as undetectable using the highly sensitive RA.

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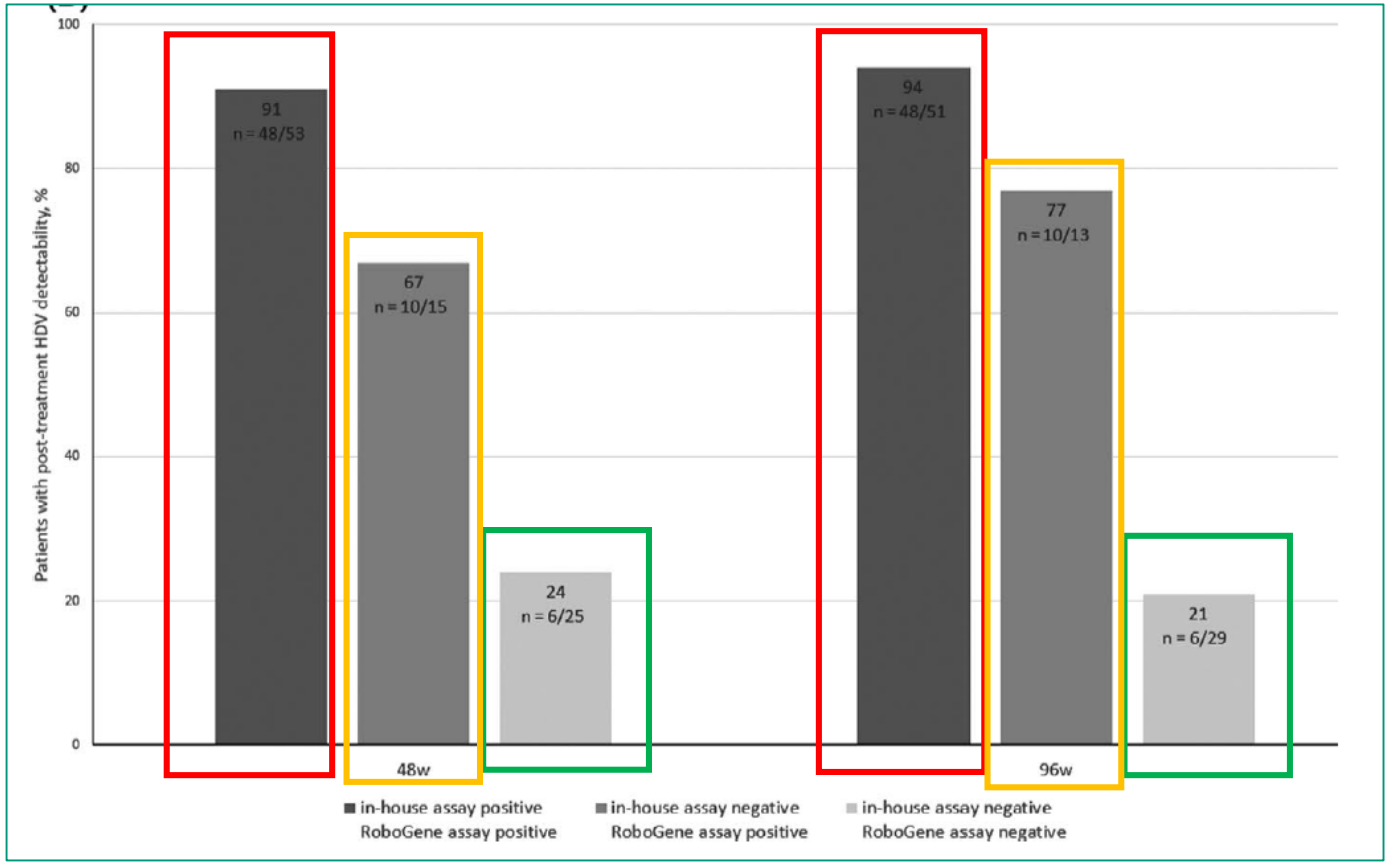
HDV relapse in post-treatment follow-up



Liver Intern 2021

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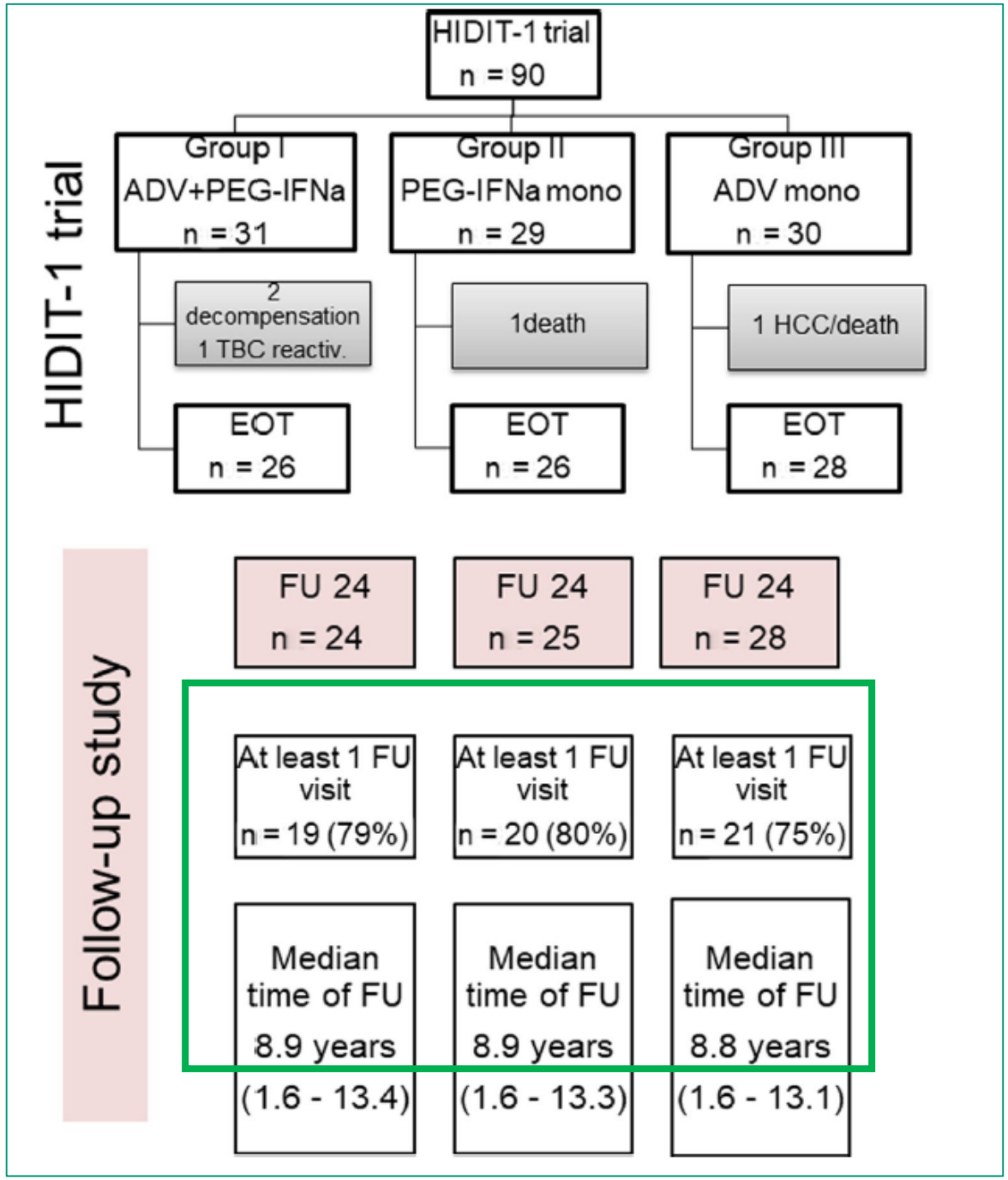
Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta

Anika Wranke[1] | Svenja Hardtke[1,2] | Benjamin Heidrich[1,2] | George Dalekos[3] | Kendal Yalçin[4] | Fehmi Tabak[5] | Selim Gürel[6] | Yilmaz Çakaloğlu[7] | Ulus S Akarca[8] | Frank Lammert[9] | Dieter Häussinger[10] | Tobias Müller[11] | Michael Wöbse[1] | Michael P. Manns[1,2] | Ramazan Idilman[12] | Markus Cornberg[1,2] | Heiner Wedemeyer[2,13] | Cihan Yurdaydin[12,14]



JVH 2020

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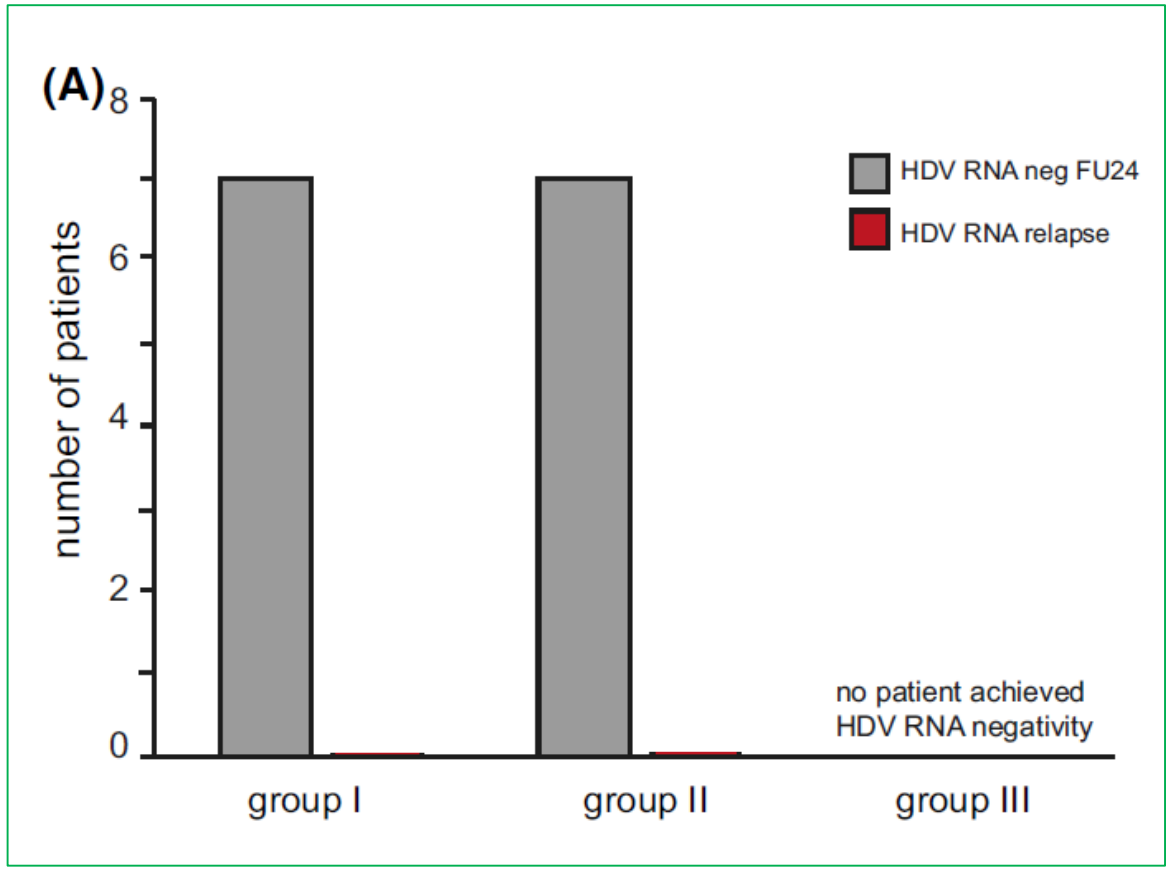
HDV-RNA relapse in the 14 HDV-RNA negative at the end of IFN treatment in the long term follow-up



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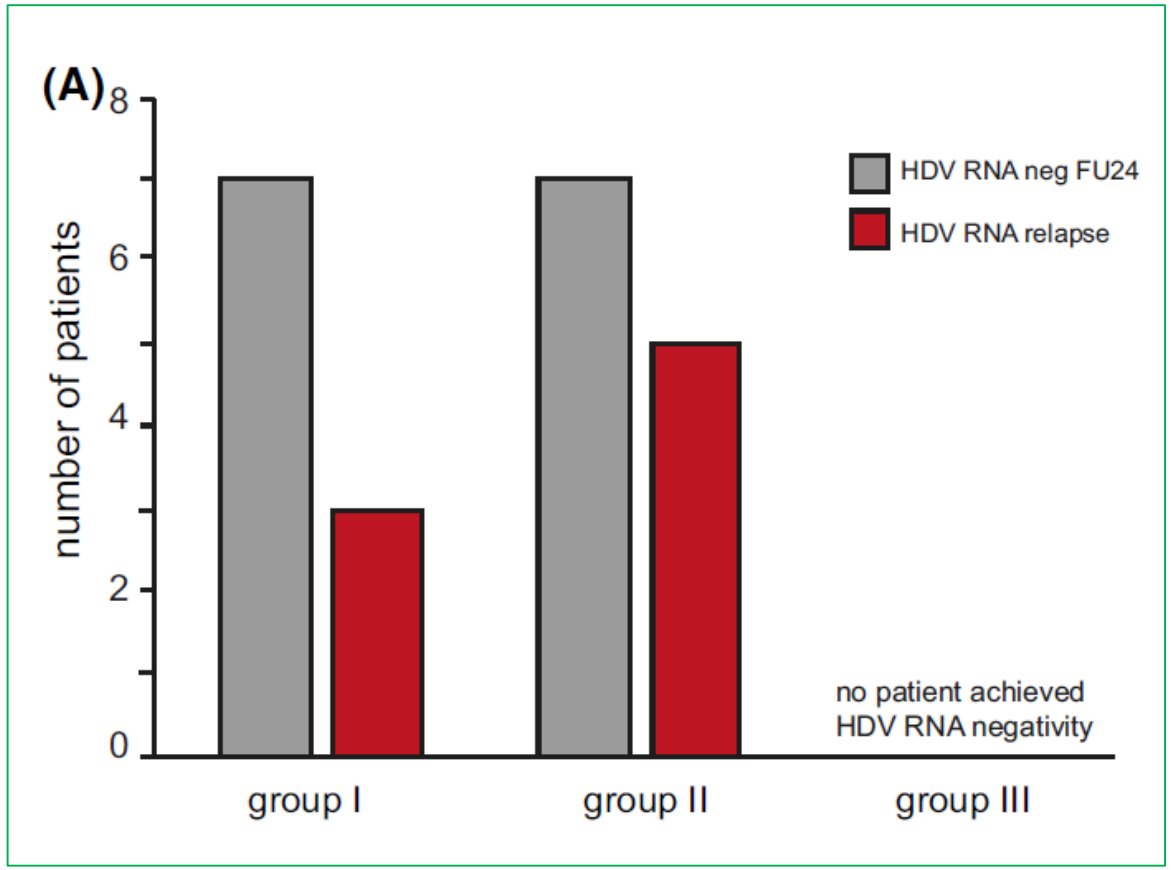

8/14 (57.1%)

JVH 2020

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  - **Long-term IFN treatment**
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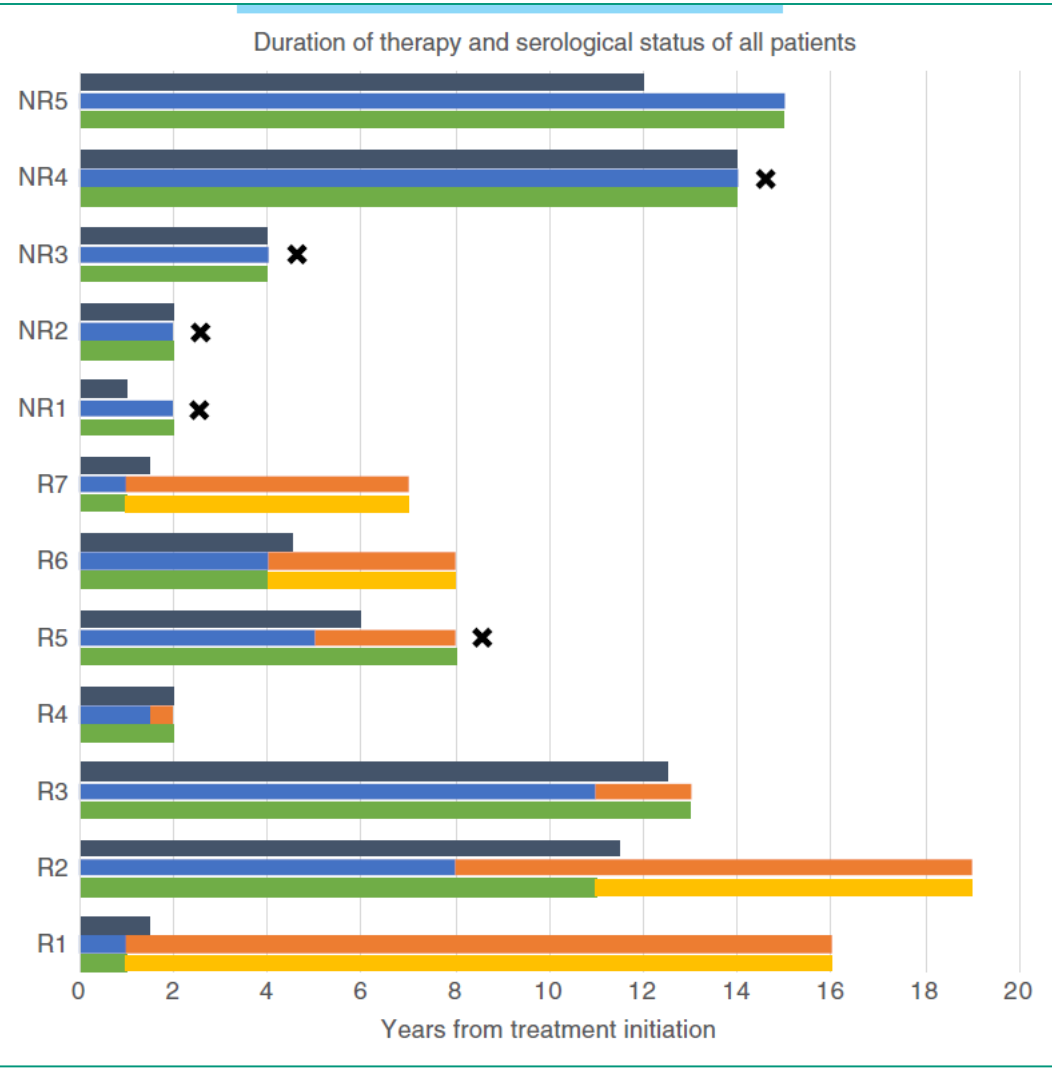
Durable virological response and functional cure of chronic hepatitis D after long-term peginterferon therapy

Julian Hercun[1] | Grace E. Kim[1] | Ben L. Da[1] | Yaron Rotman[1] | David E. Kleiner[2] | Richard Chang[3] | Jeffrey S. Glenn[4] | Jay H. Hoofnagle[5] | Christopher Koh[1] | Theo Heller[1]

12 patients treated with a long-term (median 6.1 years, range 0.8-14.3) Peg-IFN treatment in NCT00023322 trial

FIGURE 1 Duration of therapy and serological status of all patients. Grey bar: peginterferon treatment duration; Blue bar: HDV RNA positive; Orange bar: HDV RNA negative; Green bar: HBsAg positive; Yellow bar: HBsAg negative; Black star: death; NR: non-responder; R: responder



AP&T 2021

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life

MDPI

Review

HBV/HDV Co-Infection: Epidemiological and Clinica
Changes, Recent Knowledge and Future Challenges

Caterina Sagnelli, Evangelista Sagnelli *, Antonio Russo, Mariantonietta Pisaturo, Laura O
and Nicola Coppola

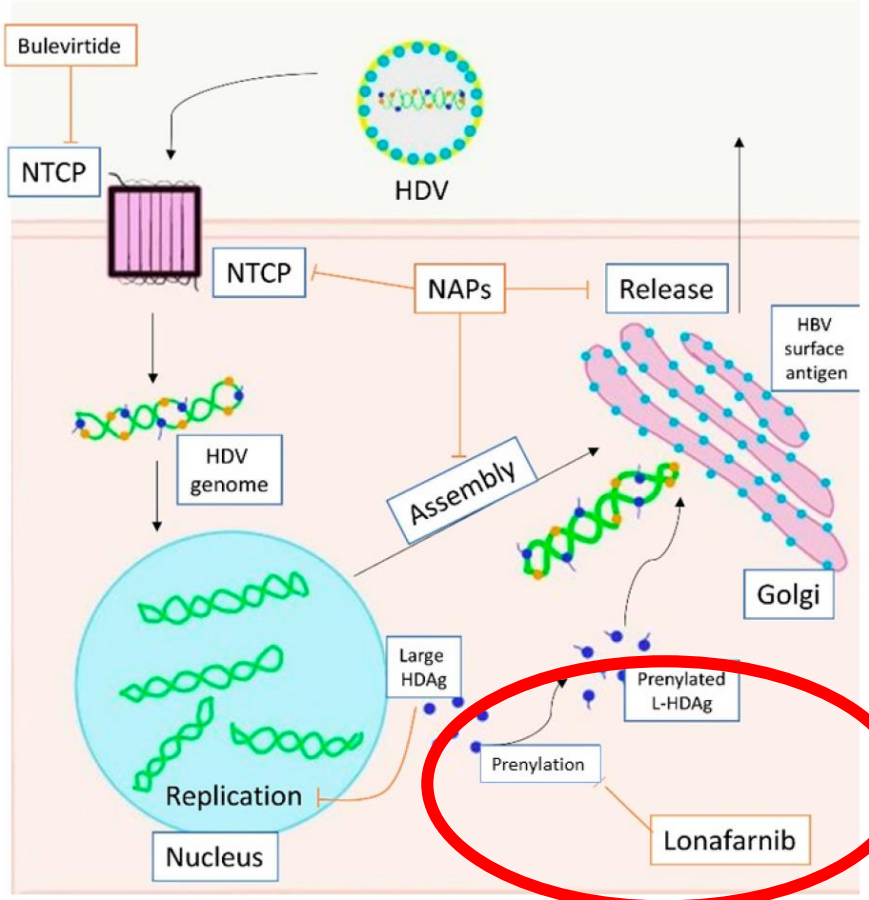


Figure 2. Action of direct anti-HDV agents on the HDV life circle. HDV enters the hepatocyte through NTCP. The replication is carried out in the nucleus. Large HDAg is farnesylated in the cytoplasm. Assembly ends in the Golgi apparatus with the bond between HBsAg and HDAg. Bulevirtide inhibits NTCP (entry), lonafarnib inhibits prenylation (farnesylation, assembly), NAPs inhibit NTCP (entry), farnesylation (assembly) and release. Footnotes: NTCP, sodium taurocholate co-transporting polypeptide; HDV, hepatitis D virus; HDAg, hepatitis D antigen; L-HDAg, large hepatits D antigen; HBV, hepatitis B virus; NAPs, nucleic acid polymers.

Sagnelli C, Life, 2021

D-LIVR Phase 3 Clinical trial

Objective

To evaluate the safety, tolerability, and efficacy of LNF boosted with RTV with or without pegIFN Alfa for treatment of chronic HDV infection compared to placebo

Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

Secondary Endpoint at Week 48

No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

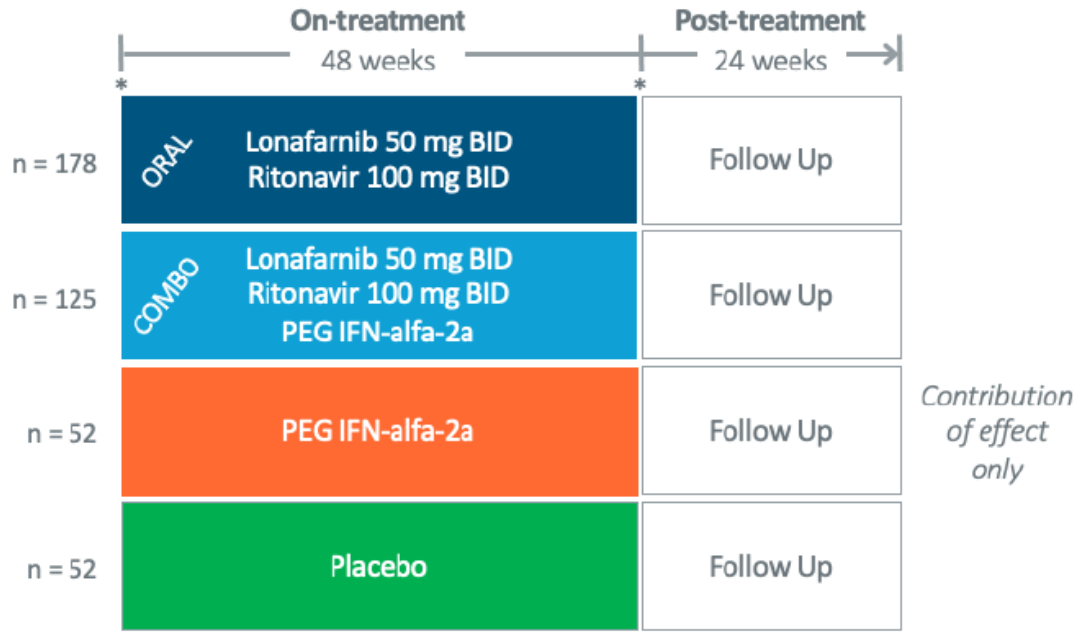
Key Inclusion criteria

CHD with compensated liver disease

HDV RNA > 500 IU/mL

ALT > 1.3X < 10X ULN

HBV DNA < 20 IU/mL

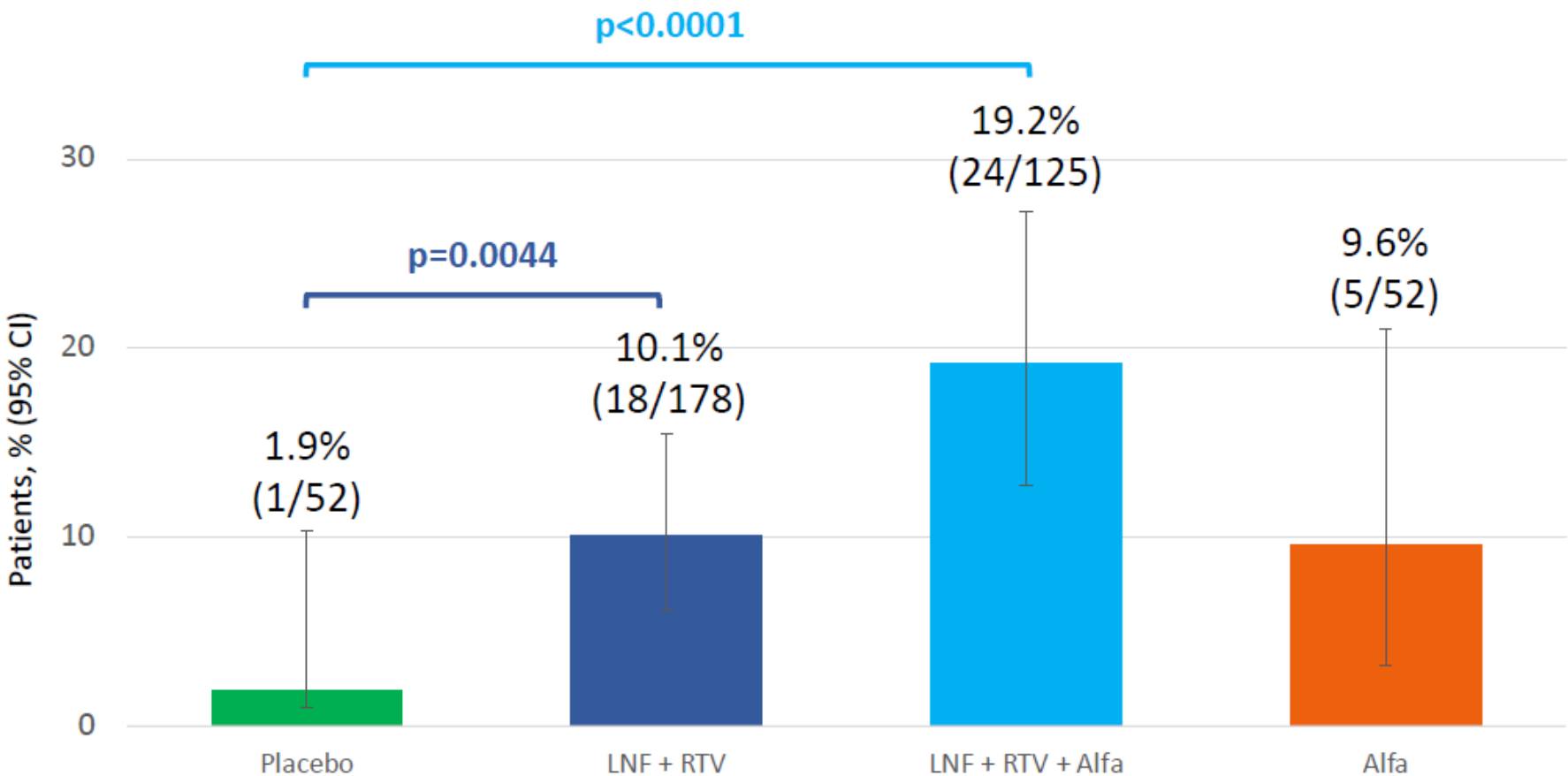


D-LIVR: Baseline Patient Characteristics

		Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=52)	Total (N=407)
Mean age, y (SD)		45.7 (10.9)	42.9 (10.8)	41.4 (11.5)	42.3 (11.0)	42.7
Men, n (%)		39 (75)	126 (71)	84 (67)	33 (64)	282 (69)
Race, n (%)	White	42 (81)	130 (73)	85 (68)	41 (79)	298 (73)
	Asian	10 (19)	40 (23)	35 (28)	10 (19)	95 (23)
	Black	0	3 (2)	3 (2)	0	6 (2)
	Other/no reported	0	5 (3)	1 (1)	1 (2)	7 (2)
Region	Asia	6 (12)	25 (14)	21 (17)	7 (14)	59 (15)
	Europe	43 (83)	127 (71)	92 (74)	41 (79)	303 (74)
	North America	1 (2)	14 (8)	9 (7)	2 (4)	26 (6)
	Other	2 (4)	12 (7)	3 (2)	2 (4)	19 (5)
Mean ALT, U/L (SD)		122 (83)	100 (69)	99 (73)	82 (47)	100 (70)
Mean HDV RNA, log IU/mL (SD)		4.97 (1.12)	4.94 (1.13)	5.14 (1.17)	4.88 (1.19)	5.00 (1.15)
HDV genotype, n (%)	1	47 (90)	174 (98)	118 (94)	52 (100)	391 (96)
	4 / 5 / 8 / not reported	1 (2) / 0 / 0 / 4 (8)	0 / 1 (0.6) / 0 / 3 (2)	0 / 0 / 1 (1) / 6 (5)	0 / 0 / 0 / 0	16 (4)
Median HBsAg, log IU/mL (range)		3.92 (2.18, 4.75)	3.83 (2.11, 4.75)	3.91 (1.16, 4.75)	3.92 (2.22, 4.63)	4.00 (1.16, 4.75)
Cirrhosis, n (%)		15 (29)	47 (26)	32 (26)	14 (27)	108 (27)

Primary Endpoint: Composite Response at Week 48

INTENT TO TREAT (ITT) POPULATION (N=405)



Key Secondary Endpoints: Histologic Response Rates at Week 48

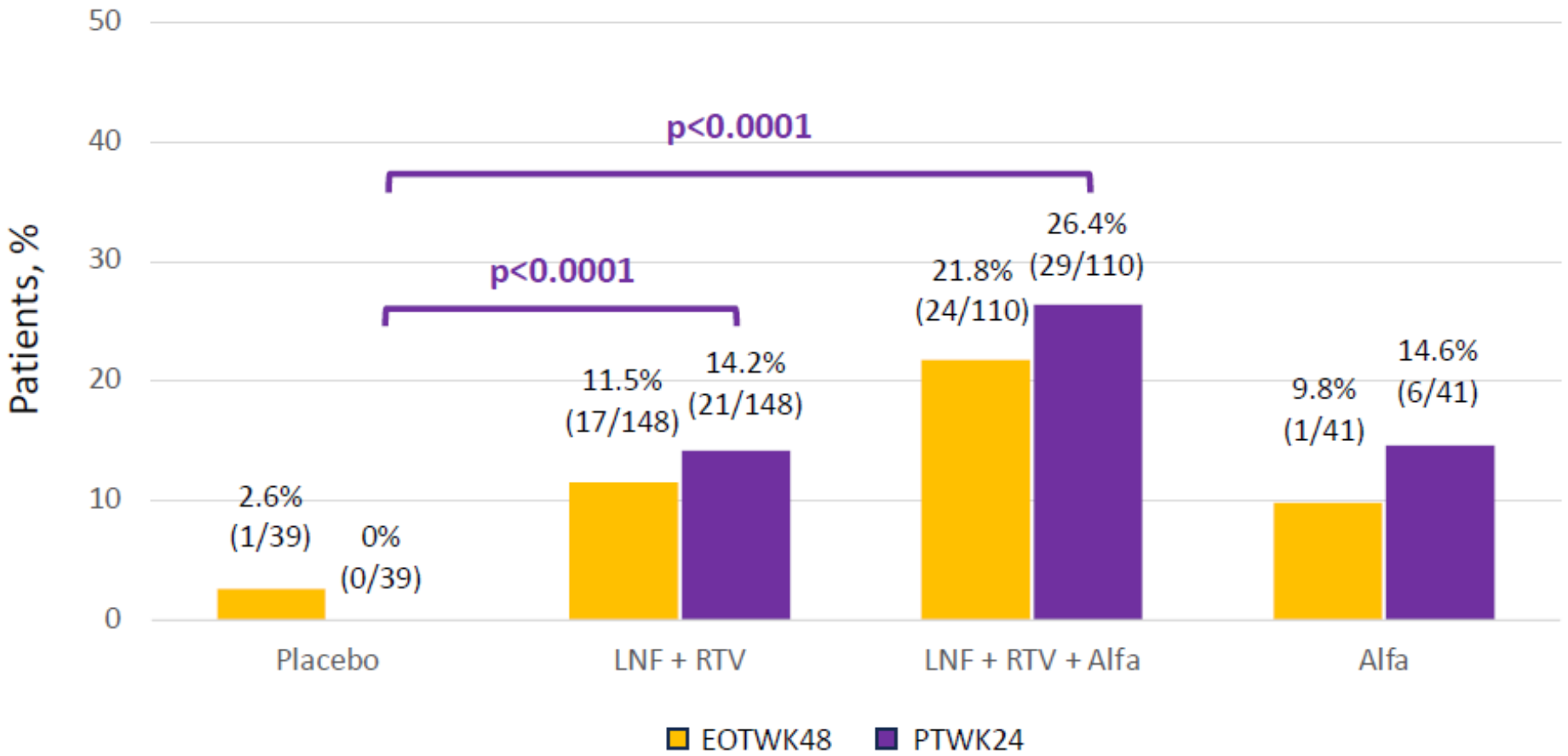
EVALUABLE PAIRED LIVER BIOPSIES (N=229)

	% (n)			
Response	LNF + RTV n=107	LNF + RTV + Alfa n=66	Alfa n=26	Placebo n=30
Histologic Composite Endpoint* In Patients with Evaluable Paired Biopsies (n=229)	33% (35) (p=0.61)	53% (35) (p=0.0139)	38% (10) (p=0.46)	27% (8)

* ≥ 2-point improvement in histology activity index (HAI) score + no worsening in Ishak fibrosis score

End of Study Results: Composite Endpoint

RANDOMIZED POPULATION, N=338



Overall Safety through Week 48

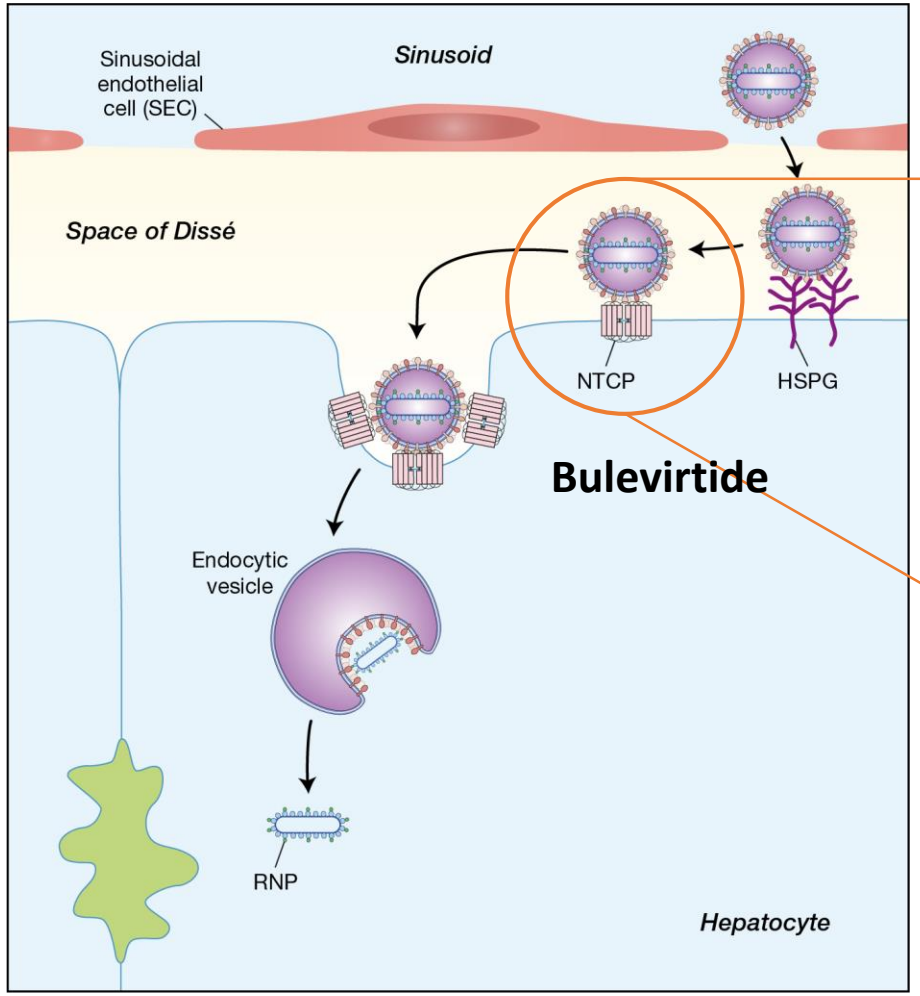
BOTH LONAFARNIB-TREATMENT REGIMENS WERE WELL-TOLERATED

	N (%)				
	Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=50)	Total (N=405)
Discontinuations	10 (19)	34 (19)	22 (18)	11 (21)	77 (19)
Patients with ≥ 1 dose interruption/missed dose	14 (27)	76 (43)	64 (51)	27 (54)	181 (45)
Patients ≥ 1 TEAE	37 (71)	168 (94)	120 (96)	48 (96)	373 (92)
Patients with serious TEAE	2 (4)	15 (8)	18 (14)	5 (10)	40 (10)
Patients with ≥ 1 TEAE leading to death	0	1 (1)[1]	1 (1)[1]	1 (2)[2]	3 (1)

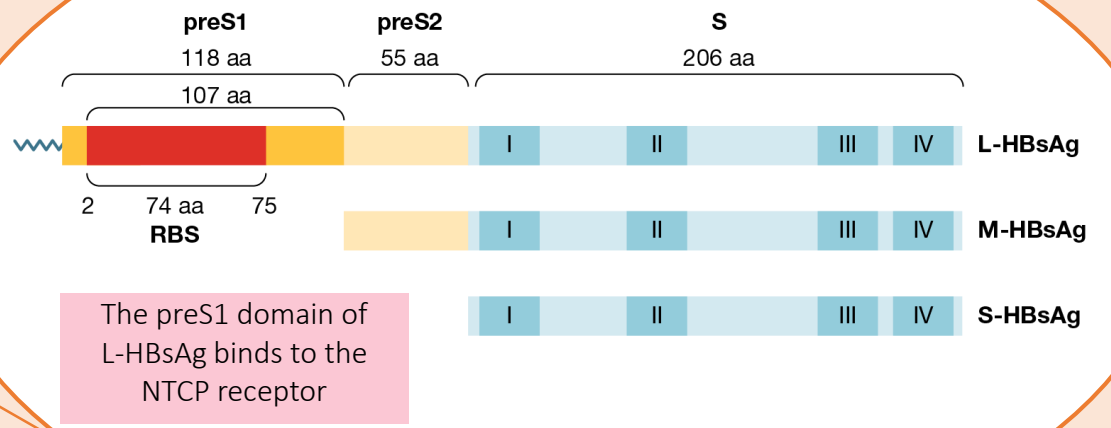
Treatment of HDV infection

- Interferon
- Lonafarnib
- **Bulevirtide**
- Future options

HDV enters the hepatocyte via the NTCP receptor



Interaction between HDV and NTCP occurs at a binding site on HBsAg



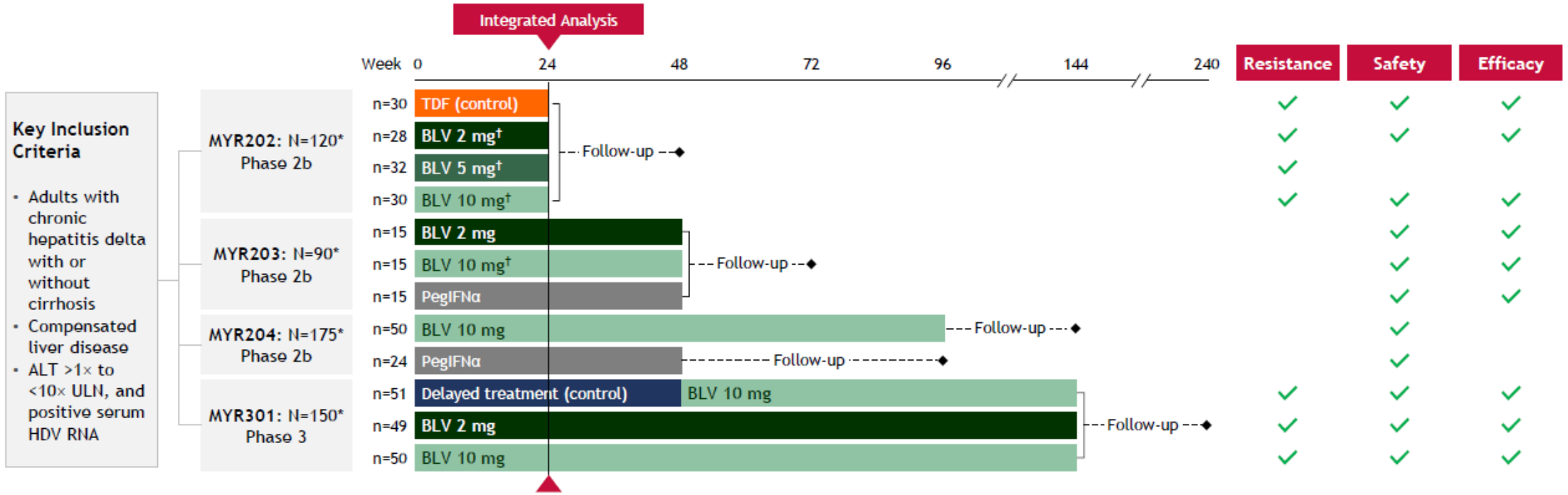
The preS1 domain of L-HBsAg binds to the NTCP receptor

urban S, et al. Gastroenterol 2014;147:48-64;
Lempp FA, et al. Nature Rev Gastroenterol Hepatol 2016;13:580-9.

AA: amino acids; HBsAg: hepatitis B antigen; HDV: hepatitis delta virus; HSPG: heparan sulfate proteoglycan; L: large; M: middle; NCTP: human sodium taurocholate cotransporting polypeptide; RBS: receptor binding site; RNP: ribonucleoprotein; S: small; SEC: sinusoidal endothelial cell.

Integrated Data Analyses from BLV Clinical Trials

Study designs of clinical trials included in integrated analyses assessing efficacy, resistance and safety of BLV monotherapy (2 mg, 5 mg or 10 mg SC QD) through 24 weeks



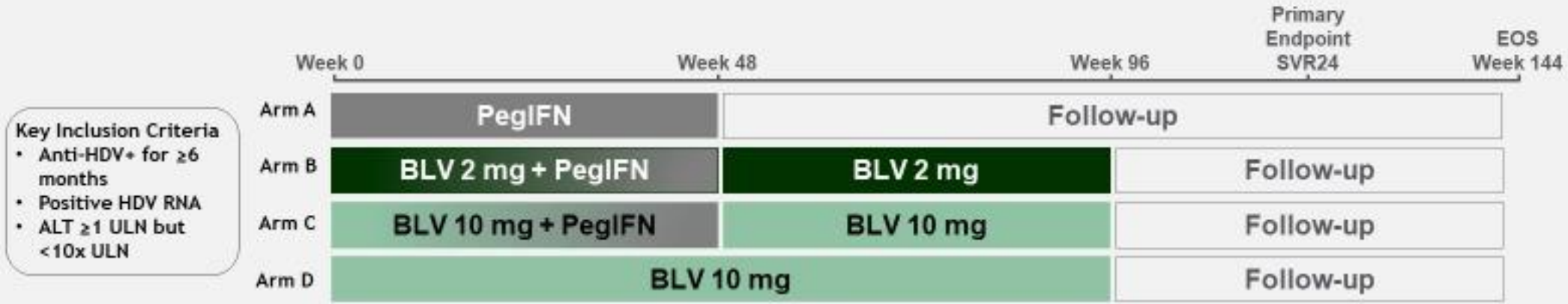
BLV: Bulevirtide

Treatment of HDV infection

- Interferon
- Lonafarnib
- **Bulevirtide**
  - **With Peg-IFN**
  - **Without Peg-IFN**
- Future options

MYR204 Study Design

Phase 2b, randomized, multi-center, open-label study



Key Inclusion Criteria

- Anti-HDV+ for ≥6 months
- Positive HDV RNA
- ALT ≥1 ULN but <10x ULN

Primary endpoint at Week 48:

- SVR24: HDV RNA undetectable (<LLoD) at Week 24 after EOT

Secondary endpoints:

- Undetectable HDV RNA
- Combined sustained response: HDV RNA undetectable or decrease ≥2 log IU/mL and ALT normalization
- SVR48: HDV RNA undetectable (<LLoD) at Week 48 after EOT
- Change in liver stiffness

ALT, alanine aminotransferase; BLV, bulevirtide; EOS, end of study; EOT, end of treatment; HDV, hepatitis D virus; LLoD, lower level of detection; PegIFN, pegylated interferon; SVR, sustained virologic response; ULN, upper limit of normal.
Reference: https://clinicaltrials.gov/ct2/show/NCT03852433

BLV: Bulevirtide

MYR204 Phase 2b Study for Finite Therapy

Baseline Characteristics

	PegIFNα n=24	BLV 2 mg + PegIFNα n=50	BLV 10 mg + PegIFNα n=50	BLV 10 mg n=50
Mean age, years (SD)	41 (8)	41 (9)	42 (9)	40 (9)
Male, 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)	15.8 (11.6)	12.8 (6.4)	12.5 (7.6)	12.7 (6.7)
Mean ALT, U/L (SD)	122 (96)	108 (77)	113 (99)	118 (108)
Median HDV RNA, log IU/mL (range)	5.2 (2.3-7.3)	5.6 (0-7.1)	5.5 (0-6.7)	5.6 (2.8-7.1)
HBV GT A / D / E/ Missing %	13 / 38 / 0 / 49	6 / 42 / 0 / 52	10 / 38 / 2 / 50	8 / 36 / 0 / 56
HDV GT 1 / 5 / 6 / not determined, %	100 / 0 / 0 / 0	96 / 2 / 2 / 0	94 / 4 / 0 / 2	98 / 2 / 0 / 0

ALT, alanine aminotransferase; BLV, bulevirtide; HDV, hepatitis D virus; PegIFNα, pegylated interferon-α.
Asselah T, et al. EASL 2021. #2717.

BLV: Bulevirtide

MYR204 Phase 2b Study for Finite Therapy

Safety Through 24 Weeks

	n (%)	PegIFNα n=24	BLV 2 mg + PegIFNα n=50	BLV 10 mg + PegIFNα 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 PegIFN	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

BLV monotherapy or combination with PegIFNα was generally safe and well tolerated

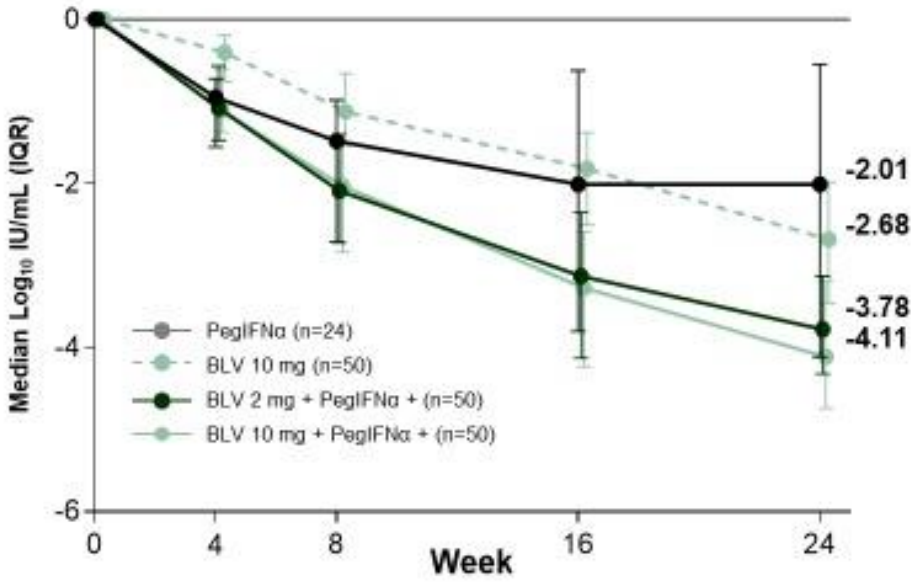
BLV, bulevirtide; D/C, discontinuation; PegIFNα, pegylated interferon-α.
* All adverse events (AEs) reported in table considered treatment emergent; only symptomatic and clinically significant total bile salt elevations were collected
†Appendicitis, pyrexia. ‡Astrocytoma+, chronic sinusitis, neither related to BLV. §Drug-induced liver injury and cholestasis, assessed as possibly related to PegIFNα but not related to BLV, and resolved. ¶Urinary tract infection, not related to BLV
+ the death was the astrocytoma referenced in serious AE and not related to BLV
Asselah T, et al. EASL 2021. #2717

BLV: Bulevirtide

MYR204 Phase 2b Study for Finite Therapy

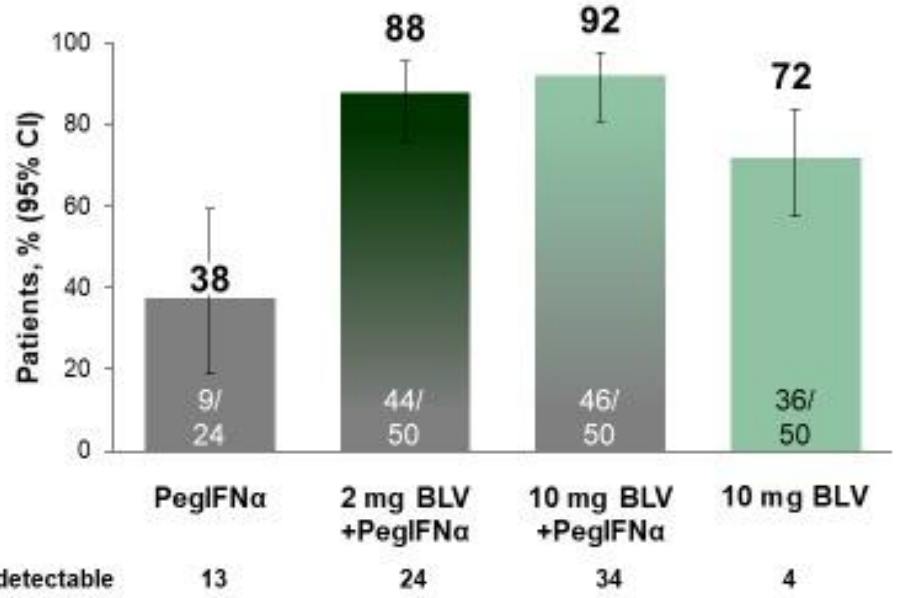
Virologic Response Through 24 Weeks

HDV RNA Levels Over Time



HDV RNA Response

Undetectable HDV RNA or ≥2 log IU/mL decline



BLV as monotherapy or in combination with PegIFNα led to a higher virologic response compared with PegIFNα monotherapy

CI, confidence interval; IQR, interquartile range
Asselah T, et al. EASL 2021. #2717

BLV: Bulevirtide

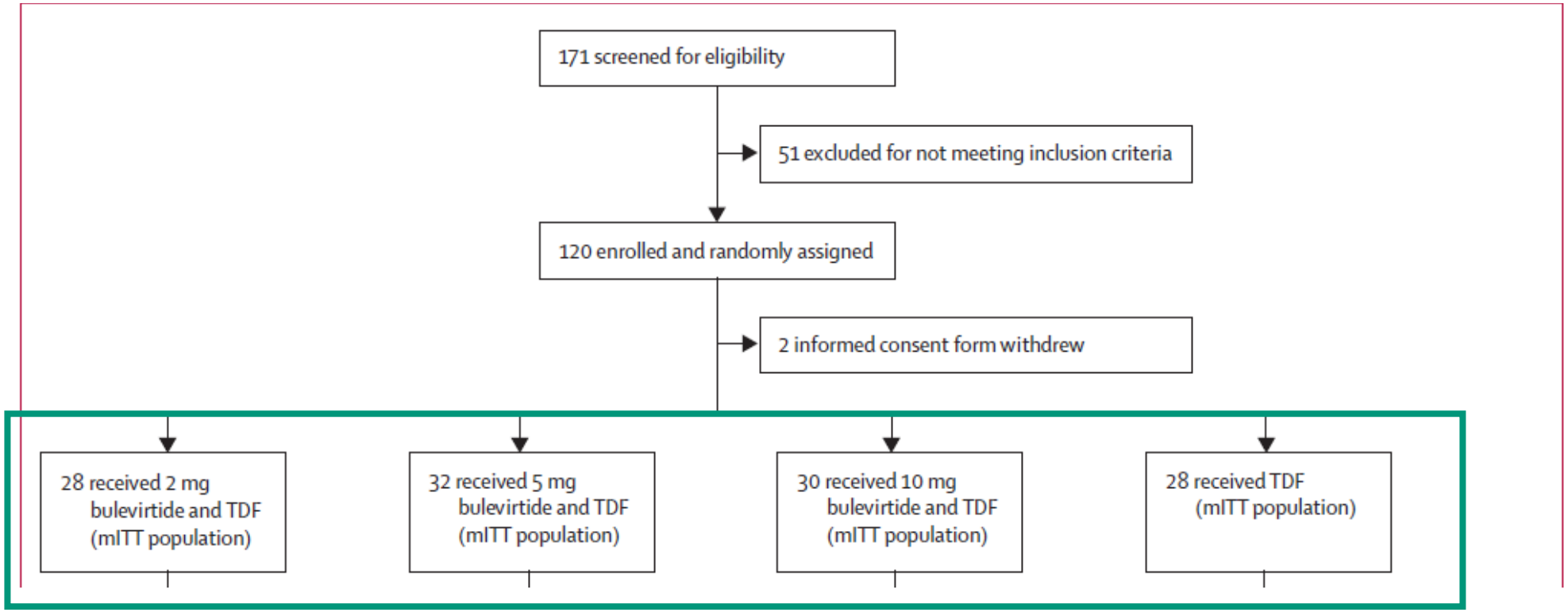
Treatment of HDV infection

- Interferon
- Lonafarnib
- **Bulevirtide**
  - With Peg-IFN
  - **Without Peg-IFN**
- Future options

Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial

Heiner Wedemeyer, Katrin Schöneweis, Pavel Bogomolov, Antje Blank, Natalia Voronkova, Tatiana Stepanova, Olga Sagalova, Vladimir Chulanov, Marina Osipenko, Viacheslav Morozov, Natalia Geyvandova, Snezhana Sleptsova, Igor G Bakulin, Ilsiyar Khaertynova, Marina Rusanova, Anita Pathil, Uta Merle, Birgit Bremer, Lena Allweiss, Florian A Lempp, Kerstin Port, Mathias Haag, Matthias Schwab, Julian Schulze zur Wiesch, Markus Cornberg, Walter E Haefeli, Maura Dandri, Alexander Alexandrov, Stephan Urban

Multicentre, parallel-group, randomised, open-label, phase 2 trial
The patients were randomly assigned (1:1:1:1) to receive 2 mg, 5 mg, or 10 mg subcutaneous bulevirtide once per day with tenofovir disoproxil fumarate (TDF) or TDF alone for 24 weeks



Lancet Infect Dis 2023

Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial

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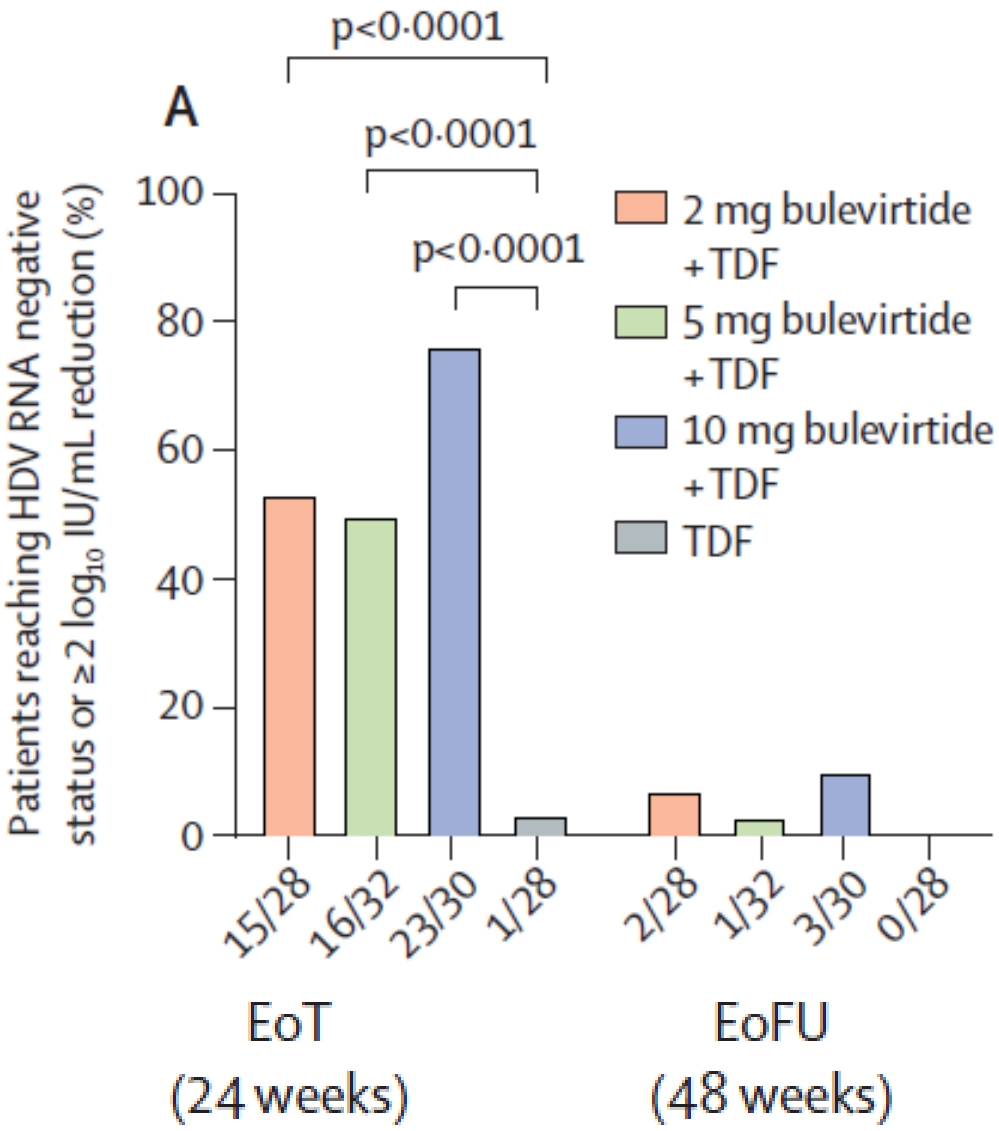
a multicentre, parallel-group, randomised, open-label,

End point: HDV-RNA negative or decline of at least 2log at end of treatment (EOT) or end of follow-up (EOFu)



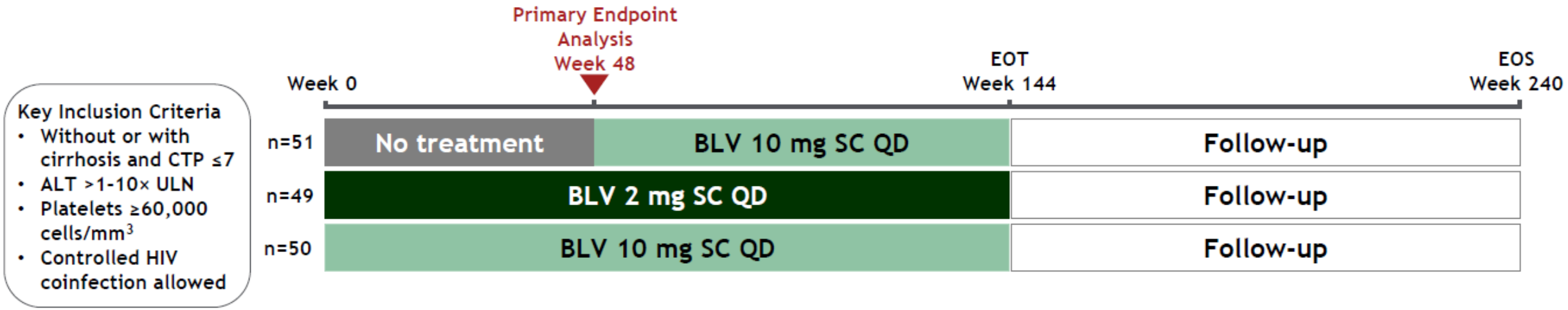
Lancet Infect Dis 2023

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*

Multicenter, open-label, randomized, Phase 3 study



Primary endpoint:

- Combined response at Week 48: HDV RNA undetectable or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization

Secondary endpoints:

- Combined response at Week 24 (key)
- Undetectable HDV RNA at Weeks 24 and 48 (key)
- ALT normalization at Weeks 24 and 48
- Change in liver stiffness (transient elastography) at Week 48
- HDV RNA undetectable after EOT

Wedemeyer H, NEJM 2023

BLV: Bulevirtide

Baseline Characteristics

	No Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
Age, mean years (SD)	41 (8)	44 (9)	41 (9)
Male, n (%)	26 (51)	30 (61)	30 (60)
Race - White, n (%)	40 (78)	41 (84)	43 (86)
Cirrhosis, n (%)	24 (47)	23 (47)	24 (48)
Liver stiffness, mean kPa (SD)	15.3 (8.9)	14.0 (8.2)	14.8 (9.3)
ALT, mean U/L, (SD)	102 (62)	108 (63)	123 (81)
HDV RNA, mean $\log_{10}$ IU/mL, (SD)	5.1 (1.4)	5.1 (1.2)	5.0 (1.5)
HDV GT 1 / 5, %	100 / 0	100 / 0	96 / 2
HBV DNA, mean $\log_{10}$ IU/mL, (SD)	0.9 (1.0)	1.3 (1.3)	1.1 (1.3)
HBV GT A / D / E / missing, %	8 / 77 / 0 / 16	2 / 90 / 0 / 8	6 / 82 / 2 / 10
HBeAg positive, n (%)	4 (8)	4 (8)	7 (14)
Previous IFN therapy, n (%)	29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)	32 (63)	31 (63)	27 (54)

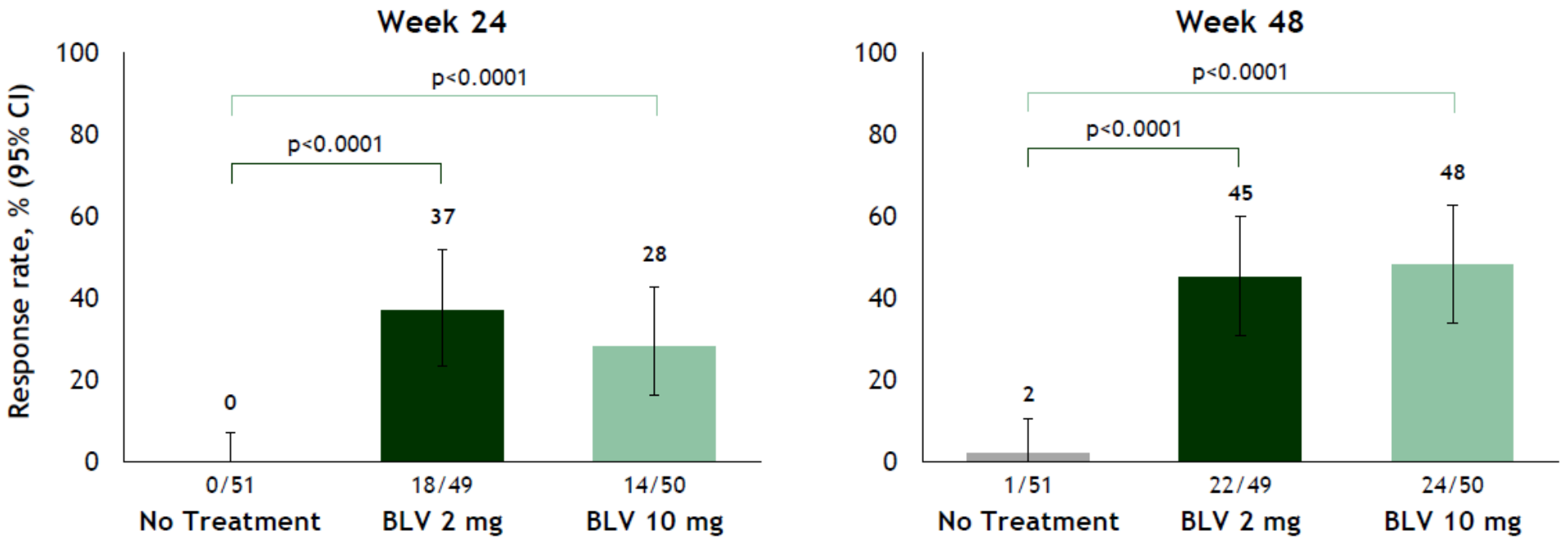
BLV: Bulevirtide

Wedemeyer H, NEJM 2023

Combined Response Through 48 Weeks

Primary Endpoint: Combined Response

Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL and ALT normalization



BLV was associated with significant combined HDV RNA declines and ALT normalization

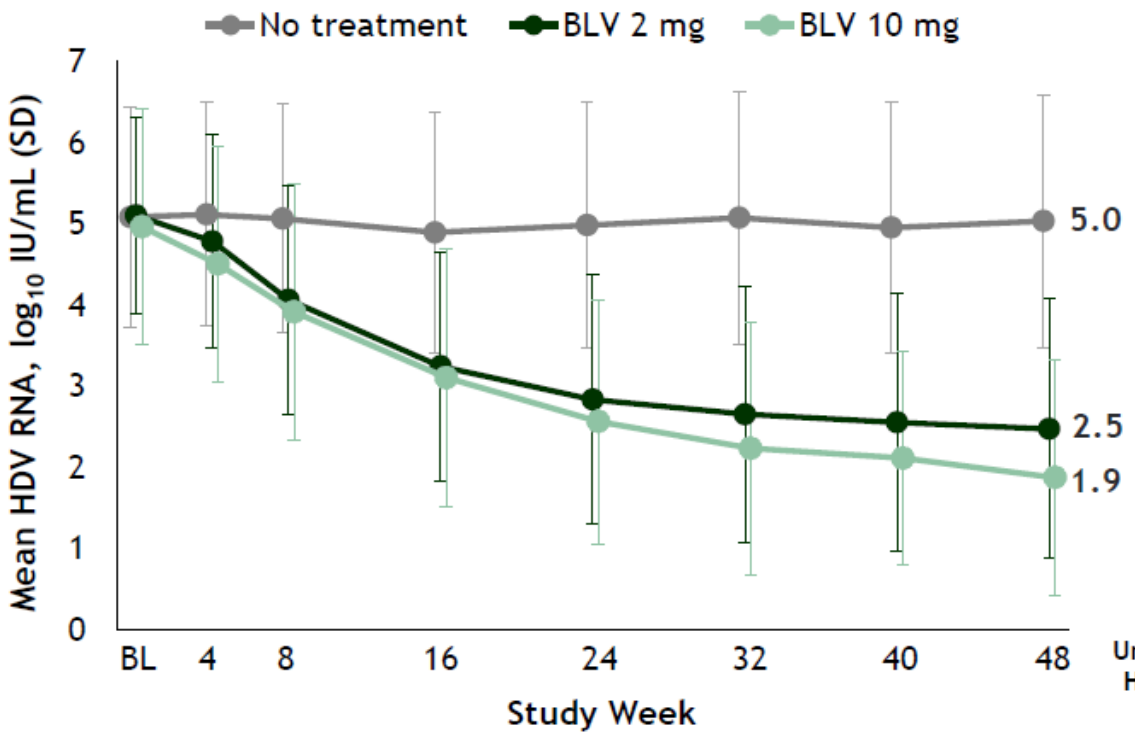
Wedemeyer H, NEJM 2023

BLV: Bulevirtide

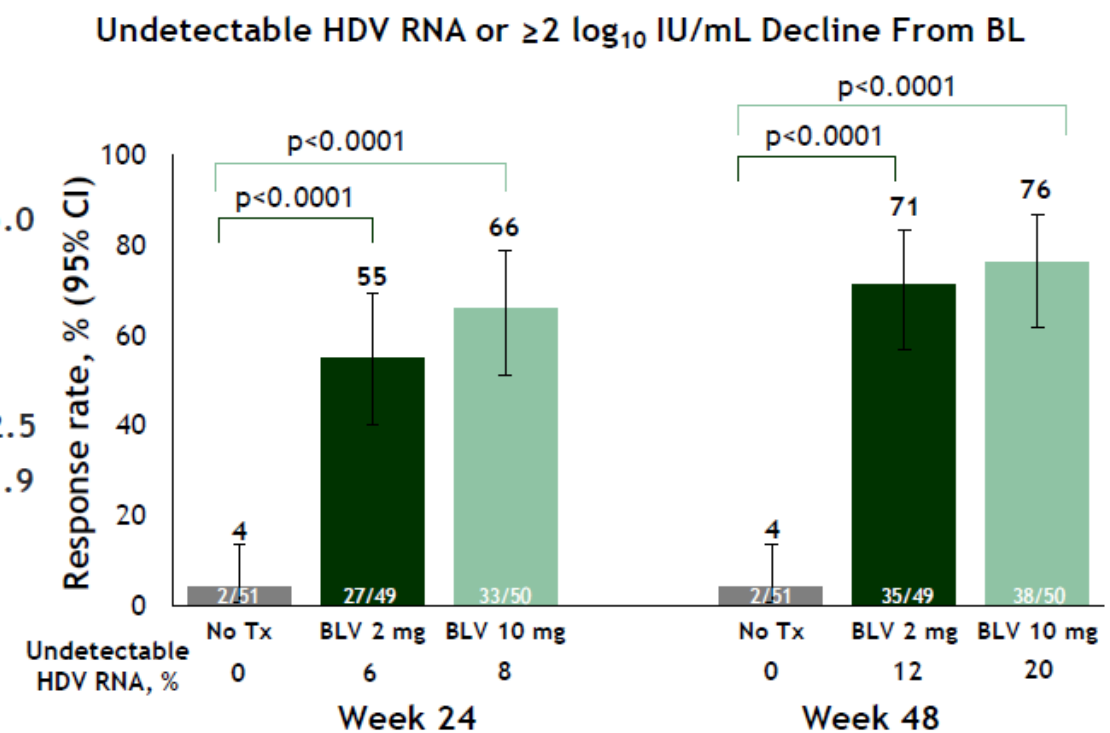
MYR301 Phase 3 Study

Virologic Response Through 48 Weeks

HDV RNA Levels Over Time



Virologic Response at Weeks 24 and 48



Similar rates of HDV RNA decline were seen with BLV 2 mg and BLV 10 mg

BLV: Bulevirtide

Wedemeyer H, NEJM 2023

ORIGINAL ARTICLE

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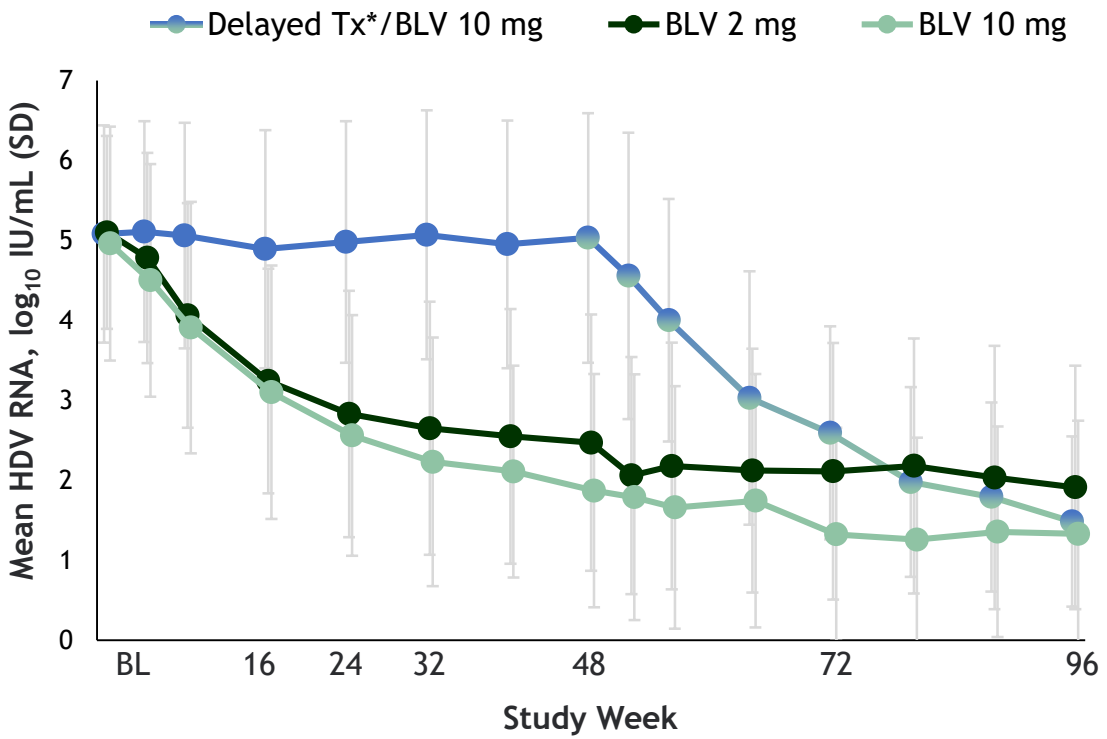
Table 3. Adverse Events during the Treatment Period and Laboratory Abnormalities.*

Event	Control (N=51)	Bulevirtide, 2 mg (N=49)	Bulevirtide, 10 mg (N=50)
		no. of patients (%)	
Adverse events that occurred during the treatment period			
Any adverse event			
Overall	39 (77)	40 (82)	44 (88)
Grade 3 or 4	3 (6)	5 (10)	4 (8)
Treatment-related adverse event			
Overall	0	24 (49)	36 (72)
Grade 3 or 4	0	1 (2)	3 (6)
Serious adverse event			
Overall	1 (2)	2 (4)	1 (2)
Treatment-related	0	0	0
Adverse event leading to treatment discontinuation	0	0	0
Non–injection-site event†			
Vitamin D deficiency	8 (16)	6 (12)	8 (16)
Leukopenia	9 (18)	6 (12)	5 (10)
Headache	0	9 (18)	10 (20)
Thrombocytopenia	8 (16)	5 (10)	5 (10)
Pruritus	0	6 (12)	8 (16)
Fatigue	1 (2)	5 (10)	7 (14)
Eosinophilia	0	5 (10)	5 (10)
Neutropenia	3 (6)	2 (4)	5 (10)
Nausea	2 (4)	3 (6)	4 (8)
Abdominal pain upper	1 (2)	0	6 (12)
Arthralgia	0	3 (6)	4 (8)
Asthenia	0	2 (4)	3 (6)
Increased total bile acid level	0	1 (2)	3 (6)
Injection-site event†			
Reaction	0	3 (6)	4 (8)
Erythema	0	2 (4)	4 (8)
Pruritus	0	1 (2)	3 (6)
Swelling	0	1 (2)	3 (6)
Grade 3 or 4 laboratory abnormality occurring in ≥1 patient in any treatment group			
Platelet count			
25,000 to <50,000/mm³‡	2 (4)	1 (2)	2 (4)
<25,000/mm³§	0	1 (2)	2 (4)
Neutrophil count of 500 to <1000/mm³‡	2 (4)	0	2 (4)

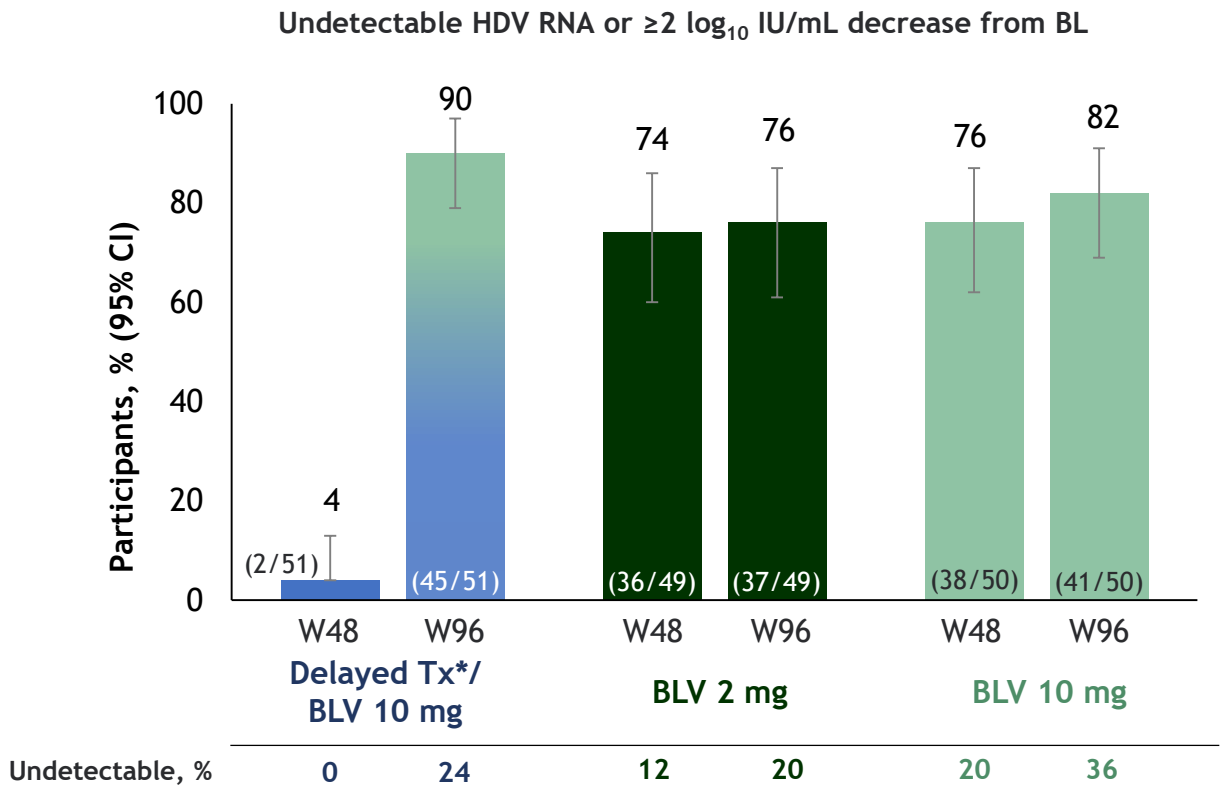
Wedemeyer H, NEJM 2023

Virologic Response Through 96 Weeks

HDV RNA Decline Over Time



Virologic Response



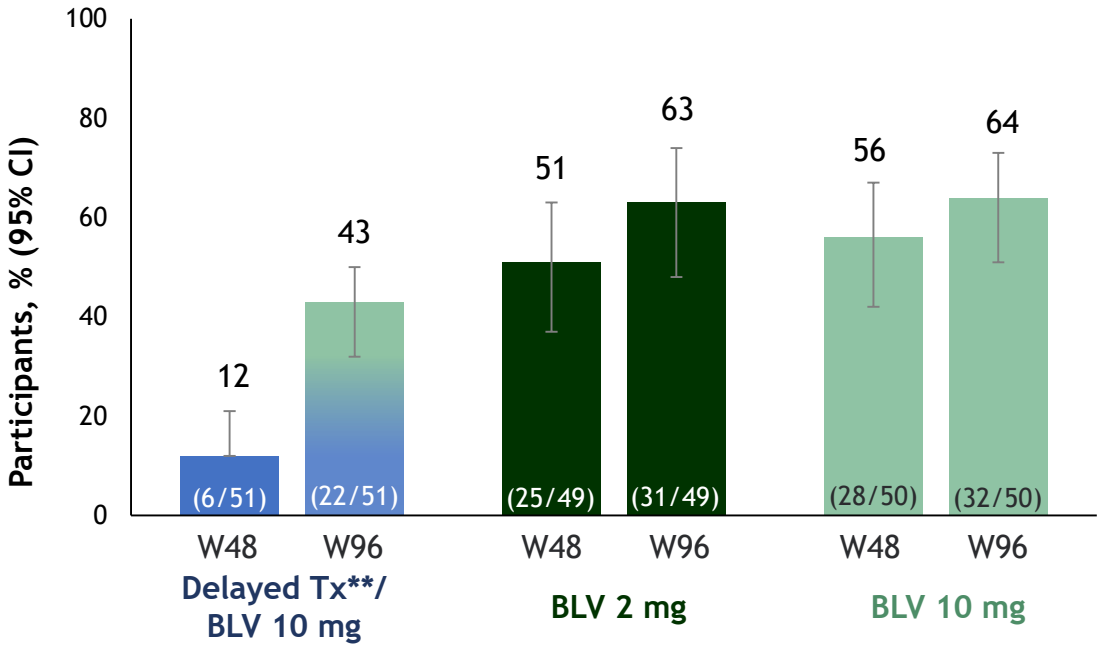
HDV RNA decline and virologic response improved with longer term BLV therapy

65 Undetectable HDV RNA defined as below lower limit of quantification (50 IU/mL) or target not detected. *Delayed treatment arm did not receive any BLV through Week 48. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; SD, standard deviation; Tx, treatment.
Wedemeyer H, et al. EASL 2023. Oral #OS-068

BLV: Bulevirtide

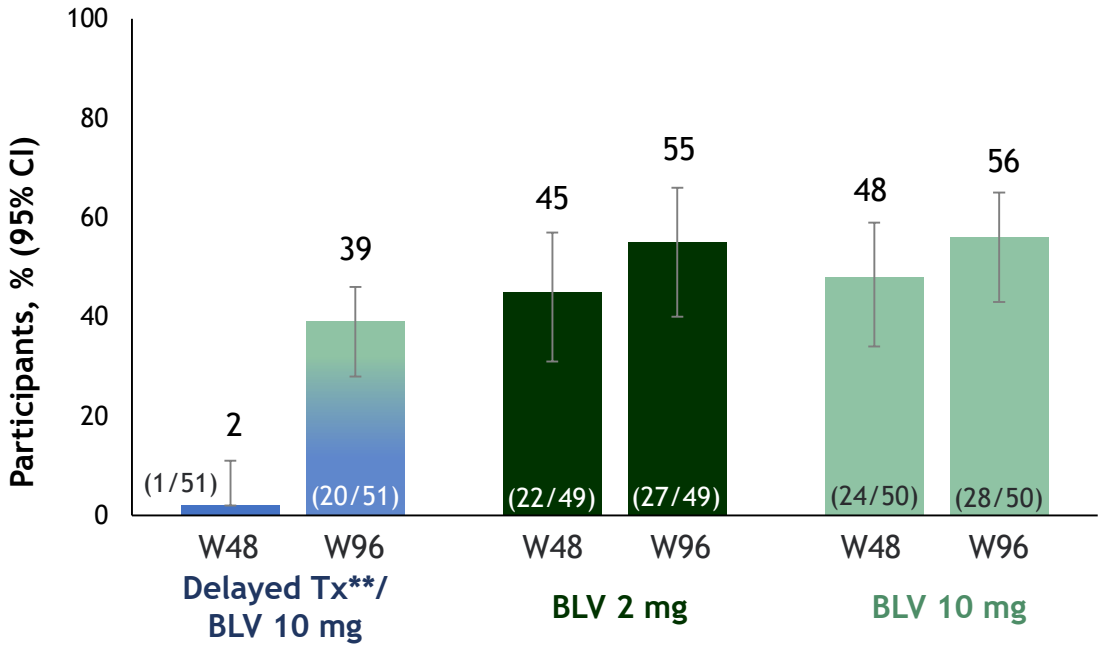
ALT and Combined Response Through 96 Weeks

ALT Normalization*



Combined Response

Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decrease from BL and ALT normalization*



ALT normalization and combined response rates improved with longer term BLV therapy

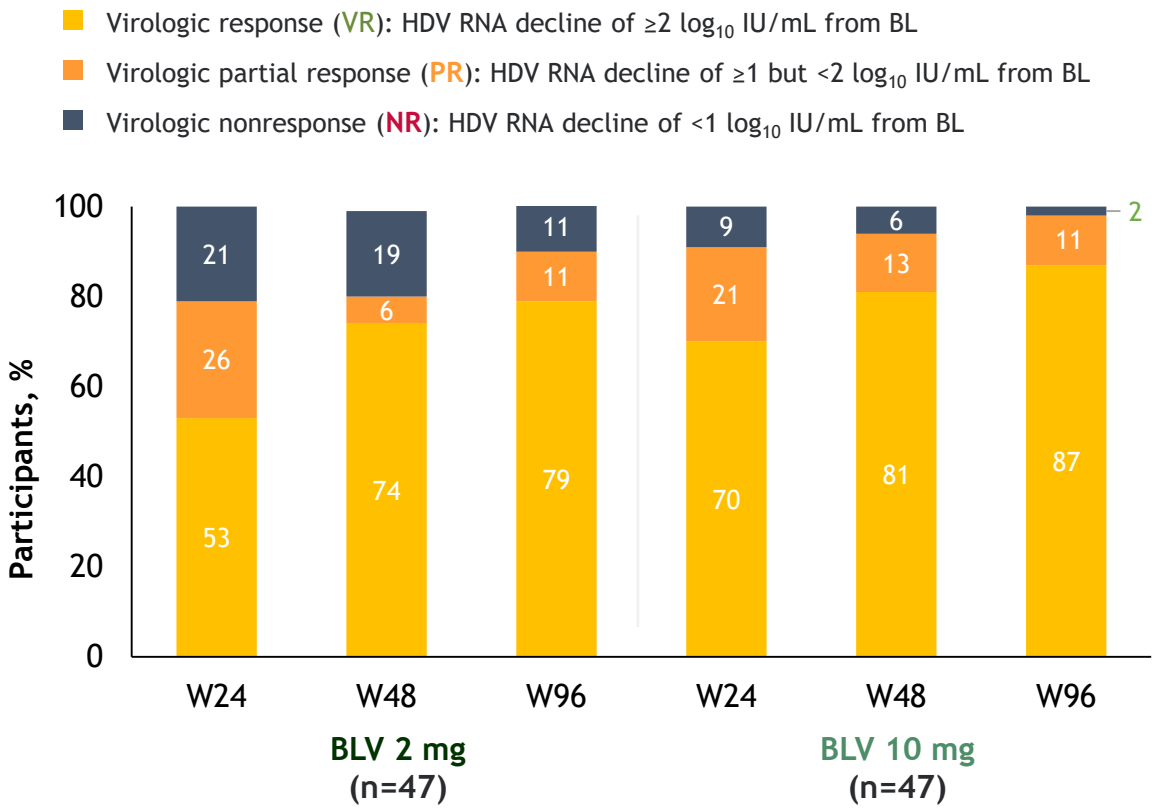
Undetectable HDV RNA defined as below lower limit of quantification (50 IU/mL) or target not detected. *ALT normalization defined at Russian sites as ≤31 U/L for women and ≤41 U/L for men, and at all other sites as ≤34 U/L for women and ≤49 U/L for men; **Delayed treatment arm did not receive any BLV through Week 48. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; Tx, treatment.

Wedemeyer H, et al. EASL 2023. Oral #OS-068

BLV: Bulevirtide

Continued BLV Treatment in Suboptimal Virologic Responders*

Change in Virologic Response Category from Week 24 to Week 96



Efficacy Responses (BLV 2 mg and 10 mg)

82% — 18 of 22 initial PR at Week 24 became VR at Week 96

43% — 6 of 14 initial NR at Week 24 became VR at Week 96

83% — ALT declined by >50% from BL in 5 of 6 patients who remained a NR at Week 96

A majority of initial PR and NR experienced virologic response with continued BLV therapy; ALT improvements were observed even in patients with suboptimal virologic response

*Suboptimal early virologic response was defined as nonresponse or partial response at Week 24. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; NR, virologic non-responder; PR, partial virologic responder; VR, virologic responder.

Lampertico P, et al. EASL 2023. Poster #LBP-20.

BLV: Bulevirtide

Interim Safety Analysis at Week 96 (1/2)

Summary of AEs

n (%)	Delayed Tx*/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 AE related to BLV	0	22 (44)	24 (49)	25 (51)	36 (72)	36 (72)
Any SAE	1 (2)	2 (4)	2 (4)	2 (4)	1 (2)	4 (8)
Any SAE related to BLV	0	0	0	0	0	0
AE leading to withdrawal of BLV	0	0	0	0	0	0
Grade 3–4 AE	4 (8)	3 (6)	5 (10)	9 (18)	4 (8)	8 (16)
Death	0	1 (2)†	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)
ISR¶	0	3 (6)	9 (18)	10 (20)	15 (30)	15 (30)

BLV was well-tolerated, with no BLV-related SAEs and no AEs leading to BLV discontinuation

*Delayed treatment arm did not receive any BLV through Week 48; **n=50; †One death due to plasma cell myeloma not related to study treatment; ‡AEs with higher frequencies in BLV groups compared to delayed treatment; ¶Grouped term included injection site (reaction, erythema, pruritus, swelling, pain, haematoma, rash, abscess, dermatitis, irritation). AE, adverse event; BLV, bulevirtide; ISR, injection site reaction; SAE, serious adverse event; Tx, treatment.

Wedemeyer H, et al. EASL 2023. Oral #OS-068

BLV: Bulevirtide

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

No virologic resistance to bulevirtide monotherapy detected in patients through 24 weeks treatment in phase II and III clinical trials for chronic hepatitis delta

Julius Hollnberger[1,2,†], Yang Liu[3,*,†], Simin Xu[3], Silvia Chang[3], Ross Martin[3], Savrina Manhas[3], Thomas Aeschbacher[3], Bin Han[3], Tahmineh Yazdi[3], Lindsey May[3], Dong Han[3], Alex Shornikov[3], John Flaherty[3], Dmitry Manuilov[3], Vithika Suri[3], Tarik Asselah[4], Pietro Lampertico[5,6], Heiner Wedemeyer[7], Soo Aleman[8], Christopher Richards[3], Roberto Mateo[3], Evguenia Maiorova[3], Tomas Cihlar[3], Hongmei Mo[3], Stephan Urban[1,2,*]

No virologic resistance to bulevirtide monotherapy detected in patients through 24 weeks treatment in phase II and III clinical trials for chronic hepatitis delta

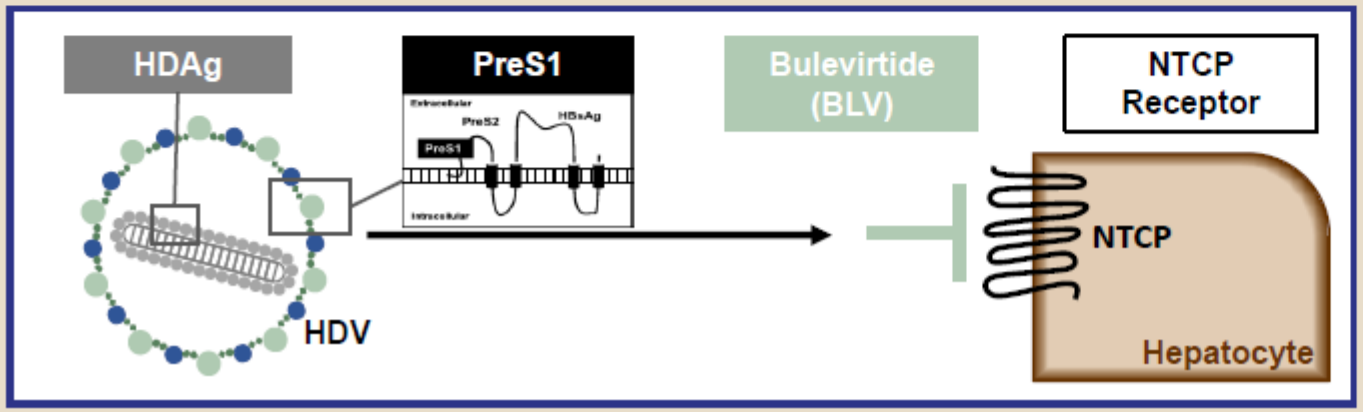
Participants with BLV treatment , n=189 | MYR202 (Phase II) + MYR301 (Phase III)

Virologic non-response (n=20) or virologic breakthrough (n=1), total 10.6% (n=21)

Resistance analysis

Baseline and week 24 | Baseline only

- **HDAg** sequencing
- **HBV PreS1** sequencing
- **BLV sensitivity** *In vitro* assay
- **NTCP** sequencing



CONCLUSION:

- No unique amino acid substitutions associated with reduced sensitivity to BLV were observed in HBV PreS1, HDV HDAg, and NTCP
- No BLV sensitivity differences were observed across different treatment outcome groups and baseline/Week 24 viruses

J Hepatol 2023

Treatment of HDV infection

- Interferon
- Lonafarnib
- **Bulevirtide (real word data)**
- Future options

72 Week BLV RWD in Patients with Cirrhosis

Multicenter real-world study of 93 patients with compensated cirrhosis treated with BLV 2 mg

Baseline Variables	Overall (n=95)
Age, years	52 (29-77)
Males	49 (52%)
European origin	90 (95%)
HDV genotype 1*	32 (97%)
HIV coinfection°	8 (8%)
BMI, Kg/m^2	25 (18-37)
CPT score A§	95 (100%)
Spleen diameter, cm	15 (9-31)
Esophageal varices@	49 (51%)
Previous ascites	19 (20%)
History of HCC#	13 (14%)
Previous IFN treatment	51 (52%)
NUC treatment	92 (97%)

Baseline Variables	Overall (n=95)
LSM, kPa	17.2 (4.7-68.1)
Bilirubin, mg/dl	1.0 (0.4-4.4)
AST, U/l	86 (7-738)
ALT, U/l	80 (26-1,074)
GGT, U/l	61 (13-362)
Albumin, g/dl	3.9 (2.9-4.7)
Creatinine, mg/dl	0.8 (0.4-1.2)
PLT, 10^3/mm^3	82 (17-330)
Bile acids, µmol/l	18 (3-306)
qHBsAg, Log IU/ml	3.7 (0.7-4.5)
HBeAg negative	92 (97%)
HBV DNA detectable	14 (15%)
HDV RNA, Log IU/ml	5.1 (1.9-7.6)

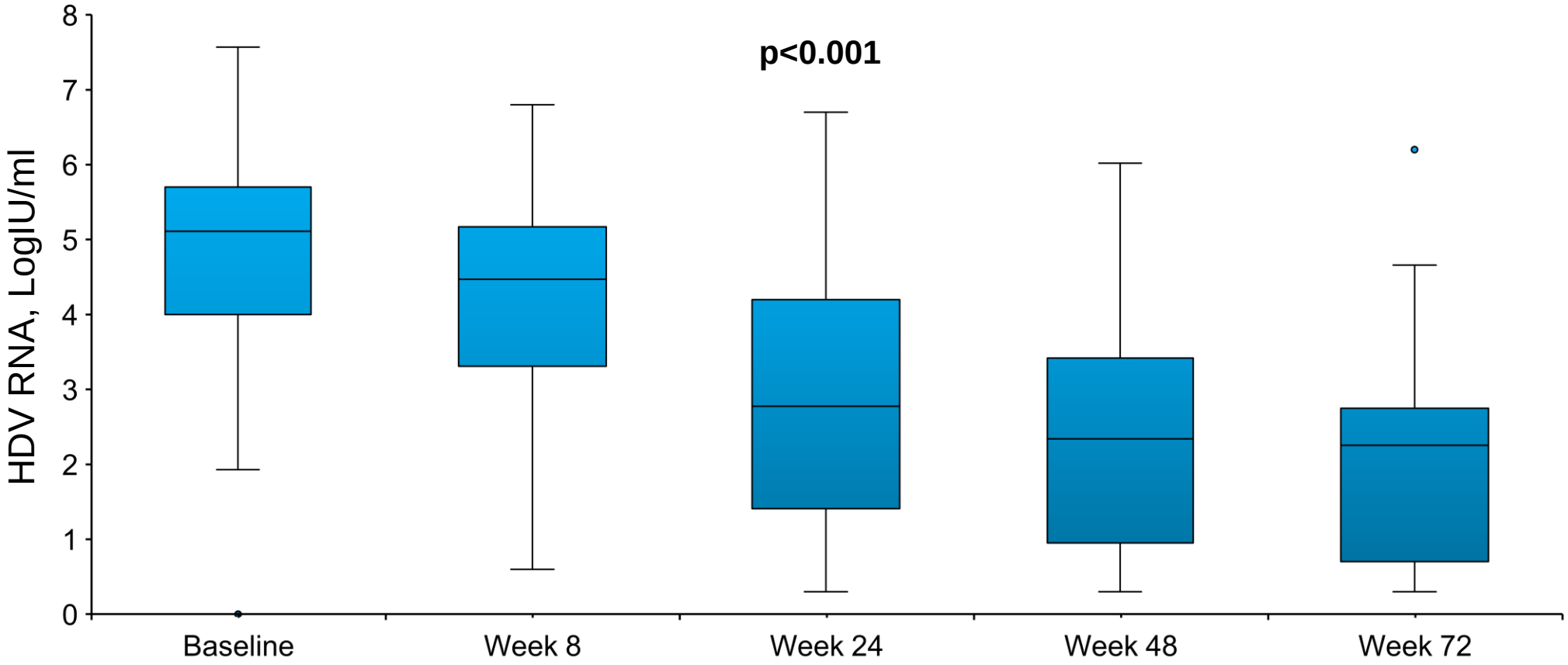
* available in 33 patients; ° all patients HIV RNA undetectable; §CPT A6 in 32 (34%); @34 (36%) on prophylaxis (33% primary; 3% secondary) #active HCC in 11 (12%)

Degasperi E, AISF 2023

72 Week BLV RWD in Patients with Cirrhosis

Multicenter real-world study of 93 patients with compensated cirrhosis treated with BLV 2 mg

HDV RNA Levels During BLV Treatment



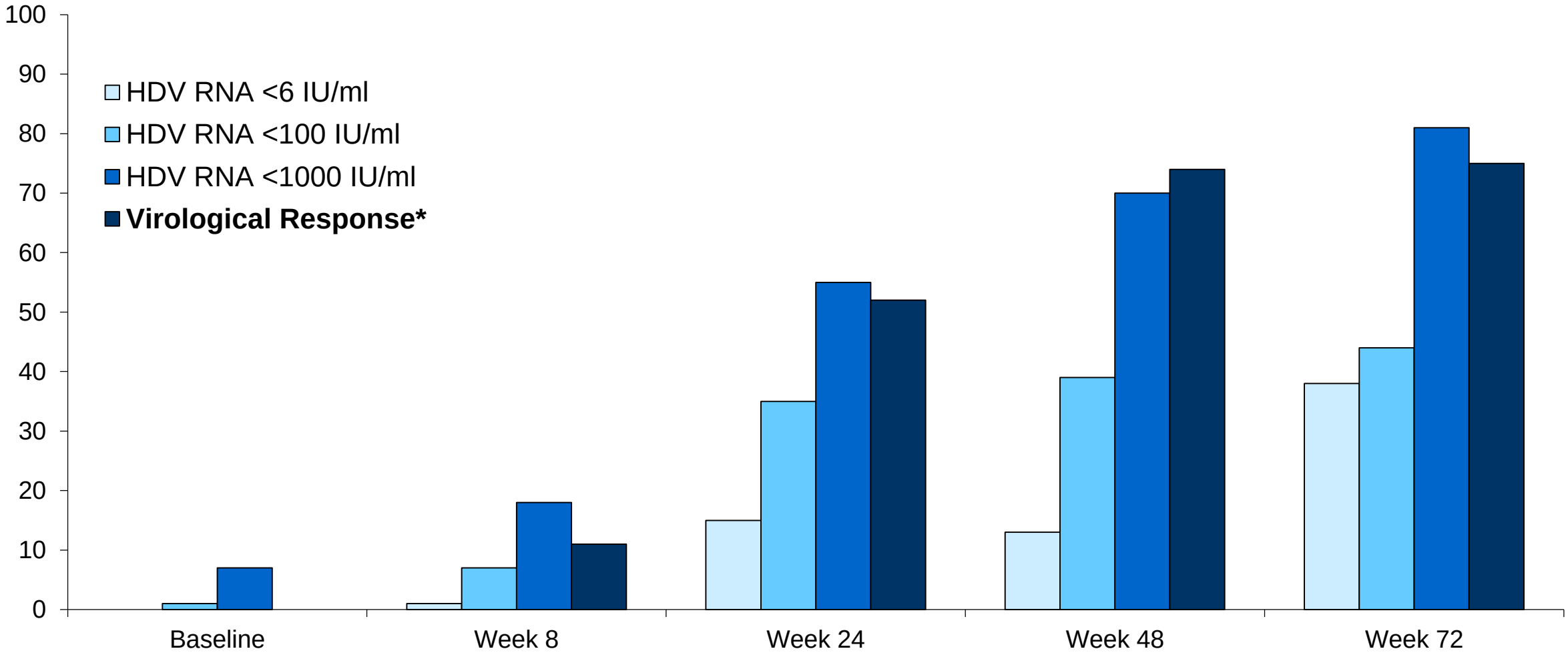
	Baseline	Week 8	Week 24	Week 48	Week 72
Median	5.1	4.5	2.8	2.3	2.3
Range	(1.9-7.6)	(0.6-6.8)	(0.3-6.6)	(0.3-6.0)	(0.3-6.2)
HDV RNA Decline (Log)			**2.1 (0.4-4.9)**	**2.5 (0.2-4.3)**	**2.8 (0.1-5.3)**

Degasperi E, AISF 2023

72 Week BLV RWD in Patients with Cirrhosis

Multicenter real-world study of 93 patients with compensated cirrhosis treated with BLV 2 mg

Virological Response During BLV Treatment



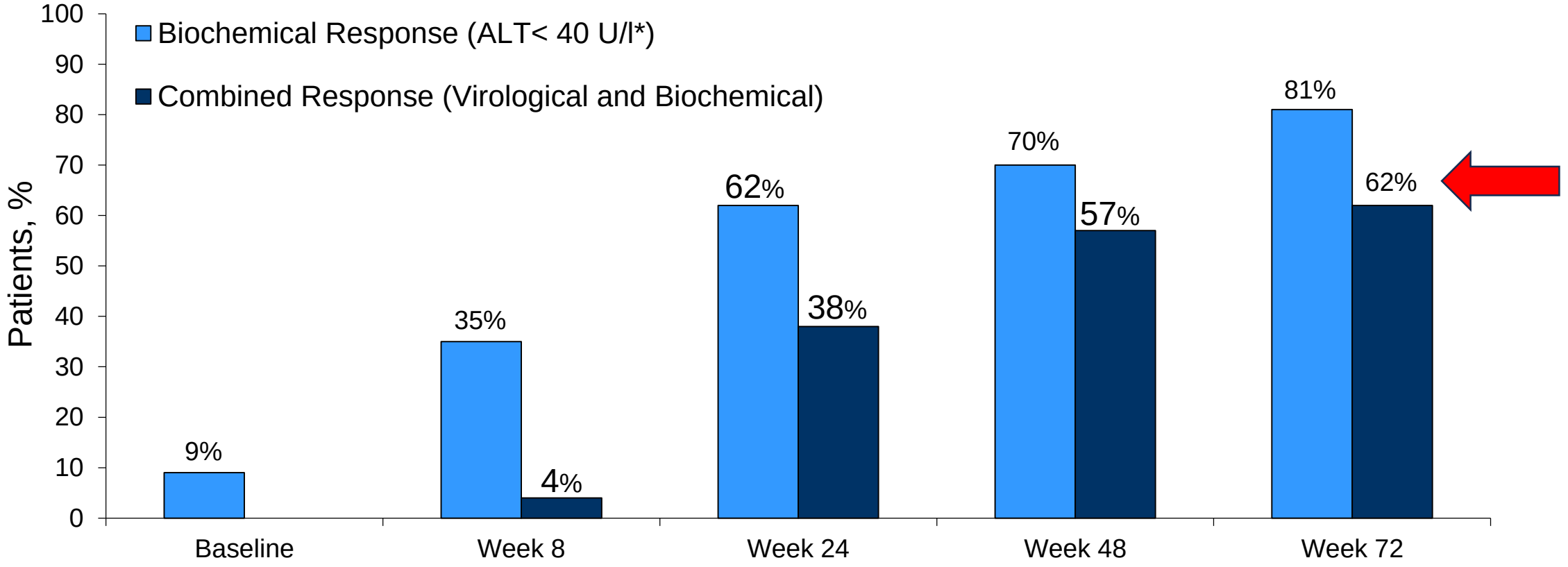
*≥2 Log decline or HDV RNA undetectable compared to baseline

Degasperi E, AISF 2023

72 Week BLV RWD in Patients with Cirrhosis

Multicenter real-world study of 93 patients with compensated cirrhosis treated with BLV 2 mg

Biochemical & Combined Response During BLV Treatment



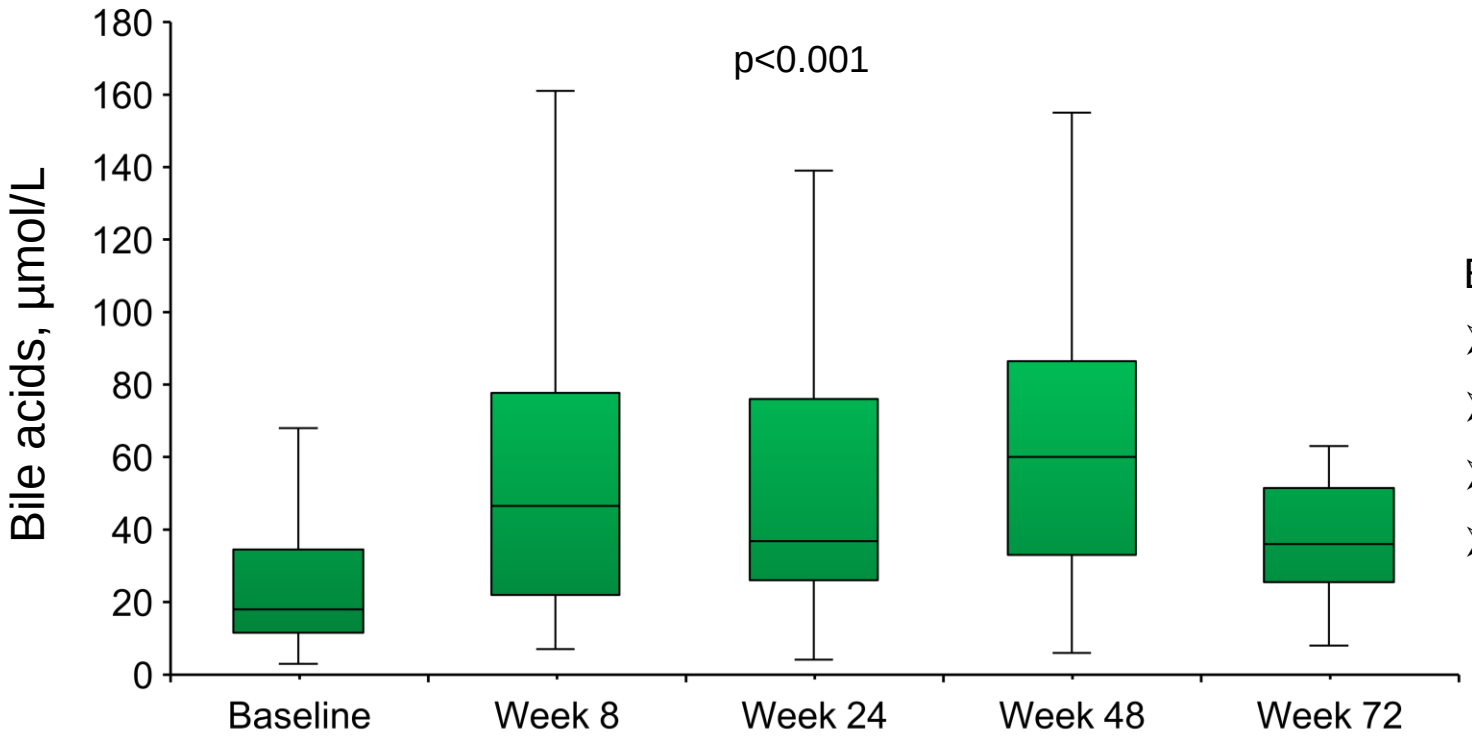
	Week 8	Week 24	Week 48	Week 72
ALT <ULN and HDV RNA <1000 IU/mL	11%	35%	52%	69%
ALT<1.5 ULN and HDV RNA <1000 IU/mL	16%	51%	70%	75%

*EASL Criteria; ALT: Alanine aminotransferase; ULN: Upper limit of normal

Degasperi E, AISF 2023

72 Week BLV RWD in Patients with Cirrhosis

Multicenter real-world study of 93 patients with compensated cirrhosis treated with BLV 2 mg



BLV-related AEs

- Significant bile acids elevation
- Mild, transient pruritus in n=12 (13%)
- Injection site reactions in n=6 (6%)
- No discontinuations due to BLV-related AEs

Liver-related events and SAEs

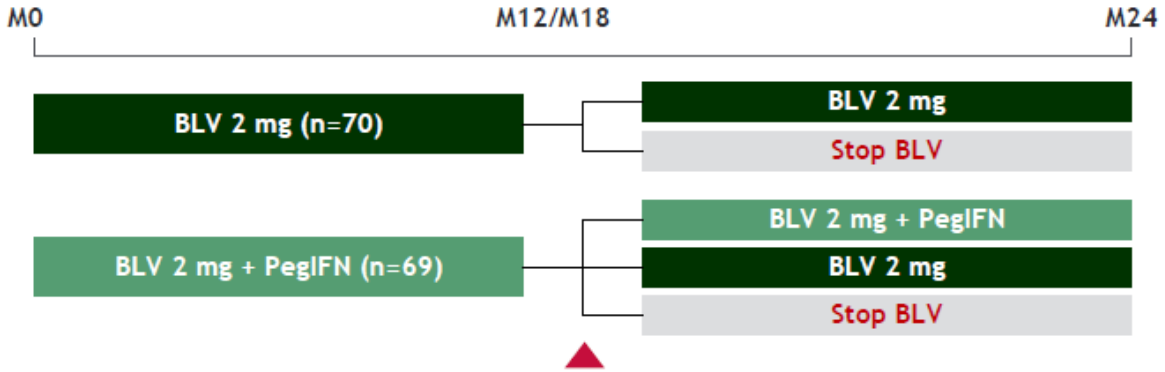
- N=2 decompensating events (n=1 ascites with portal vein thrombosis; n=1 variceal bleeding)
- N=5 with de-novo HCC
- N=5 undergoing liver transplantation (n=3 for HCC, n=2 for ESLD)
- N=1 death due to pneumonia (BLV-unrelated)

BLV: Bulevirtide; AE: adverse event; SAE: serious adverse event; HCC: hepatocellular carcinoma; ESLD: end-stage liver disease

Degasperi E, AISF 2023

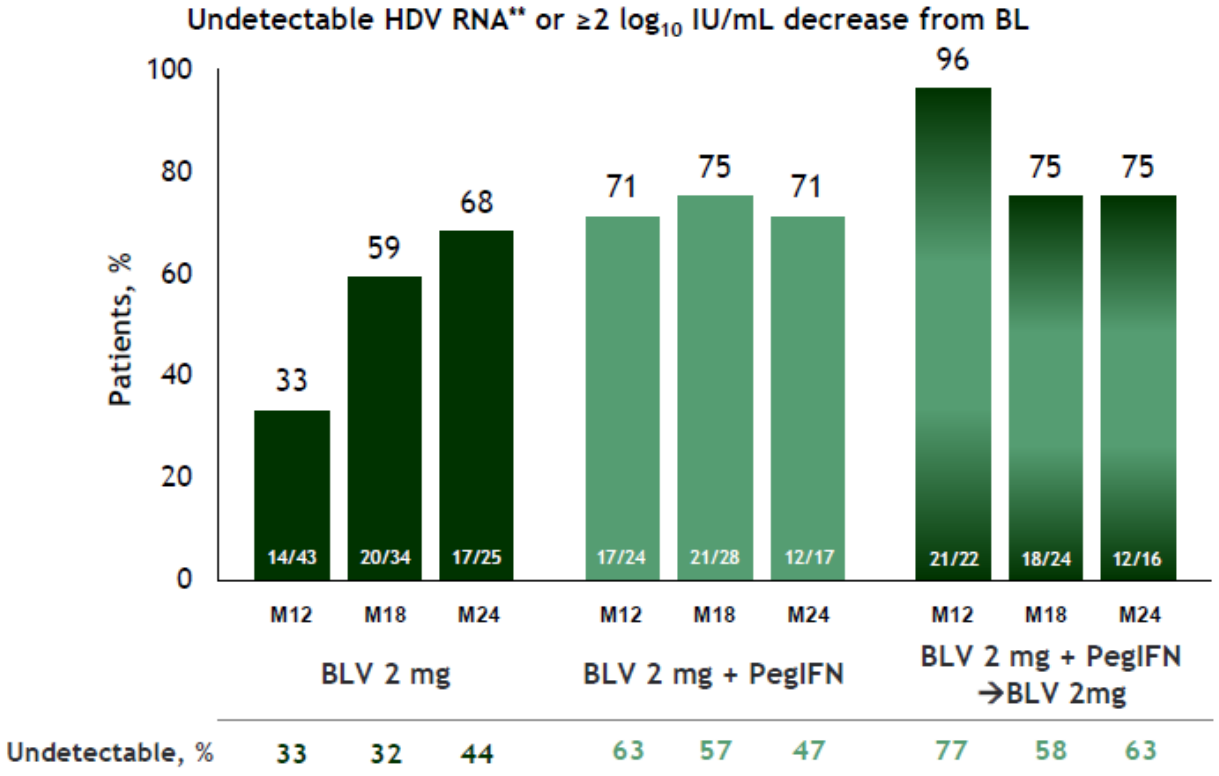
Two-Year Early Access Program RWD from France

A multicenter, open-label, observational prospective study of 139 patients treated with BLV 2 mg ± PegIFN*



Baseline Characteristics	BLV 2 mg n=70	BLV 2 mg + PegIFN n=69
Age, mean years (range)	42 (12)	40 (11)
Male, n (%)	50 (71.4)	45 (65.2)
Country of birth (Europe/Africa)**, n (%)	47 (67)/21 (30)	35 (52)/32 (48)
Cirrhosis, n (%)	44 (62.9)	42 (60.9)
Liver stiffness**, mean kPa (SD)	16.7 (14)	13.3 (9)
ALT†, mean IU/L, (SD)	94 (54)	124 (97)
HDV RNA, median log_{10} IU/mL, (IQR)	6.52 (1)	6.52 (1)
Current NA use, n (%)	56 (80)	51 (73.9)
HIV infection, n (%)	13 (18.6)	6 (8.7)

On Treatment Virologic Response



Virologic response increased with BLV 2 mg monotherapy over time; the majority of patients treated for 24 months with BLV ± PegIFN achieved a virological response

de Ledinghen V, AASLD 2022

Research article JHEP|Reports

Treating hepatitis D with bulevirtide – Real-world experience from 114 patients

In a joint effort with 16 German hepatological centers, retrospective data from 114 patients treated with bulevirtide (2mg) for chronic hepatitis D were evaluated

Table 1. Baseline patient characteristics.

Baseline patient characteristics (N = 114)	
Age, mean ± SD	47 ± 11
Male/female	80/34 (70%/30%)
Cirrhosis	59 (52%)
FibroScan >15 kPa	22
Esophageal varices	31
Histologically confirmed	8
Platelets <100,000/μl	44
Child-Pugh grade	
Child-Pugh A	54
Child-Pugh B	4
Child-Pugh C	1
FIB-4, median	2.9
Below 1.3	12%
Above 2.67	52%
Fibroscan® kPa, median (n = 40)	15.9
Above 25 kPa	18%
Below 10 kPa	22.5%
BMI, median (n = 98)	26
ALT U/L, mean ± SD	115 ± 102
Albumin g/L, mean ± SD (n = 111)	41 ± 6
Below 35 g/L, %	17%
Bilirubin μmol/L, mean ± SD	15 ± 10
Platelets $*10^3$/μl, median	122
Treatment with NAs (n = 113)	108 (96%)
Tenofovir disoproxil	71
Entecavir	16
Previous PEG-IFNa treatment (n = 110)	55 (50%)

Dietz-Fricke C, JHep Rep 2023

Research article JHEP|Reports

Treating hepatitis D with bulevirtide – Real-world experience from 114 patients

In a joint effort with 16 German hepatological centers, retrospective data from 114 patients treated with bulevirtide (2mg) for chronic hepatitis D were evaluated

Table 2. Comparison of disease characteristics at baseline and after 12 and 24 weeks of bulevirtide treatment.

Patient characteristics (n = 33)	Baseline	Week 12	Week 24	Post hoc *p* value
Virologic response, n (%)	–	7/33 (21%)	19/33 (58%)	
Virologic non-response, n (%)	–	9/33 (27%)	3/33 (9%)	
ALT U/L, mean ± SD	114 ± 73	53 ± 35	47 ± 32	<0.001*
Mean ALT change U/L ± SD		-61 ± 55	-68 ± 66	<0.001**, 0.627***
Albumin g/L, mean ± SD	41 ± 5	41 ± 6	42 ± 6	No *post hoc* test, ANOVA $p = 0.237$
Below 35 g/L, %	12%	15%	9%	
Bilirubin µmol/L, mean ± SD	14 ± 9	14 ± 11	14 ± 11	No *post hoc* test, ANOVA $p = 0.712$
Platelets $*10^3$/µl, median	133	149	157	No *post hoc* test, ANOVA $p = 0.104$

*Baseline *vs.* week 12, **baseline *vs.* week 24, ***week 12 *vs.* week 24.
Data points from baseline, week 12 and 24 were compared with repeated-measurement ANOVA and *post hoc* Bonferroni-corrected t tests. *p* values <0.05 were assumed statistically significant.
ALT, alanine aminotransferase.

Virologic response: a ≥ 2 log decline from baseline or HDV RNA undetectable or below the lower limit of quantification

Virologic non-response: a maximum decrease of HDV RNA by 1 log or an increase.

Dietz-Fricke C, JHep Rep 2023

Response-guided long-term treatment of chronic hepatitis D patients with bulevirtide—results of a "real world" study

Mathias Jachs[1,2] | Caroline Schwarz[3] | Marlene Panzer[4] | Teresa Binter[1,2] | Stephan W. Aberle[5] | Lukas Hartl[1,2] | Kristina Dax[6] | Elmar Aigner[7] | Albert F. Stättermayer[1,2] | Petra Munda[1] | Ivo Graziadei[8] | Heidemarie Holzmann[5] | Michael Trauner[1,2] | Heinz Zoller[4] | Michael Gschwantler[3] | Mattias Mandorfer[1,2] | Thomas Reiberger[1,2] | Peter Ferenci[1]

Background and Aim: Bulevirtide (BLV) blocks the uptake of the hepatitis D virus (HDV) into hepatocytes via the sodium/bile acid cotransporter NTCP. BLV was conditionally approved by the EMA but real-life data on BLV efficacy are limited.

Methods: Patients were treated with BLV monotherapy. Patients who did not achieve further decreases in HDV-RNA after 24 weeks were offered PEG-IFN as an add-on therapy in a response-guided manner.

Results: Twenty-three patients (m: 10, f: 13; mean age: 47.9 years, cirrhosis: 16; median ALT: 71 IU/ml; median HDV-RNA: 2.1×10^5 copies/ml) started BLV monotherapy (2 mg/day: 22; 10 mg/day: 1). Twenty-two completed ≥24 weeks of treatment (24–137 weeks): Ten (45%) were classified as BLV responders at week 24. BLV was stopped in two patients with >6 months HDV-RNA undetectability, but both became HDV-RNA positive again. One patient was transplanted at week 25. One patient terminated treatment because of side effects at week 60. Ten patients are still on BLV monotherapy. Adding PEG-IFN in eight patients induced an HDV-RNA decrease in all (1.29 ± 0.19 [SD] log within 12 weeks). HDV-RNA decreased by >2log or became undetectable in 45%(10/22), 55%(11/20), 65% (13/20) and 69% (9/13); and ALT levels normalised in 64% (14/22), 85% (17/20), 90% (18/20) and in 92% (12/13) patients at weeks 24, 36, 48 and 60, respectively. Portal pressure decreased in 40% (2/5) of patients undergoing repeated measurement under BLV therapy.

Conclusion: Long-term BLV monotherapy is safe and effectively decreases HDV-RNA and ALT—even in patients with cirrhosis. The optimal duration of BLV treatment alone or in combination with PEG-IFN remains to be established. An algorithm for a response-guided BLV treatment approach is proposed.

23 patients treated in 6 Austrian hospitals:
- **22 with 2mg; 1 with 10mg**
- **Cirrhosis in 16**

At week 24:
- **10 (45%) virological response (≥ 2 log decline from baseline or HDV RNA undetectable)**
- **1 stopped BLV for ADR**

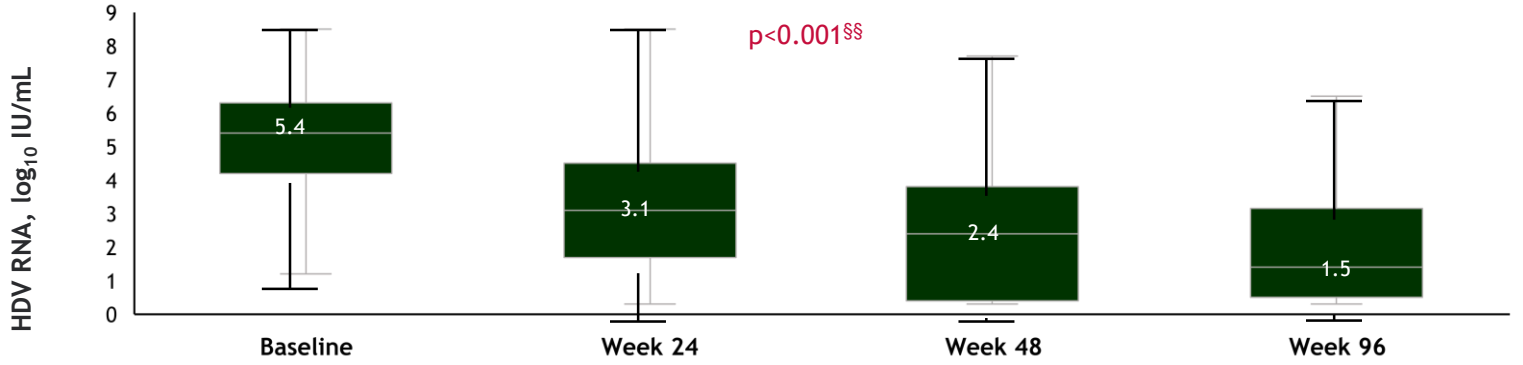
AP&T 2022

96 Week BLV RWD in Pan-European Cohort with Compensated Cirrhosis

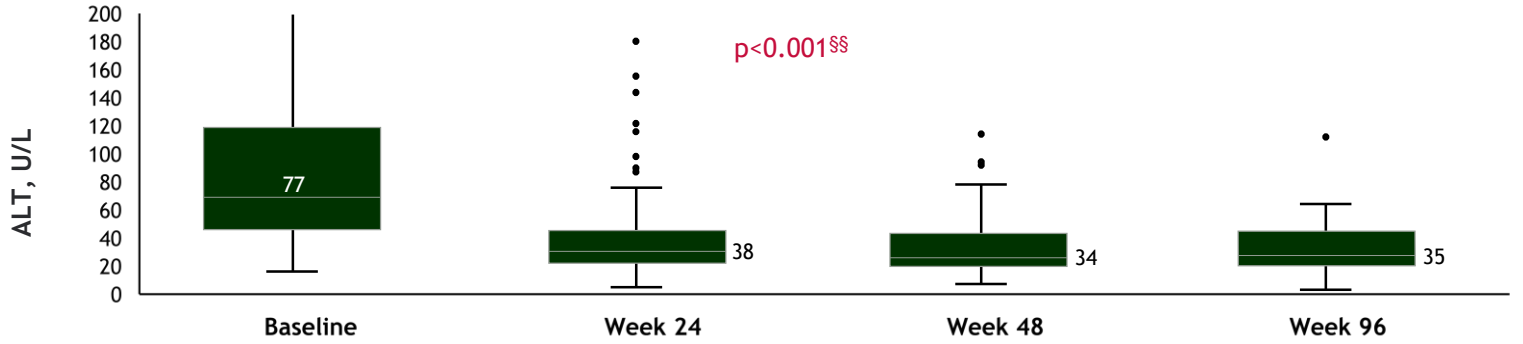
Retrospective, multicenter analysis of BLV 2 mg in 176 patients from 37 centers*

Demographics and Baseline Disease Characteristics	BLV 2 mg n=176
Age, median years (range)	50 (19–82)
Male, n (%)	104 (59)
HIV coinfection**, n (%)	15 (9)
CPT score A†, n (%)	176 (100)
Esophageal varices‡, n (%)	65 (54)
Previous ascites, n (%)	21 (12)
History of HCC§, n (%)	15 (9)
Liver stiffness, median kPa (range)	18.3 (6.4–75.0)
ALT, median U/L, (range)	77 (23–1,074)
Platelets, median $10^3/mm^3$ (range)	89 (17–330)
HDV RNA, median log_{10} IU/mL (range)	5.4 (1.2–8.5)
NA treatment, n (%)	160 (91)
Previous IFN treatment, n (%)	103 (59)

HDV RNA Levels



ALT Levels



BLV 2 mg up to 96 weeks was effective in a large European cohort with cirrhosis, reinforcing clinical trial findings

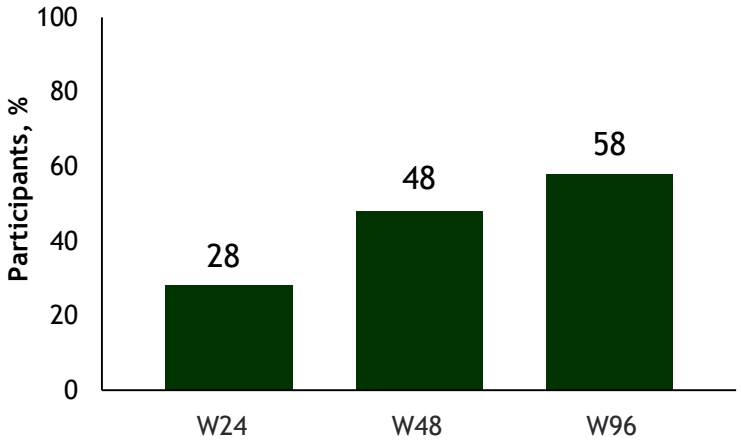
*Centers in Italy, France, Germany, and Austria; **All patients HIV RNA undetectable; †CPT A6 in 49 (28%); ‡46 (26%) patients on prophylaxis; §Active HCC in 11 patients (6%) still receiving treatment; §§Week 96 compared to baseline. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HCC, hepatocellular carcinoma; IFN, interferon; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

Degasperi E, et al. EASL 2023. Oral #LBP-11; Degasperi E, et al. HDIN 2023

96 Week BLV RWD in Pan-European Cohort with Compensated Cirrhosis

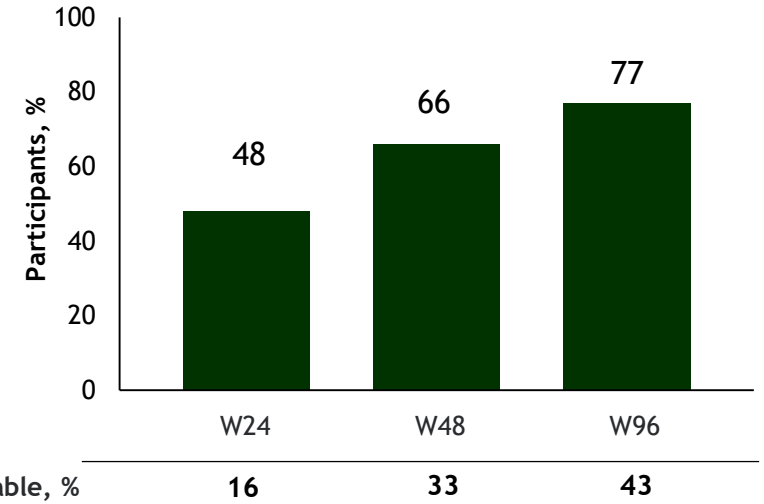
Combined Response (n=176)

Undetectable HDV RNA* or ≥2 log10 IU/mL decrease from BL and ALT normalization



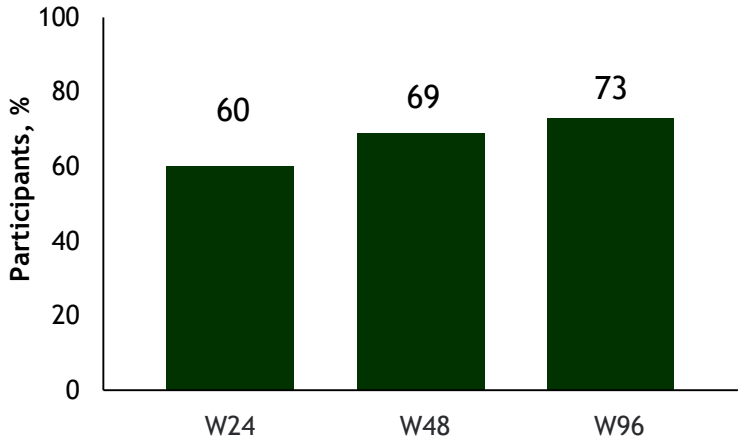
Viral Response (n=176)

Undetectable HDV RNA* or ≥2 log_{10} IU/mL decrease from BL



ALT Normalization (n=176)

ALT <40 U/L (EASL Criteria)



Safety profile:

- 3 patients experienced decompensating events and 7 instances of de-novo HCC occurred
- 6 liver transplantations and 2 deaths unrelated to BLV occurred

In a large European cohort with cirrhosis, viral response and ALT normalization increase with longer term BLV therapy

*LLOQ <6 IU/mL. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; LLOQ, lower limit of quantification.

Degasperi E, et al. EASL 2023. Oral #LBP-11; Degasperi E, et al. HDIN 2023

Research Article
Viral Hepatitis

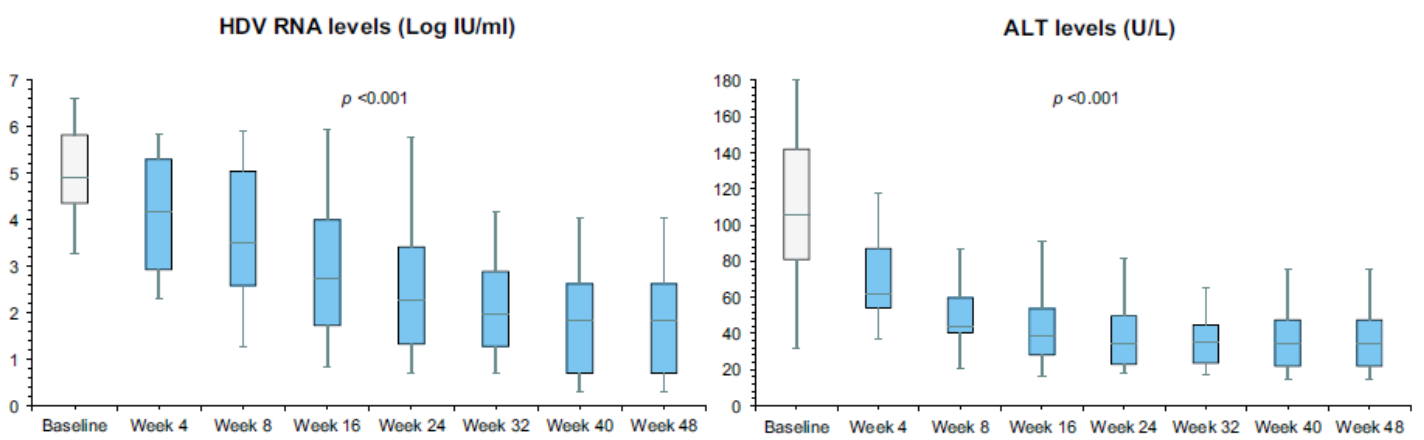
JOURNAL OF HEPATOLOGY

Bulevirtide monotherapy for 48 weeks in patients with HDV-related compensated cirrhosis and clinically significant portal hypertension

Elisabetta Degasperi[1], Maria Paola Anolli[1], Sara Colonia Uceda Renteria[2], Dana Sambarino[1], Marta Borghi[1], Riccardo Perbellini[1], Caroline Scholtes[3,4], Floriana Facchetti[1], Alessandro Loglio[1], Sara Monico[1], Mirella Fraquelli[5], Andrea Costantino[5], Ferruccio Ceriotti[2], Fabien Zoulim[3,4], Pietro Lampertico[1,6,*]

18 consecutive patients with HDV-related compensated cirrhosis and clinically significant portal hypertension who started BLV 2 mg/day were enrolled in this single-center

18 patients with HDV-related cirrhosis and clinically significant portal hypertension treated with bulevirtide monotherapy 2 mg/day for 48 weeks



Results at week 48

- 78% Virological response (≥2 log decline)
- 23% HDV RNA undetectable (<6 IU/ml)
- 11% Virological non-responders (<1 log decline at wk 24)
- 83% Biochemical response (ALT cut-off 41 U/L ♀; 59 U/L ♂)
- 67% Combined response

- Improved biochemical variables (AST, GGT, gammaglobulins)
- Improved liver function parameters (albumin, cholinesterase)
- No symptomatic adverse effects
- Asymptomatic increase in bile acids

J Hepatol 2023

Case Report

JOURNAL OF HEPATOLOGY

A 3-year course of bulevirtide monotherapy may cure HDV infection in patients with cirrhosis

Maria Paola Anolli[1], Elisabetta Degasperi[1], Lena Allweiss[2,3], Angelo Sangiovanni[1], Marco Maggioni[4], Caroline Scholtes[5,6], Valerie Oberhardt[7], Christoph Neumann-Haefelin[7], Maura Dandri[2,3], Fabien Zoulim[5,6], Pietro Lampertico[1,8,*]

Table 1. Time course of biochemical and virological variables during and after BLV treatment.

Variables	Baseline (pre-treatment)	End of therapy with BLV (week 144)	Off-therapy week 12	Off-therapy week 24	Off-therapy week 36	Off-therapy week 48	Off-therapy week 72
ALT (IU/L)/AST (IU/L)	232/179	28/36	23/30	44/50	31/36	30/33	20/26
ALP (IU/L)/GGT (IU/L)	185/231	85/110	82/77	88/226	110/72	56/68	65/89
Total bilirubin (mg/dl)	0.4	0.6	0.6	0.6	0.6	0.7	0.6
pCHE (IU/L)	4,479	7,805	7,200	8,440	8,313	8,923	7,816
Albumin (g/dl) /gamma-globulin (g/dl)	3.6/2.9	4.6/1.0	4.5/1.0	4.5/1.1	4.3/1.0	4.6/1.1	4.5/1.0
Immunoglobulin G (mg/dl)	3,077	1,285	1,240	1,160	1,185	1,221	1,129
AFP (ng/dl)	21	4	3	4	4	5	3
PT-INR	1.1	1.1	1.1	1.0	1.2	1.1	1.2
Platelet count (x10⁹/L)	74	110	137	115	144	144	160
ANA/AMA/ASMA/LKM	-/-/-/-	-/-/-/-	-/-/-/-	-/-/-/-	—	-/-/-/-	—
Liver stiffness (kPa)	17.6	10.9	8.5	11.5◦	—	10.6	6.9
Spleen length (cm)	14.0	13.0	—	14.5	—	14.5	12.2
Creatinine (mg/dl)	0.82	0.84	0.93	0.99	0.84	0.93	0.8
HBsAg (IU/ml)	9,091	5,045	2,873	3,238	2,347	2,316	2,014
HBcrAg (log U/ml)	4.5	3.5	3.5	3.4	3.4	3.4	—
HBV DNA (IU/ml)	TND	TND	TND	TND	TND	TND	TND
HBV RNA (cp/ml)	<160*	<16§	<16	<16	—	<16	—
HDV RNA (IU/ml)	392,000	TND	TND	TND	TND	TND	TND
Bile acids (μmol/L)	35	55	8	15	—	11	1
Esophageal varices on EGD	F1 RCS-†	No×	—	—	—	No	—
Intrahepatic HBsAg	—	Focally positive (1.4% of liver biopsy)■	—	—	—	Focally positive (0.4% of liver biopsy)	—
Intrahepatic HBcAg	—	Negative■	—	—	—	Negative	—
Intrahepatic HDAg	—	Negative■	—	—	—	Negative	—
Intrahepatic HDV RNA	—	Negative■	—	—	—	Negative	—

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle

J Hepatol 2023

Case Report

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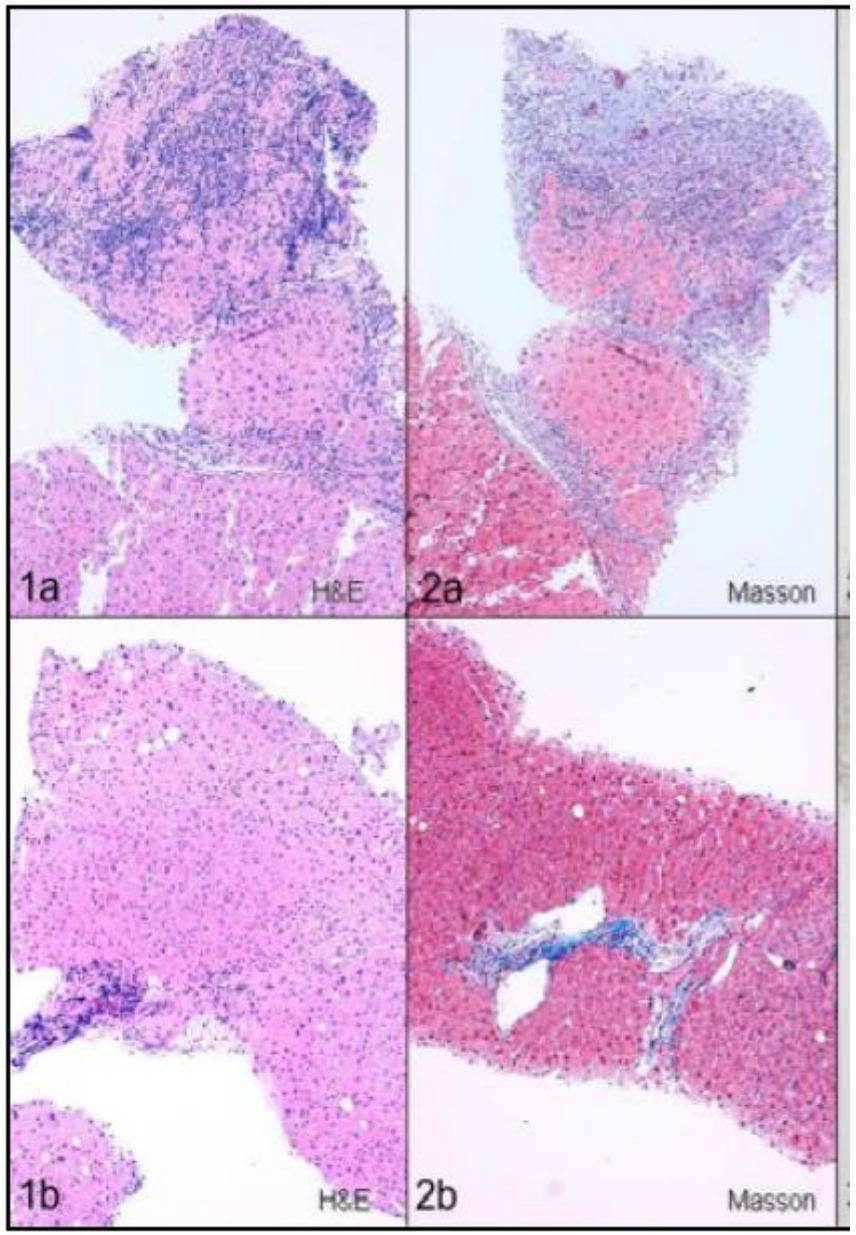
During treatment

48 weeks after BLV discontinuation

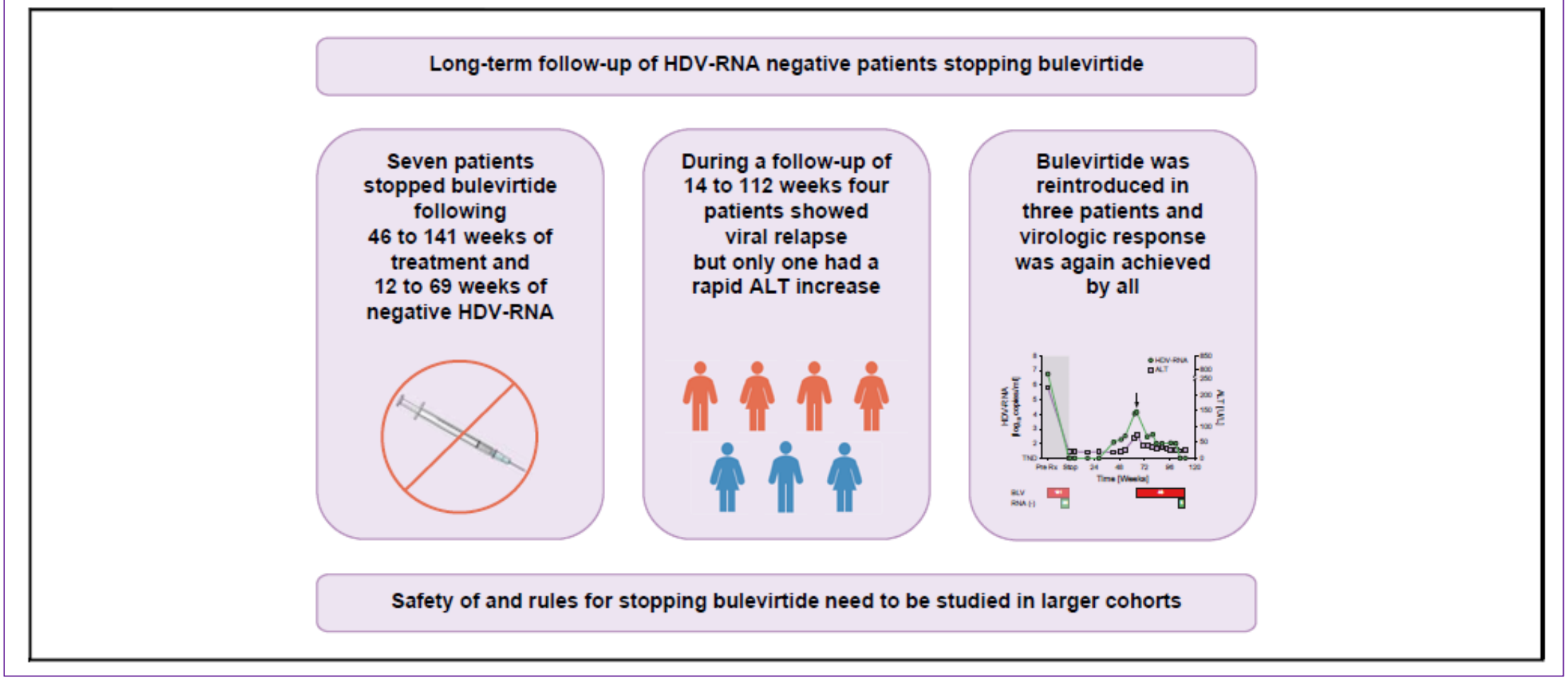


J Hepatol 2023

Research article JHEP|Reports

Long-term follow-up of patients discontinuing bulevirtide treatment upon long-term HDV-RNA suppression

Mathias Jachs,[1,2,*] Marlene Panzer,[3] Lukas Hartl,[1,2] Michael Schwarz,[1,2] Lorenz Balcar,[1,2] Jeremy V. Camp,[4] Petra Munda,[1,2] Mattias Mandorfer,[1,2] Michael Trauner,[1,2] Stephan W. Aberle,[4] Heinz Zoller,[3] Thomas Reiberger,[1,2,†,*] Peter Ferenci[1,†,‡]



J HepRep 2023

Research article JHEP|Reports

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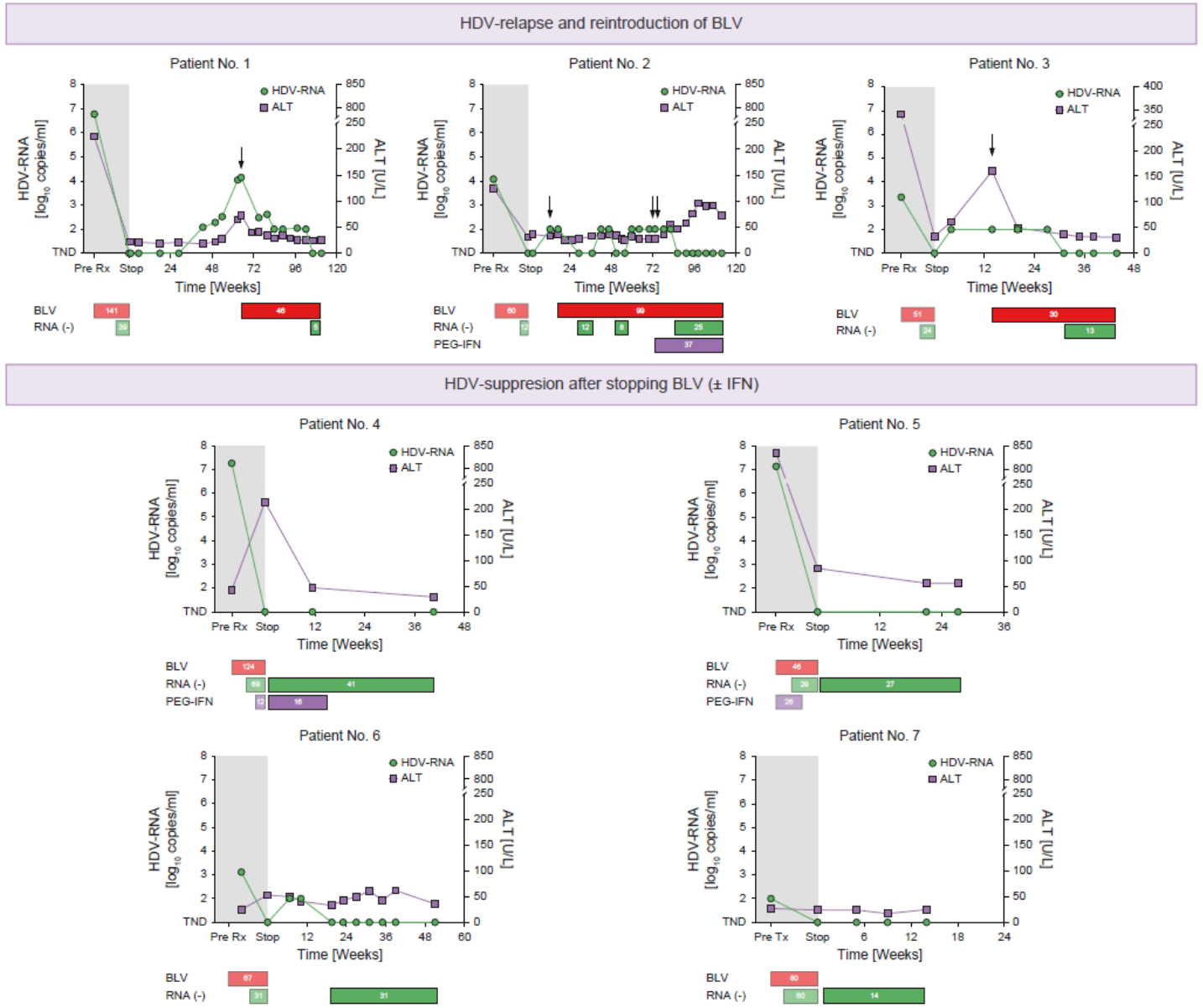


Fig. 1. HDV-RNA and ALT levels in six patients who reached 24 weeks of follow-up after BLV discontinuation, stratified by HDV relapse *vs.* HDV suppression at the last follow-up. BLV and IFN treatment and HDV-RNA suppression duration pre-/post-BLV cessation are indicated for each patient. BLV and IFN (re) introduction during follow-up is highlighted by one and two arrows, respectively. ALT, alanine aminotransferase; BLV, bulevirtide; IFN, interferon; PegIFN, pegylated interferon-α2a.

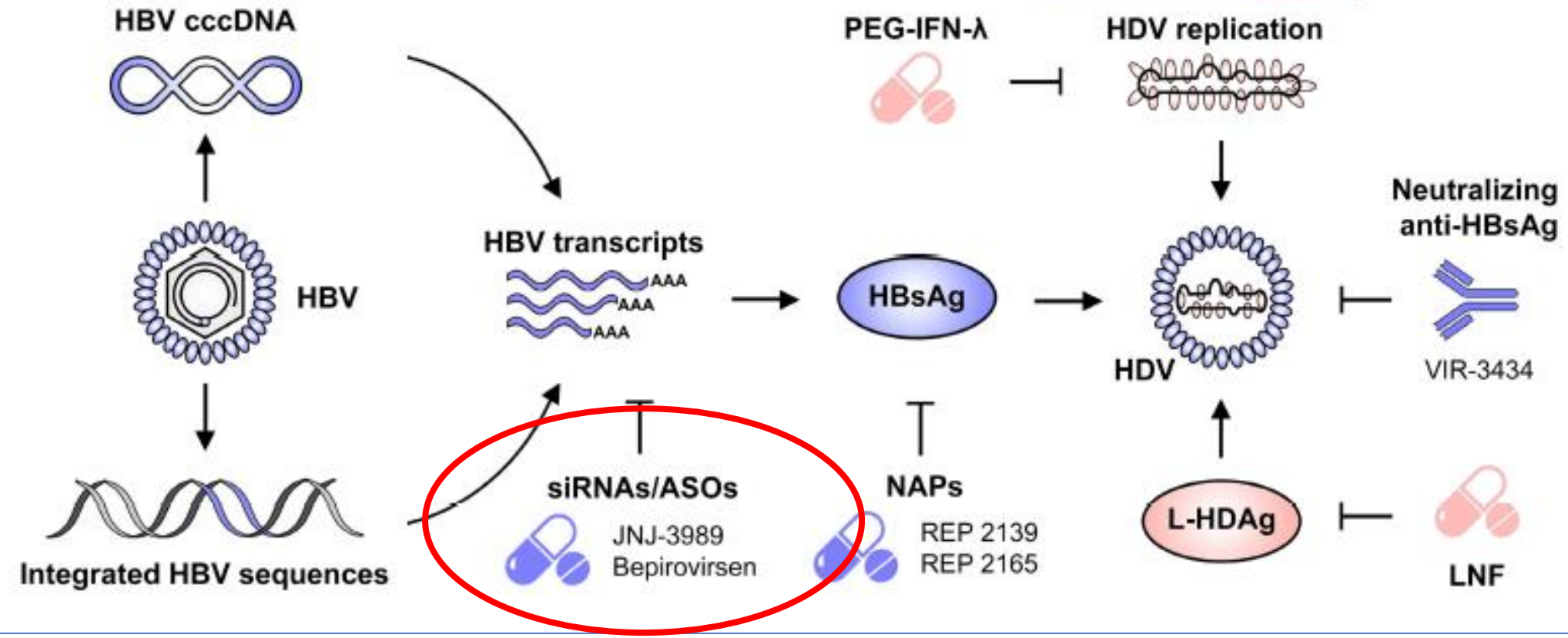
Treatment of HDV infection

- Interferon
- Lonafarnib
- Bulevirtide
- **Future options**

Emerging anti-HDV drugs and HBV cure strategies with anti-HDV activity

Armando A. Roca Suarez[1,2] | Enkhtuul Batbold[3] | Birke Bartosch[1,2] | Naranjargal Dashdorj[3,4] | Barbara Testoni[1,2] | Fabien Zoulim[1,2,5]

Liver INTERNATIONAL —WILEY



Liv internat 2023

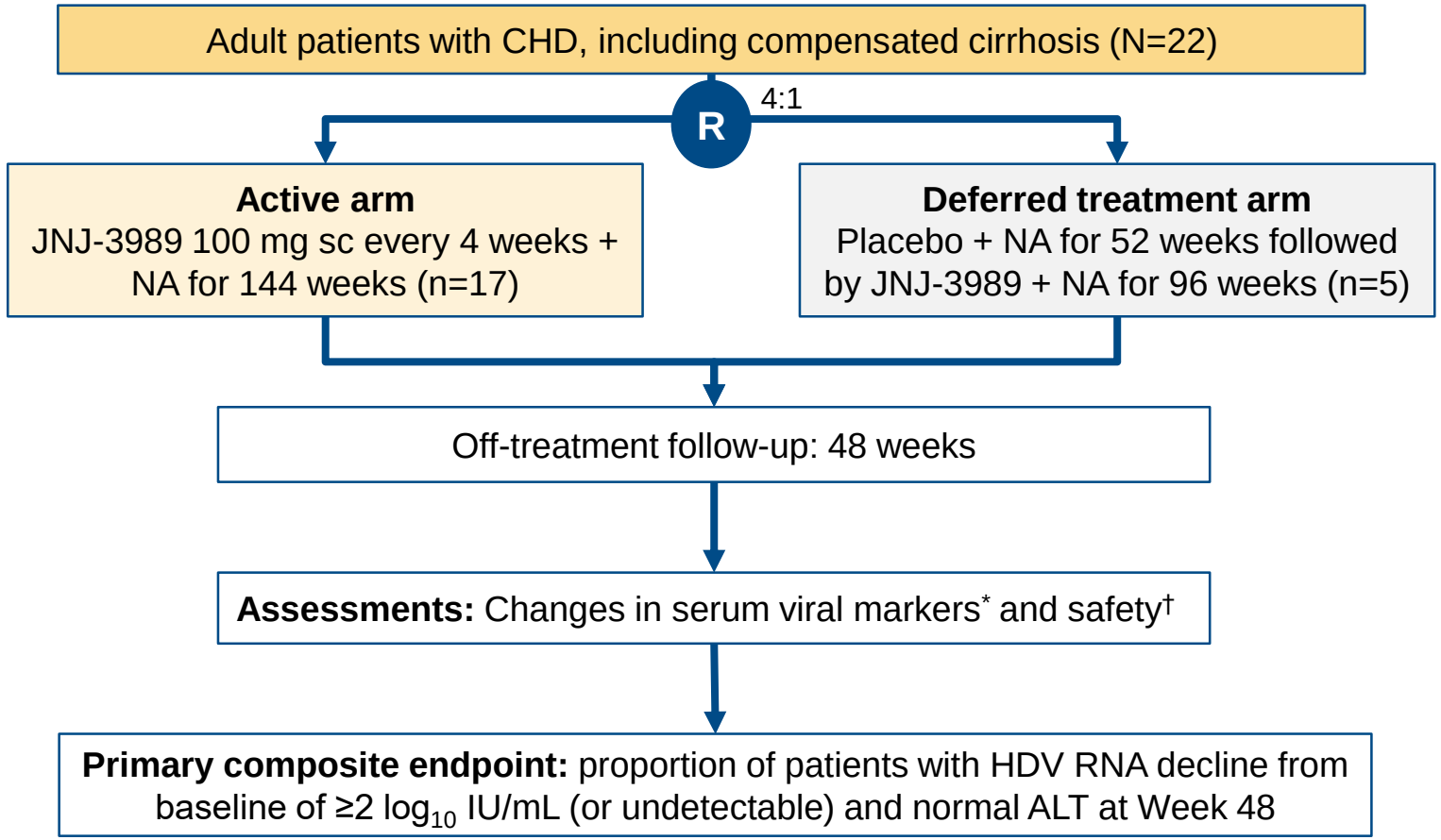
Treatment with siRNA JNJ-73763989 plus NA decreases HBsAg and HDV RNA levels in patients with CHD: part 1 of the REEF-D study

BACKGROUND & AIMS

- HDV requires HBsAg to form infectious viral particles
- siRNA JNJ-3989 has been shown to reduce HBsAg in chronic HBV
- **AIM:** To evaluate the effect of JNJ-3989 in patients with CHD to investigate whether reduction of HBsAg will lead to a reduction in HDV replication

METHOD

- REEF-D is a 2-part, phase 2, multicenter, randomized, double-blind, placebo-controlled study
- Antiviral activity in Part 1 was used to expand this study (Part 2)



Data from Part 1, Week 48 interim analysis are reported here

*HBsAg and HDV RNA; †ALT levels

Wedemeyer H et al. EASL 2023; OS-030

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Treatment with siRNA JNJ-73763989 plus NA decreases HBsAg and HDV RNA levels in patients with CHD: part 1 of the REEF-D study

RESULTS

	Active arm (n=17)	Deferred treatment arm (n=5)
Achieved primary composite endpoint, n (%)	4 (23.5)	0
HBsAg change from baseline, mean (SE), log_{10} IU/mL*	-1.75 (0.29)	0.07 (0.04)
HDV RNA change from baseline, mean (SE), log_{10} IU/mL*	-1.52 (0.38)	-0.23 (0.15)

- 12 (70.6%) patients in the active arm experienced treatment-emergent ALT elevations† (Week 8–20), which were associated with HDV RNA rebound, limited transient HBV DNA increase in most patients, but no clear impact on HBsAg decline
  - Grade 3/4 ALT elevations were observed, with no cases of decompensation
  - Treatment was discontinued early in 8 patients
  - In general, ALT levels returned to baseline values after treatment discontinuation
- 5 patients did not experience ALT elevations
  - 4 (80.0%) achieved the primary composite endpoint
  - 2 (40.0%) had HDV RNA below the LLOQ of the assay
- Aside from ALT elevations, safety outcomes were unremarkable
- Predefined criterial to initiate Part 2 of the study were met
- ALT flares, predominantly in patients with high HBsAg and HDV RNA levels at baseline, led to exclusion of patients with cirrhosis or HBsAg >10,000 IU/mL and HDV RNA >100,000 IU/mL

CONCLUSION

- JNJ-3989 leads to a simultaneous reduction of HBsAg and HDV RNA in patients with CHD (first proof-of-concept)
- ALT elevations were frequent, associated with HDV RNA increases and treatment discontinuation
- Patients without ALT elevations generally had a continuous reduction in HDV RNA (80% met the primary endpoint)

*Out of 9 atients still on treatment at Week 48; †(≥3× upper limit of normal [ULN] and ≥2× nadir.

Wedemeyer H et al. EASL 2023; OS-030

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Emerging anti-HDV drugs and HBV cure strategies with anti-HDV activity

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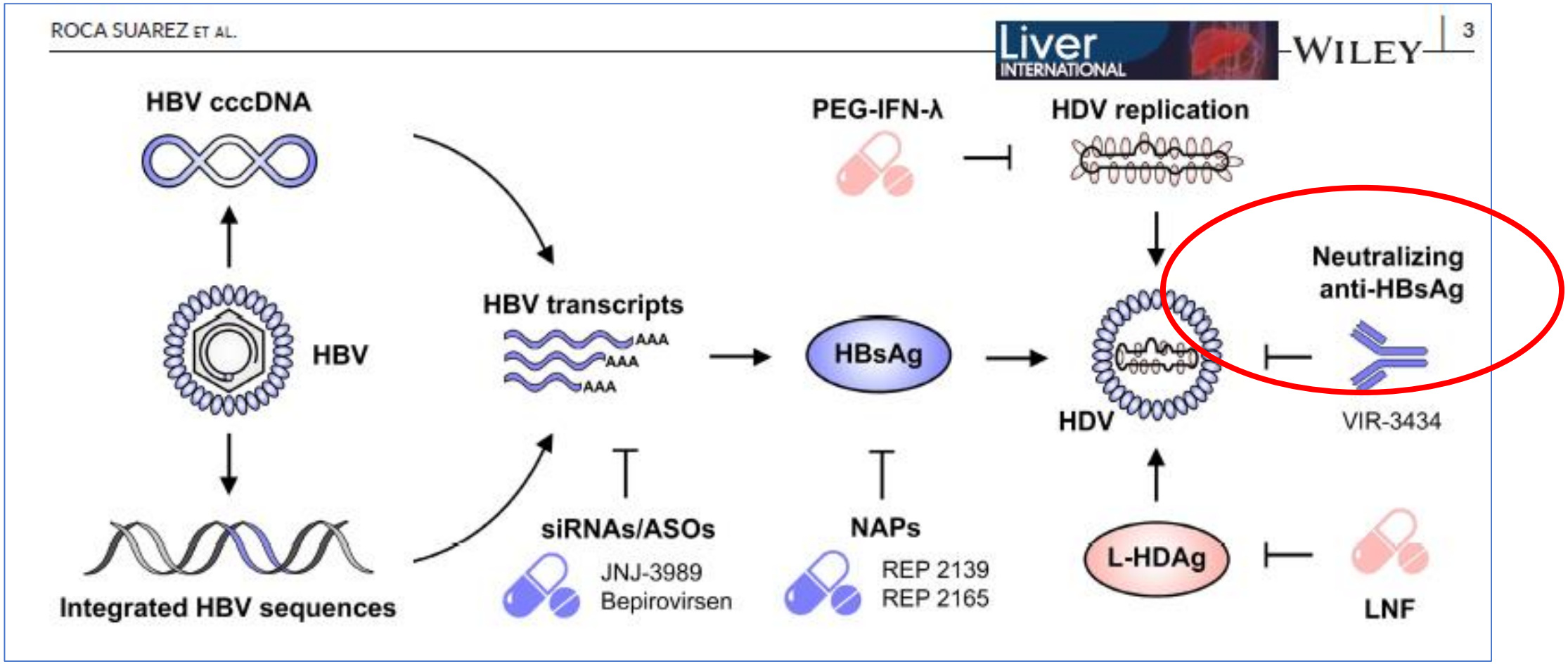
Liver INTERNATIONAL —WILEY— 3



Liv internat 2023

Safety and efficacy of anti-pre-S1 domain mAb (HH-003) treatment in patients with co-infection of chronic HBV and HDV: a single center, open-label, phase 2 trial

BACKGROUND & AIMS

- HH-003 is a human mAb targeting the preS1 domain of the large envelope protein of HBV and HDV
  - HH-003 prevents the binding of preS1 to NTCP, the cellular receptor for HBV and HDV, thereby blocking viral infection and re-infection of hepatocytes
- **AIM:** To evaluate the safety and efficacy of HH-003 in patients with chronic HBV and HDV co-infection

METHODS

Open-label, phase 2 trial (NCT05674448)
Adult (age 18–70 years) patients who were serum anti-HDV IgG+ and HDV RNA+ at screening, with ≥6 months of HBV infection
(N=9)

↓

20 mg/kg HH-003 IV Q2W for 24 weeks, with 24 weeks follow-up

↓

Assessment of response at week 24 and 48
- Virological response (serum HDV RNA below the limit of detection, or a ≥2 $\log_{10}$ IU/mL decline from baseline)
- Biochemical response (ALT normalization, defined as ≤33 U/L for women and ≤41 U/L for men)
- Serum HDV RNA was measured using RoboGene HDV RNA Quantification kit 2.0

Niu J, et al. EASL 2023; LBP-24

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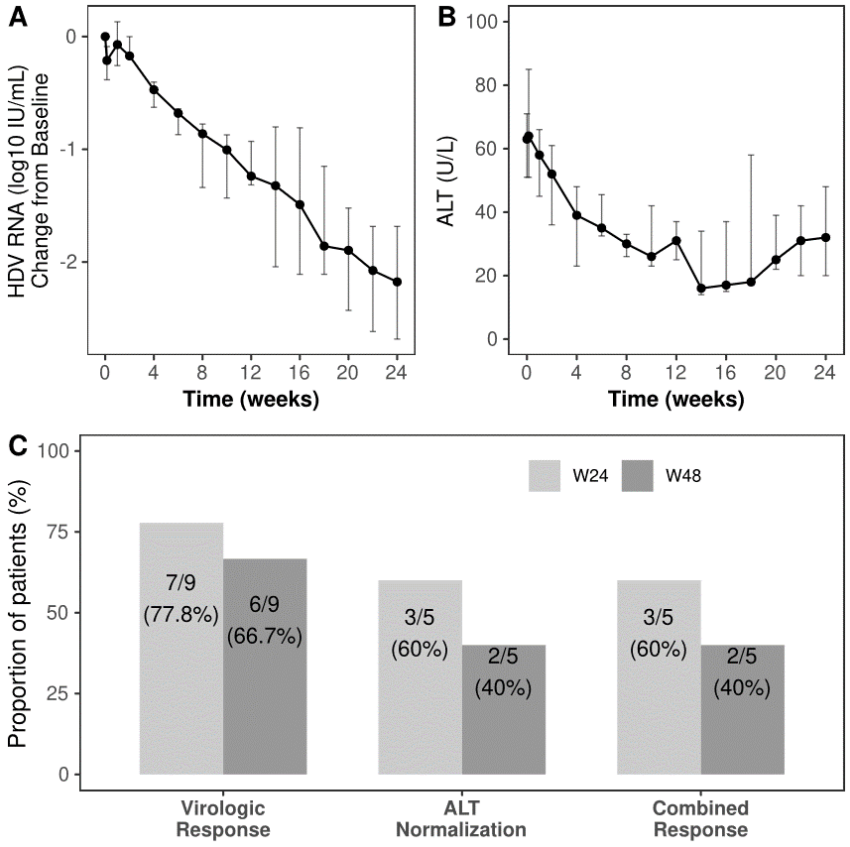
RESULTS

Virological response and baseline ALT

Variable, median (range)	N=9
HDV RNA at baseline, log_{10} IU/mL	3.48 (1.58–5.40)
ALT at baseline, U/L	36.0 (21.0–86.0)
HDV RNA change from baseline at week 24, log_{10} IU/mL	-2.18 (-3.88–0.35)
HDV RNA change from baseline at week 48, log_{10} IU/mL	-1.98 (-3.64–0.72)

- One patient (11.1%) suffered grade 1 abdominal discomfort and grade 2 asthenia
  - No grade ≥3 AEs or serious AEs occurred
  - No participants discontinued treatment due to AEs

Efficacy outcomes*



- All 4 participants with normal ALT levels at baseline continued to have normal ALT levels while receiving treatment with HH-003

CONCLUSION

- Treatment with HH-003 led to a significant decrease in HDV RNA level and ALT normalization, with an acceptable safety profile in participants with co-infection of HBV and HDV
- HH-003 may provide a new treatment option for patients with HBV and HDV co-infection; a large-scale study will be conducted to confirm the antiviral effect of HH-003

*(A) Reduction in serum HDV RNA during the HH-003 treatment period, median and IQR. (B) Change in serum ALT in 5 participants with abnormal ALT at baseline, median and IQR. (C) Proportions of patients achieving virological, biochemical, and combined response at weeks 24 and 48.

Niu J, et al. EASL 2023; LBP-24

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Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis delta virus☆

European Association for the Study of the Liver*

Screening	Screening for anti-HDV antibodies should be performed with a validated assay at least once **in all HBsAg+ individuals**
	HDV RNA should be tested **in all anti-HDV positive individuals** using a standardized and sensitive reverse transcription PCR assay to diagnose active HDV infection
Treatment	**All patients with CHD should be considered for antiviral treatment**
	Finite or prolonged treatments are the two approaches used in CHD aimed to cure or control the infection and disease
	All patients with CHD and compensated liver disease should be considered for treatment with BLV • The optimal dose and duration of treatment have not yet been defined
	All patients with CHD and compensated liver disease, irrespective of cirrhosis, should be considered for treatment with PegIFNα
	The combination of PegIFNα and BLV may be considered in patients without PegIFNα intolerance or contraindications
Monitoring	Patients with CHD should be monitored during and after treatment using virological markers, biochemical markers, liver imaging, histology, and for clinical events

CHD, chronic hepatitis delta; PegIFNα, pegylated interferon alpha.
EASL, J Hepatol. 2023; Article in Press.

J Hepatol 2023

Open issues

- What treatment for whom?
- Duration of treatment
- End-point
- Long-term follow-up

Liver disease	Controindication to Peg-IFN	Standard therapy
Chronic hepatitis or compensated cirrhosis without oesophageal varices	no	Peg-IFN+Bulevirtide 2mg for 48 weeks
	yes	Bulevertide 2mg
Compensated cirrhosis with oesophageal varices	Yes	Bulevertide 2mg
Decompensated cirrhosis	yes	unknown

Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on hepatitis delta virus☆

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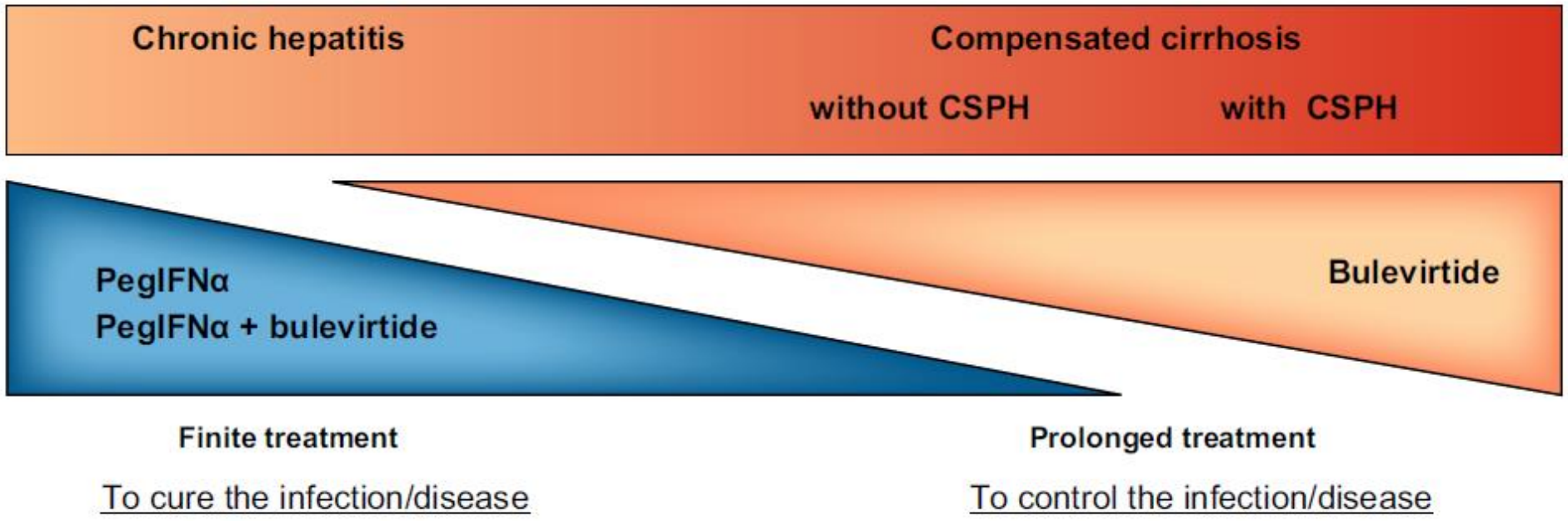

Additional factors influencing the treatment schedule

- Phase of HBV infection (HBeAg/anti-HBe status; HBV DNA and HBsAg levels)
- IFNα contraindication, tolerability
- Patient's will and compliance to treatment

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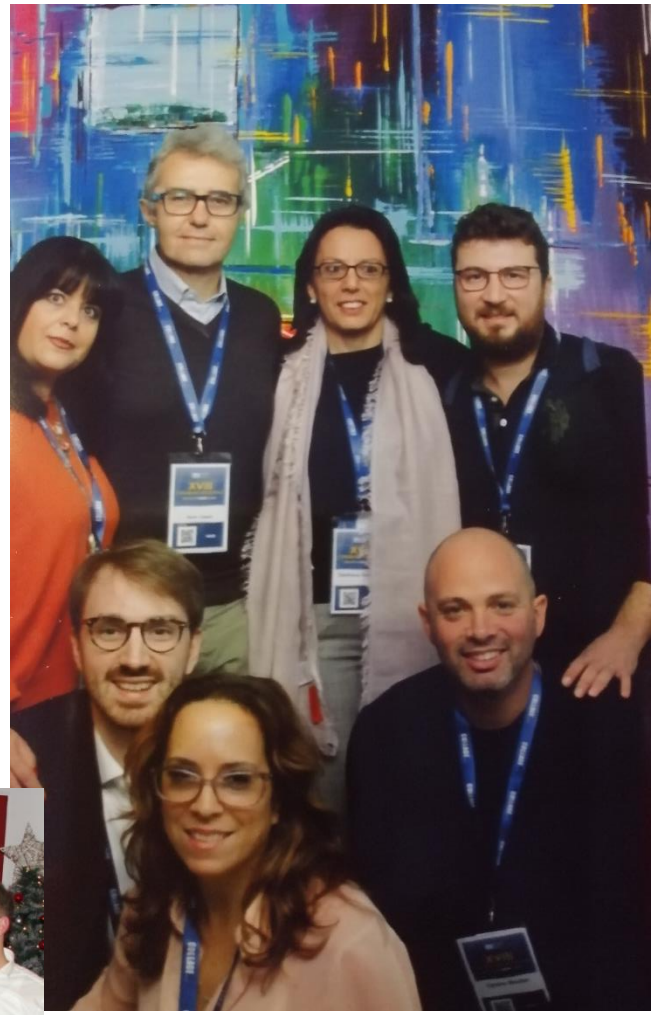
Grazie per l'attenzione



NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

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