DeltaCure 2024
State of the Art Lecture:

MY JOURNEY WITH HDV

CIHAN YURDAYDIN, MD

Department of Gastroenterology & Hepatology
Koç University Medical School, Istanbul, TR

YESTERDAY

TODAY

TOMORROW

Before yesterday-1990s: emotional times

- I enjoyed being a member of the so called “supradiaphragmatic hepatologists (SDHs)” and as a good SDH we ignored (disliked) viral hepatitis
- Hepatic encephalopathy- GABA hypothesis or the GABA/benzodiazepine hypothesis
  - Flumazenil was by far the best drug for HE in randomized controlled clinical trials

Lack of evidence ≠ lack of efficacy

Pruritis of cholestasis was of central (opioid) origin

Fatigue of cholestasis was of central (serotoninergic) origin
I was almost a central serotonin expert

But… viral hepatitis was on the rise

and I was ‘smart’ enough to find the neglected virus: HDV

HDV-Yesterday 1

Identification of a Prenylation Site in Delta Virus Large Antigen

Jeffrey S. Glenn,* John A. Watson, Christopher M. Havel, Judith M. White

During replication, hepatitis delta virus (HDV) switches from production of small to large delta antigen. Both antigen isoforms have an HDV genome binding domain and are packaged into hepatitis B virus (HBV)–derived envelopes but differ at their carboxyl termini. The large antigen was shown to contain a terminal CXXX box and undergo prenylation. The large, but not the small, antigen formed secreted particles when expressed singly with HBV surface antigen. Mutation of Cys^{211} in the CXXX box of the large antigen abolished both prenylation and particle formation, suggesting that this site is important for virion morphogenesis.

HDV-Yesterday 2

Yurdaydin et al. J Hepatol 2008

ADF vs Peg IFN+ADF vs Peg IFN

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*

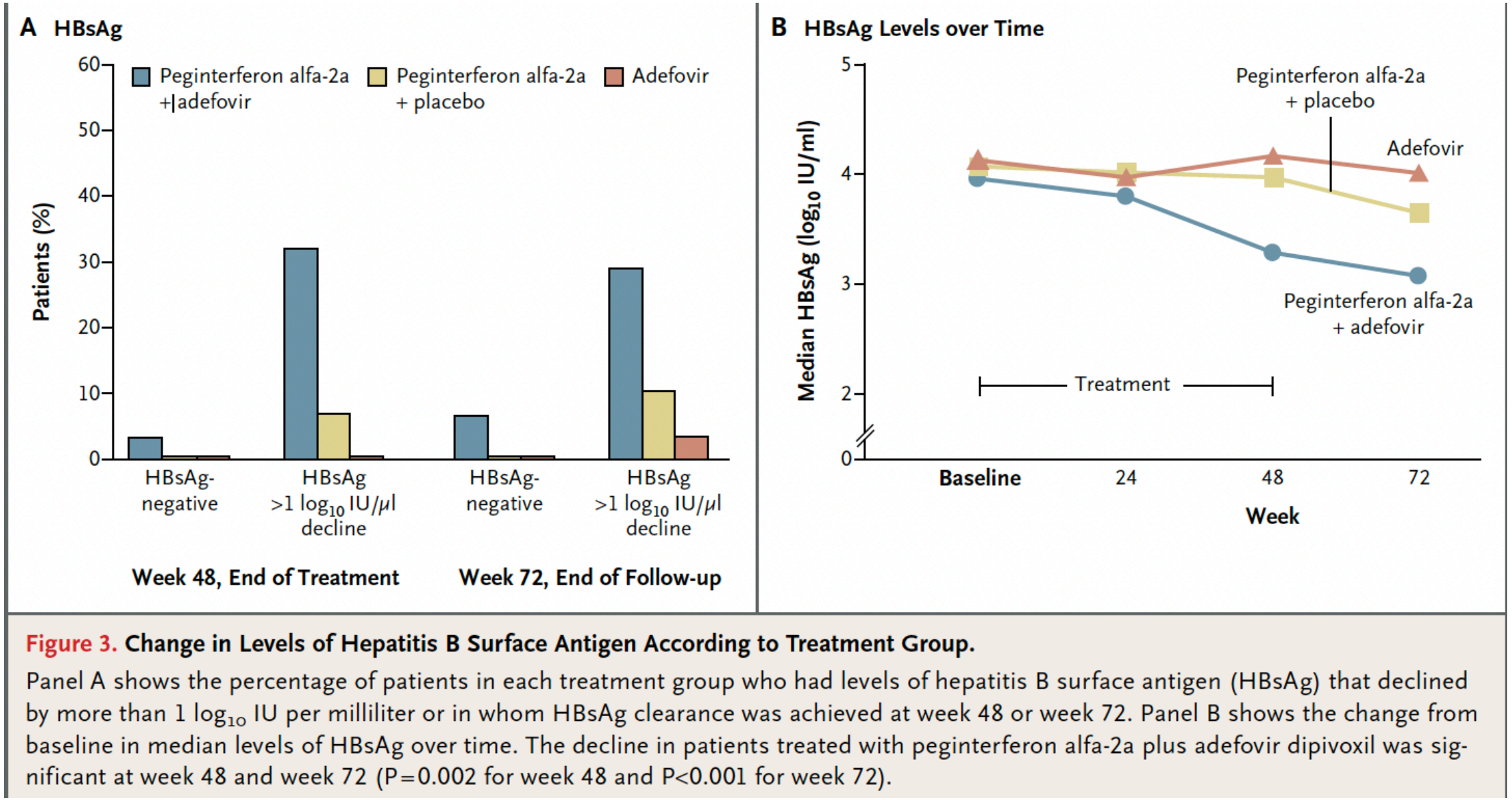


Figure 3. Change in Levels of Hepatitis B Surface Antigen According to Treatment Group.

Panel A shows the percentage of patients in each treatment group who had levels of hepatitis B surface antigen (HBsAg) that declined by more than 1 $\log_{10}$ IU per milliliter or in whom HBsAg clearance was achieved at week 48 or week 72. Panel B shows the change from baseline in median levels of HBsAg over time. The decline in patients treated with peginterferon alfa-2a plus adefovir dipivoxil was significant at week 48 and week 72 ($P=0.002$ for week 48 and $P<0.001$ for week 72).

Wedemeyer, Yurdaydin et al. NEJM

PegIFN vs PegIFN + TDF for 2 years

- Germany + Turkey + Greece + Romania + Brasil
- Germany + Turkey + Greece + Romania - Brasil
- Reason: in the meantime, Peg IFN had been reimbursed by the state insurance and pts started to use PegIFN in the Amazon region.

International Journal of Infectious Diseases 46 (2016) 82–88

Contents lists available at ScienceDirect

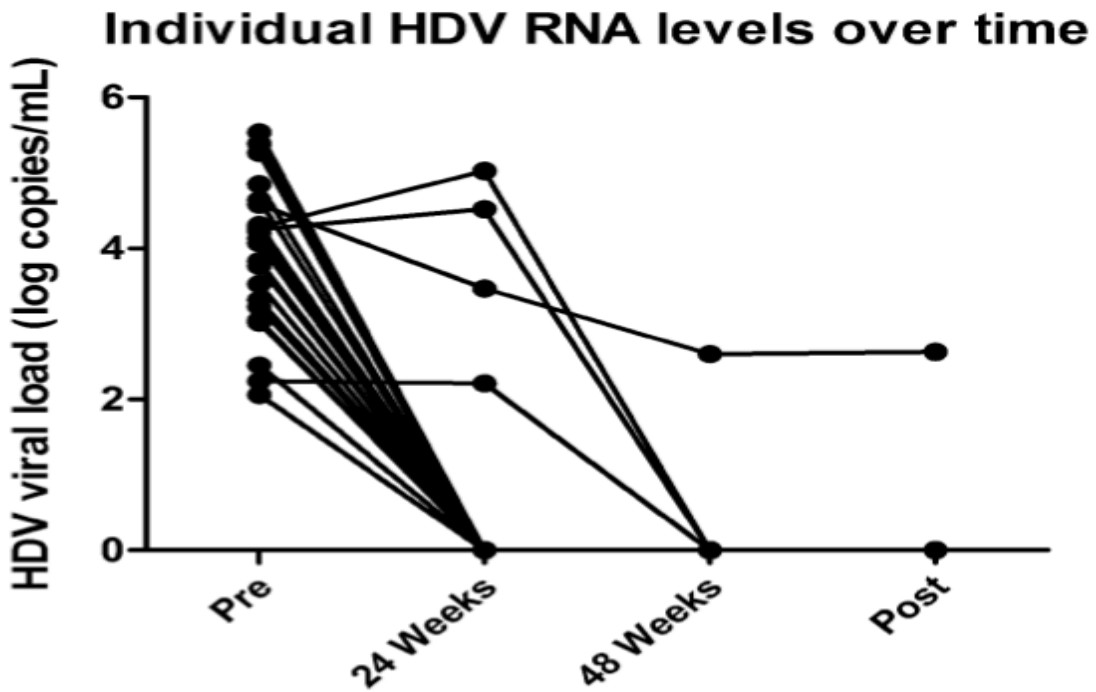
International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Treatment of hepatitis delta virus genotype 3 infection with peg-interferon and entecavir

Lourdes Maria Pinheiro Borzacov [a], Larissa Deadame de Figueiredo Nicolete [a], Luan Felipo Botelho Souza, Alcione Oliveira dos Santos, Deusilene Souza Vieira, Juan Miguel Villalobos Salcedo *

Research Center for Tropical Medicine of Rondônia – CEPEM/SESAU, and Federal University of Rondônia – UNIR, Rua da Beira, 7671 -BR364, Km 3.5 Bairro Lagoa, Porto Velho, Rondônia, Brazil



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, Selim Gürel, Stefan Zeuzem, Andreas Erhardt, Stefan Lüth, Georg, Ramazan Idilman, Kristina Weber, Judith Stift, Markus Cornberg,*

HEPATOLOGY, VOL. 0, NO. 0, 2021

Clinical

Association of Pegylated I

Onur Keskin,* Heine[illegible] Lisa Sandmann,[1] Cihan Yurdaydin,[2,3] Katja Deterding,[1] Birgit Bremer,[1] Michael P. Manns,[1,6] Markus Cornberg,[1,4-6] Heiner Wedemeyer,[7] [illegible]achou,[§] Xheni Deda,* George N. Dalekos,[§] HIDIT-II Study Group [illegible]ilcen Pehlivan,[‖] Stefan Zeuzem,[¶] Kendal Yalçın,[#] Selim Gürel,[**] Fehmi [illegible]amazan Idilman,* Hakan Bozkaya,* Michael Manns,[‡] and Cihan Yurdaydin*,[§§]

ORIGINAL ARTICLE

JOURNAL OF VIRAL HEPATITIS JVH WILEY

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]

CrossMark

HDV-Yesterday 1

Identification of a Prenylation Site in Delta Virus Large Antigen

Jeffrey S. Glenn,* John A. Watson, Christopher M. Havel, Judith M. White

During replication, hepatitis delta virus (HDV) switches from production of small to large delta antigen. Both antigen isoforms have an HDV genome binding domain and are packaged into hepatitis B virus (HBV)–derived envelopes but differ at their carboxyl termini. The large antigen was shown to contain a terminal CXXX box and undergo prenylation. The large, but not the small, antigen formed secreted particles when expressed singly with HBV surface antigen. Mutation of Cys^{211} in the CXXX box of the large antigen abolished both prenylation and particle formation, suggesting that this site is important for virion morphogenesis.

Received: 6 October 2020 | Revised: 4 October 2021 | Accepted: 21 November 2021

DOI: 10.1002/hep.32259

ORIGINAL ARTICLE

A phase 2 dose-finding study of lonafarnib and ritonavir with or without interferon alpha for chronic delta hepatitis

Cihan Yurdaydin[1,2,3] | Onur Keskin[1] | Esra Yurdcu[2] | Aysun Çalişkan[1] | Soner Önem[1] | Fatih Karakaya[1] | Çağdaş Kalkan[1] | Ersin Karatayli[2,4] | Senem Karatayli[2,4] | Ingrid Choong[5] | David Apelian[5] | Christopher Koh[6] | Theo Heller[6] | Ramazan Idilman[1] | A. Mithat Bozdayi[2] | Jeffrey S. Glenn[7,8]

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YESTERDAY

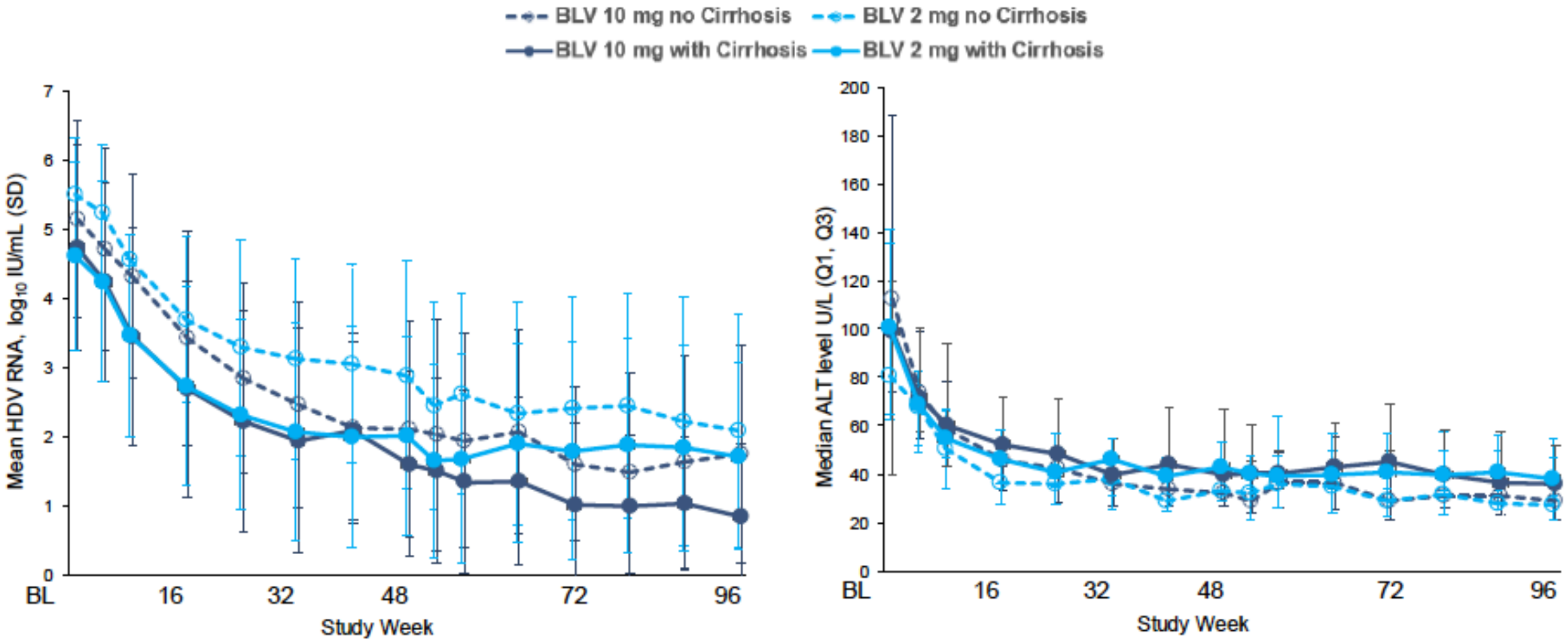
TODAY

TOMORROW

Bulevirtide becomes the first drug receiving first conditional approval for HDV treatment in July 2020

Last year in May 2023 this was followed by full marketing authorisation by the European Medical Agency (EMA)

HDV RNA and ALT Levels Over 96 Weeks based on Cirrhosis Status



- Declines in both HDV RNA and ALT over time were consistent across subgroups regardless of cirrhosis status

Real-world experience from off-label bulevirtide treatment for chronic hepatitis D in patients with decompensated liver disease

Christopher Dietz-Fricke[1#], Elisabetta Degasperi[2#], Mathias Jachs[3#], Benjamin Maasoumy[1], Florian P. Reiter[4], Andreas Geier[4], Julia M. Grottenthaler[5], Christoph P. Berg[5], Kathrin Sprinzl[6], Stefan Zeuzem[6], Juliana Gödiker[7], Bernhard Schlevogt[7,8], Toni Herta[9], Johannes Wiegand[9], Roberta Soffredini[2], Heiner Wedemeyer[1], Katja Deterding[1#], Thomas Reiberger[3#], Pietro Lampertico[2,10#]

# contributed equally

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Table 1.
Baseline patient characteristics of all 21 patients included in the anlaysis; [1] Upper GI endoscopy was available in n=17 patients

Patient characteristics	
Patients (n, %)	21 (100%)
Age (mean)	50.9 ± 9.6
Gender	male n=11, female n=10
Child-Pugh	
- Stage A	3 (14%)
- Stage B	17 (81%)
- Stage C	1 (5%)
MELD (median, range)	12 (7-18)
Ascites (n, %)	12 (57%)
Esophageal varices[1] (n, %)	15 (71%)
History of variceal hemorrhage (n, %)	2 (10%)
Encephalopathy (n, %)	1 (5%)
Hepatocellular Carcinoma (n, %)	1 (5%)
Albumin g/L (median, range)	31 (28 - 51)
INR (median, range)	1.3 (1.0 – 1.7)
Bilirubin µmol/l (median, range)	30.8 (8.0 – 82.0)
Platelet count / µl (median, range)	67,000 (17,000 – 180,000)
ALT IU/L (median, range)	72 (31 - 307)
History of interferon treatment	7 (33%)

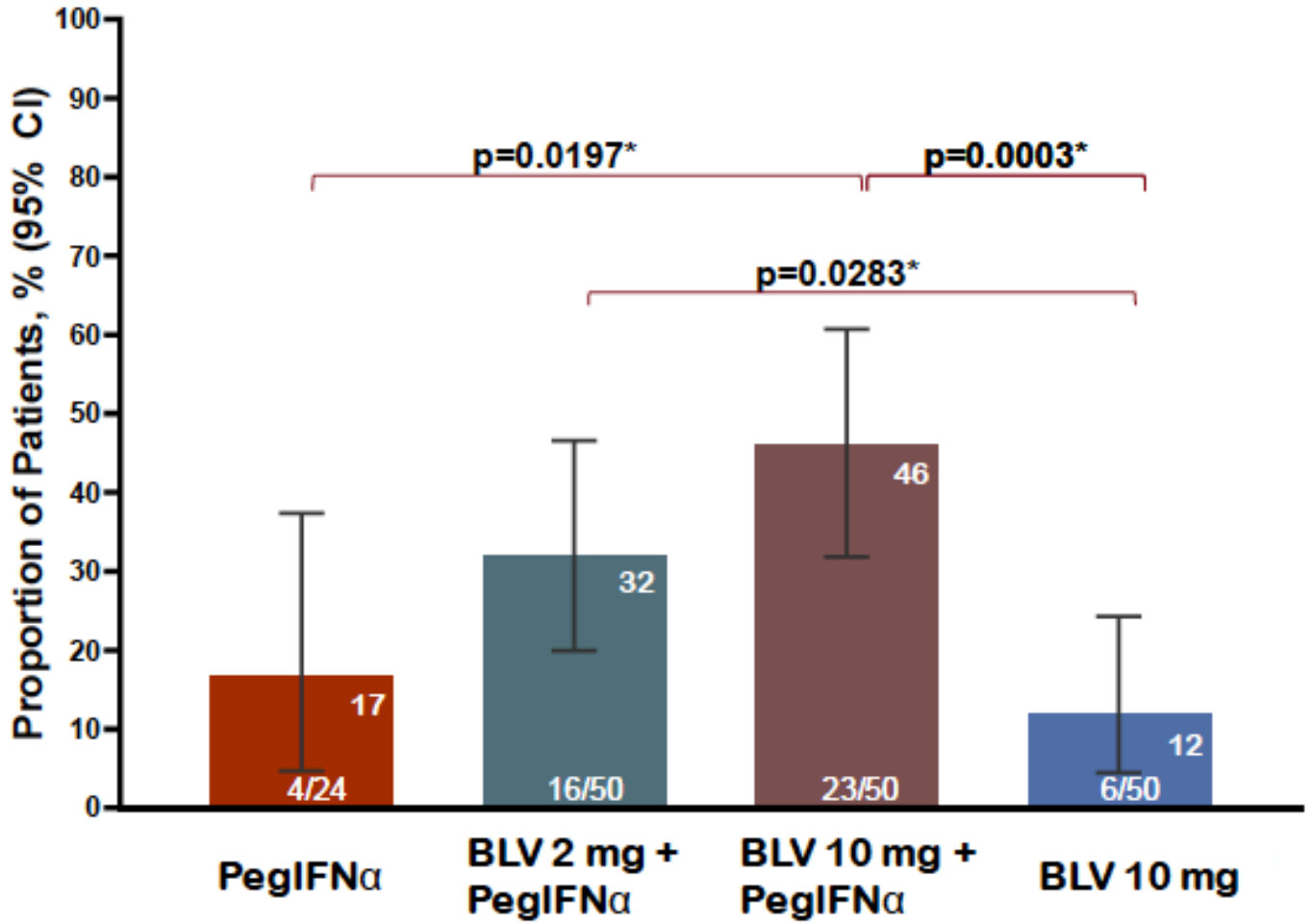
Efficacy

- Viral response in 67%, normal ALT in 86%, combined response in 38%
- Median MELD and Child-Pugh-Scores were stable
- On-treatment recompensation from Child-Pugh B to A in 41% (7/17)
- Ascites improvement in 6 patients

Safety

- De-novo ascites in 3 patients, worsening of ascites in 2 patients
- Liver transplantation in three patients
- Death due to acute-on-chronic liver failure in 1 case

HDV RNA Undetectable at Week 24 after EOT

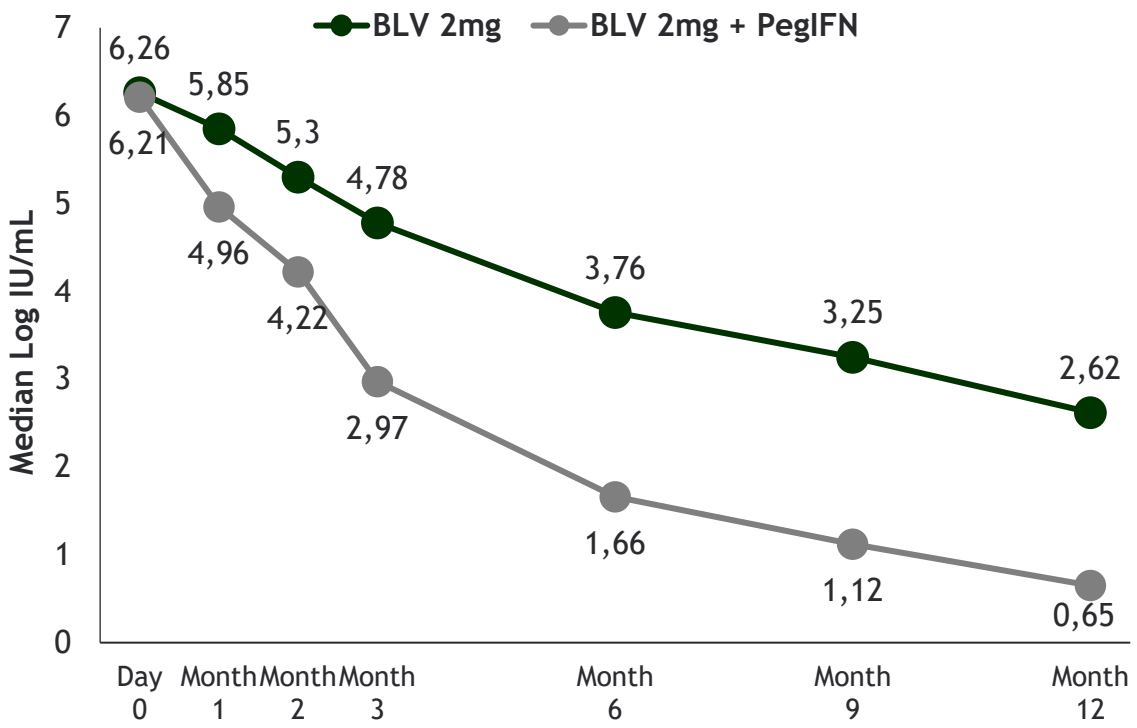


- Significantly higher rate with BLV 10 mg + PegIFNα vs. BLV 10 mg or PegIFNα monotherapy
- Significantly higher rate with BLV 2 mg + PegIFNα vs. BLV 10 mg monotherapy

* Only significant comparison by Fisher's Exact Test, p-value <0.05 are shown on graph; Full Analysis Set, Missing=Failure. **BLV**, bulevirtide; **CI**, confidence interval; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha.

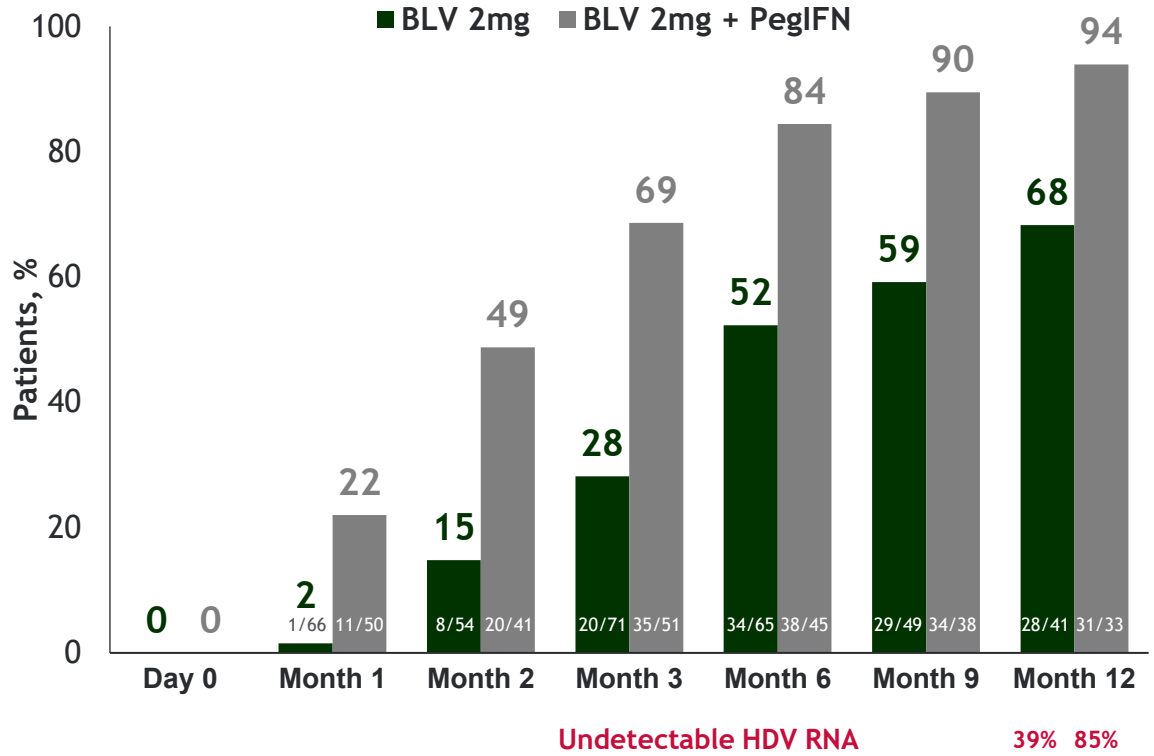
Virologic Response Over 12 Months

Changes in HDV RNA Levels Over Time (PP)



HDV RNA Response (PP)

Undetectable HDV RNA or ≥2 log IU/mL decline



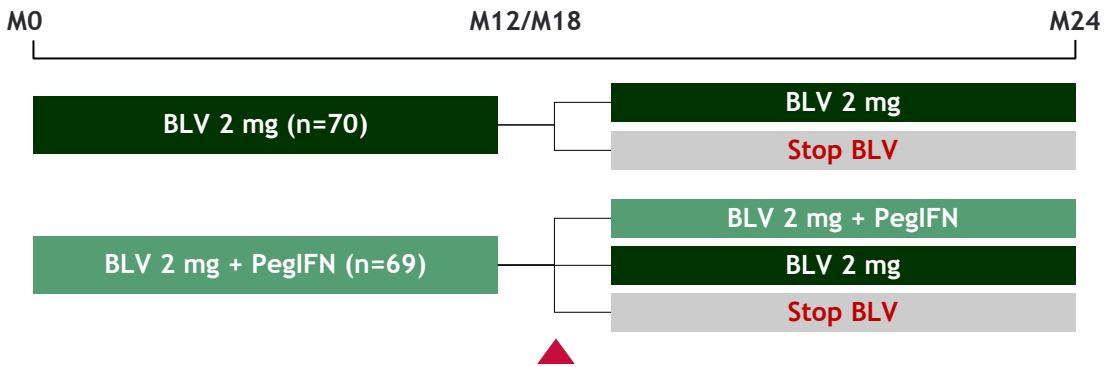
BLV 2mg monotherapy or in combination with PegIFN led to considerable HDV RNA declines

PP, Per protocol analysis. Study not powered to compare the two treatment regimens
de Ledinghen V, et al. AASLD 2021. Oral 21

‡

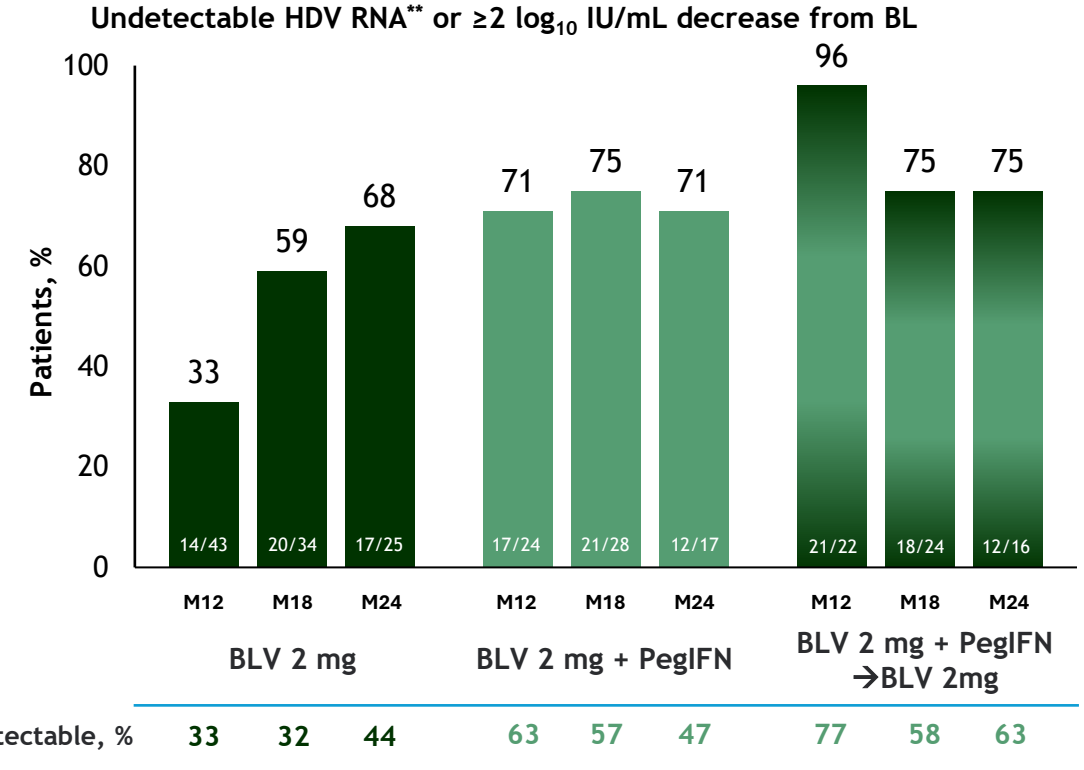
Two-Year Early Access Program RWD from France

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



Undetectable, %	33	32	44	63	57	47	77	58	63

Virologic response increased with BLV 2 mg monotherapy over time, leading to similar response rates at 24 months compared to combination regimens

*Study not powered to compare all treatment regimens; **Missing data; †17 patients had ALT <40 IU/L at baseline and were included in the analysis. ALT, alanine aminotransferase; BLV, bulevirtide; NA, nucleos(t)ide analogue; PegIFN, pegylated interferon.

de Lédinghen V, et al. AASLD 2022. Oral #28

Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta: Primary Endpoint Results from a Phase 2b Open-Label, Randomized, Multicenter Study MYR204

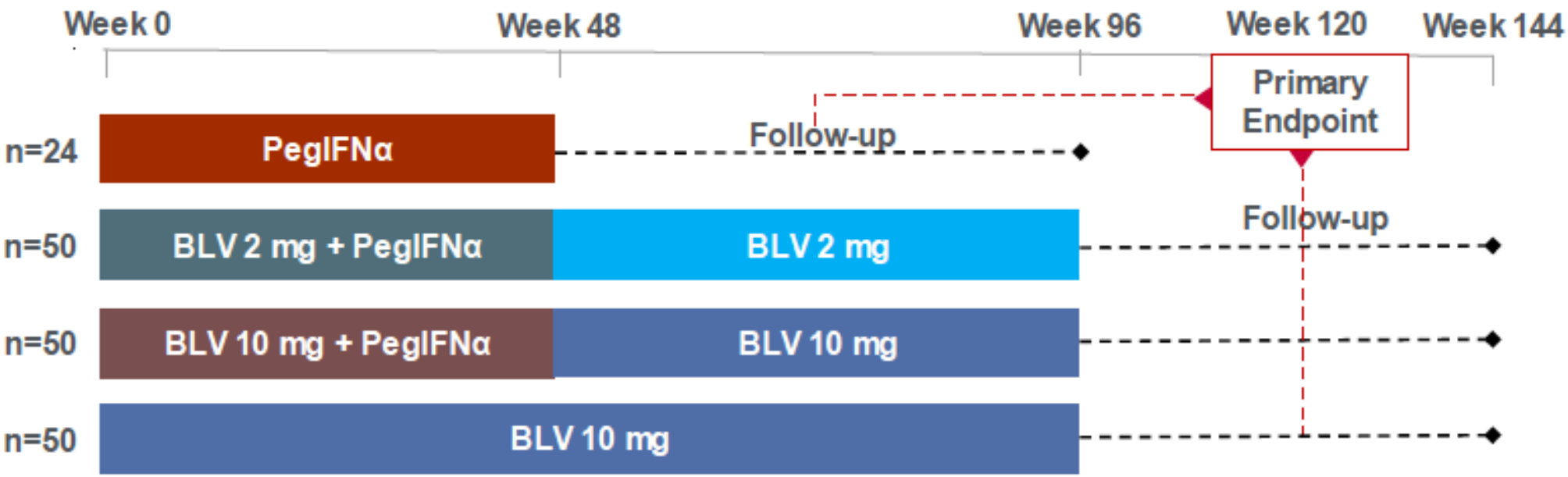
Tarik Asselah[1], Pietro Lampertico[2,3], Heiner Wedemeyer[4], Adrian Streinu-Cercel[7], Victor Pantea[8], Stefan Lazar[9], Gheorghe Placinta[8], George Sebastian Gherlan[15,16], Pavel Bogomolov[10], Tatyana Stepanova[5], Viacheslav Morozov[6], Vladimir Chulanov[11], Vladimir Syutkin[12], Olga Sagalova[13], Vladimir Gorodin[14], Dmitry Manuilov[17], Renee-Claude Mercier[17], Lei Ye[17], John F. Flaherty[17], Anu Osinusi[17], Audrey H. Lau[17], Ben L. Da[17], Marc Bourliere[18], Vlad Ratziu[19], Stanilas Pol[20], Marie-Noëlle Hilleret[21], Fabien Zoulim[22]

[1]Hôpital Beaujon APHP, Université de Paris, INSERM, Clichy, France; [2]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; [3]CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [4]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany; [5]LLC Clinic of Modern Medicine, Moscow, Russian Federation; [6]LLC Medical Company "Hepatolog", Samara, Russian Federation; [7]Matei Bals National Institute of Infectious Diseases, Bucharest, Romania; [8]Infectious Clinical Hospital "T. Ciorba", Chisinau, Moldova; [9]Dr. Victor Babes Foundation, Infectious and Tropical Diseases Hospital, Bucharest, Romania; [10]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation; [11]Sechenov University, Moscow. Russian Federation; [12]Institute of Emergency Medicine n.a. NV Sklifosovsky, Moscow, Russian Federation; [13]Southern Ural State Medical University, Chelyabinsk, Russian Federation; [14]"Specialized Clinical Infectious Diseases Hospital", Krasnodar, Russian Federation; [15]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [16]Dr. Victor Babes Foundation, Bucharest, Romania; [17]Gilead Sciences, Foster City, United States; [18]Hôpital Saint Joseph, Marseille, France; [19]CH Pitié-Salpétrière, Paris, France; [20]Hôpital Cochin, Paris, France; [21]Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; [22]Hospital Croix Rousee, Lyon, France.

AASLD - The Liver Meeting, 10–14 November 2023

MYR204, a Phase 2b study addresses a major treatment gap for HDV, a finite treatment regimen that results in sustained off-treatment viral response

Study Design

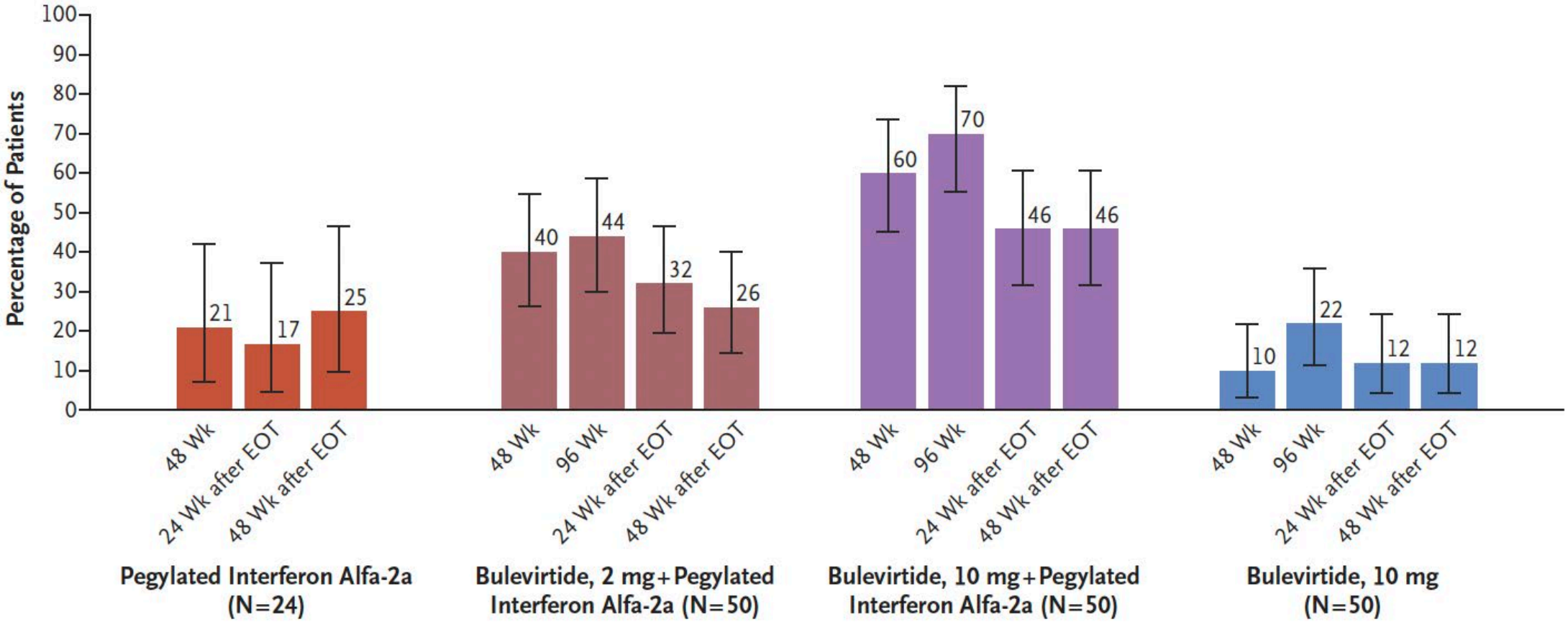


- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key Inclusion Criteria

- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh (CTP) ≤6
- ALT >1× - <10× ULN; Platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrollment

Undetectable HDVRNA on and off-treatment



Asselah T et al, NEJM 2024

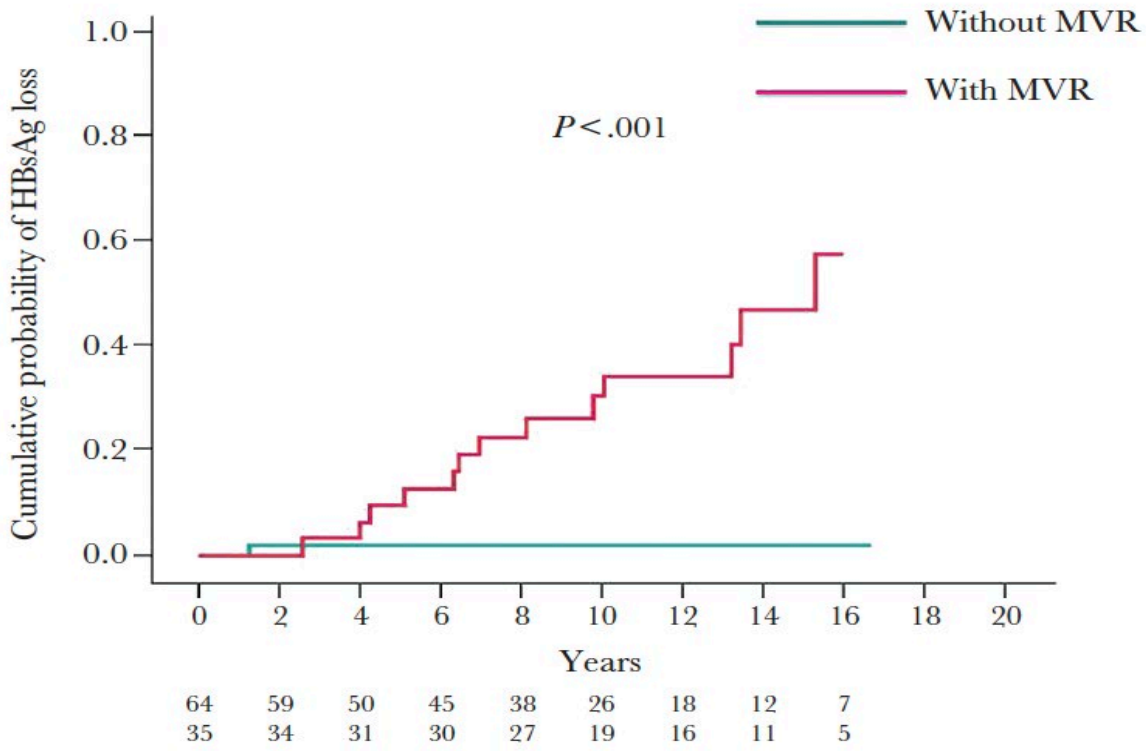
HBsAg Endpoints At Week 24 after EOT

		PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
HBsAg	HBsAg response: ≥1 log_{10} decrease IU/mL, n (%)	4 (17)	8 (16)	8 (16)	1 (2)
	HBsAg loss, n (%)	0	4 (8)	2 (4)	0
	with seroconversion, n (%)	0	3 (6)	2 (4)	0
	Mean change from BL in HBsAg, log_{10} IU/mL (SD)	-0.56 (0.813)	-1.08 (1.654)	-0.69 (1.039)	-0.12 (0.640)

- HBsAg loss was seen with BLV 2 mg or 10 mg in combination with PegIFNα

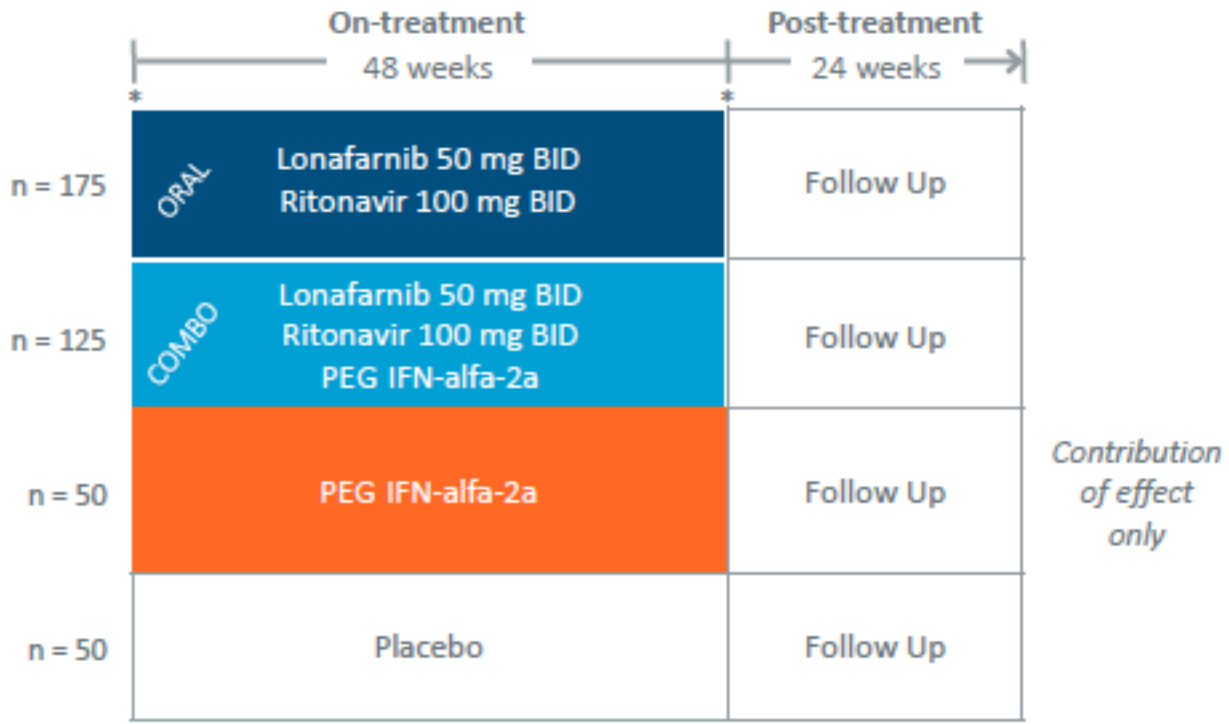
BL, baseline; BLV, bulevirtide; EOT, end of treatment; HBsAg, hepatitis B surface antigen; PegIFNα, pegylated interferon alpha; SD, standard deviation.

Interferon is not an optimal treatment for chronic hepatitis delta but needs 'fair treatment' by us. Keskin & Yurdaydin. Hepatology 2020



Yurdaydin et al, JID 2018

D-LIVR Phase 3 Global Study



Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

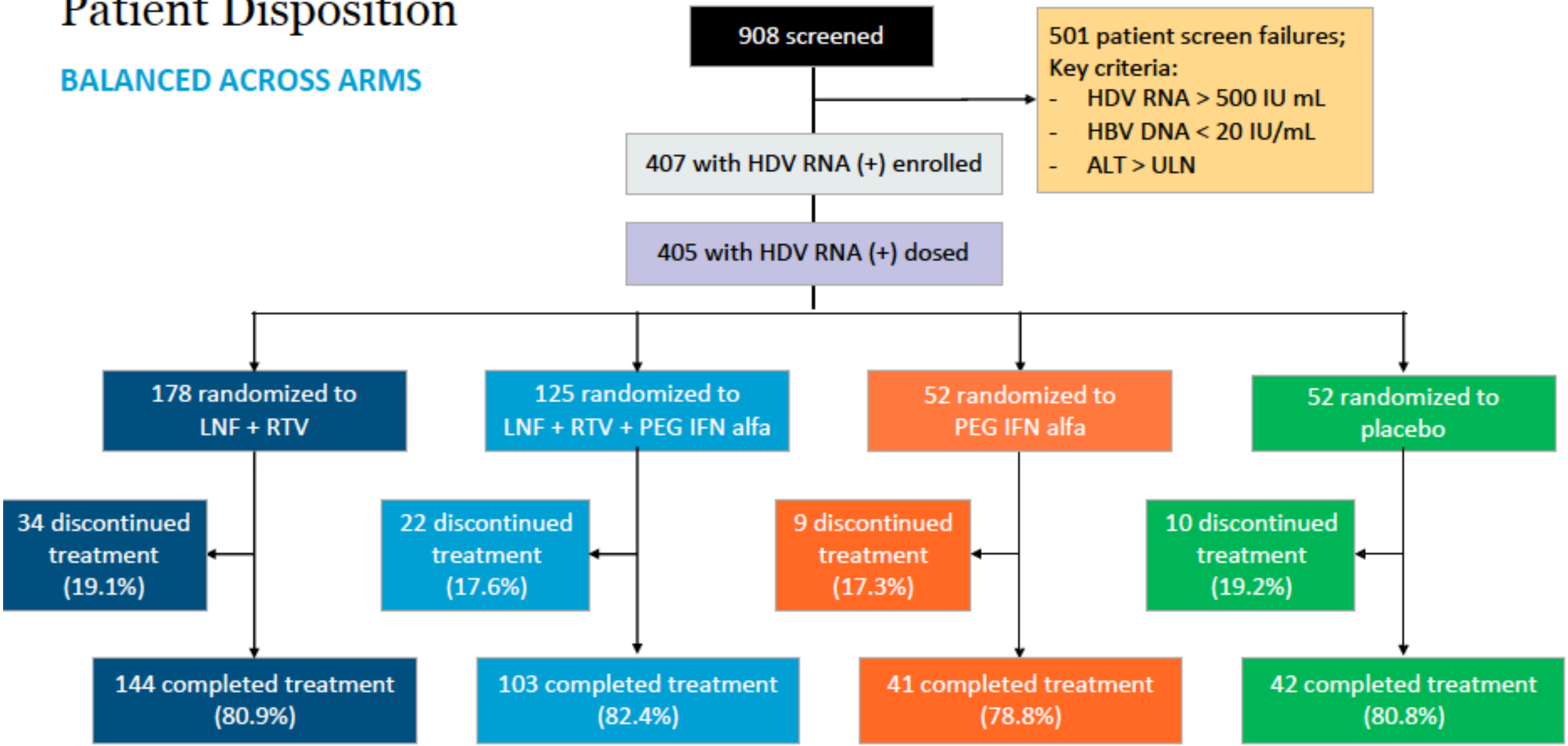
Secondary Endpoint at Week 48

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

* Liver biopsy
All patients will be maintained on background HBV nucleoside therapy.

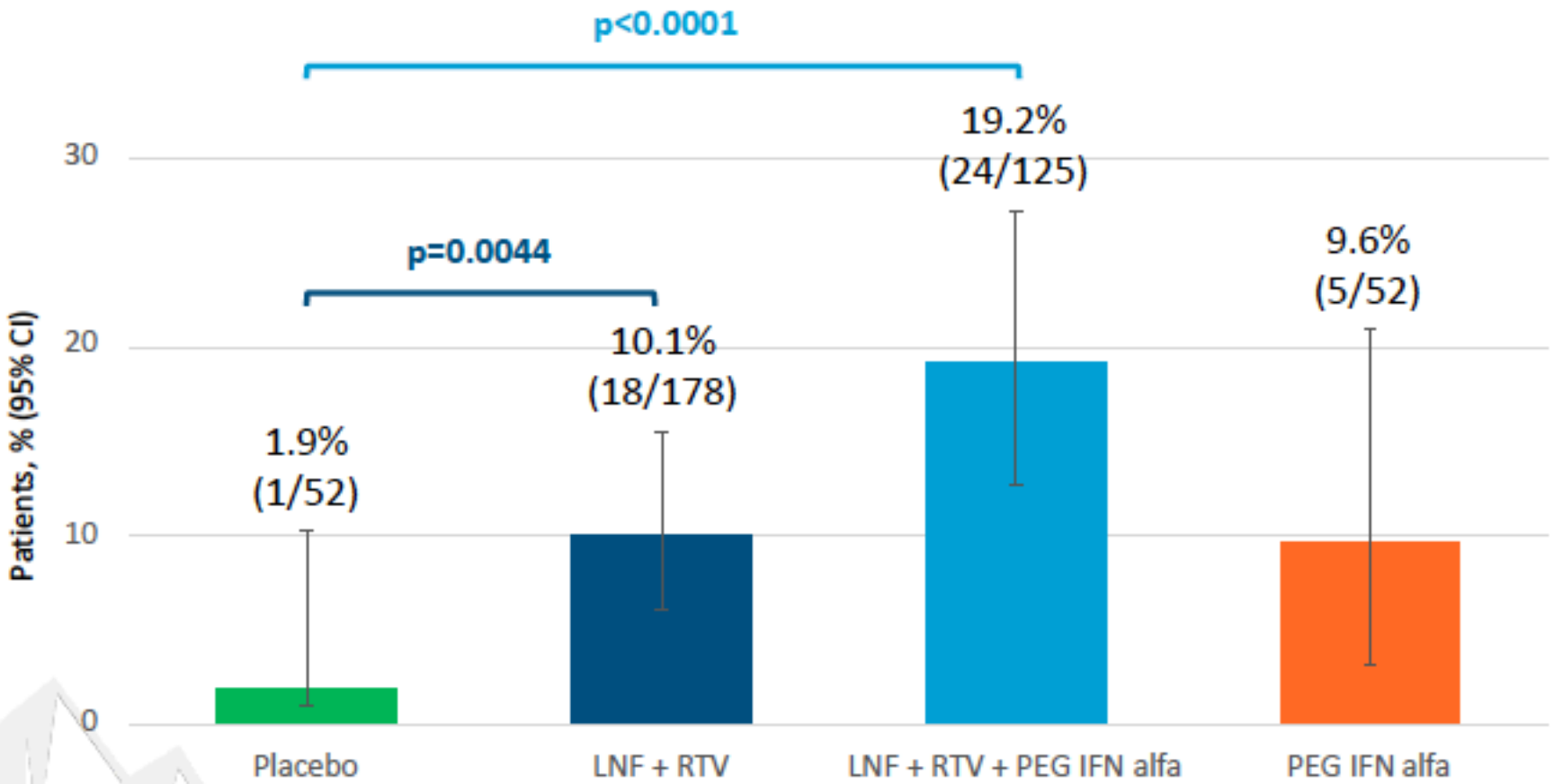
Patient Disposition

BALANCED ACROSS ARMS

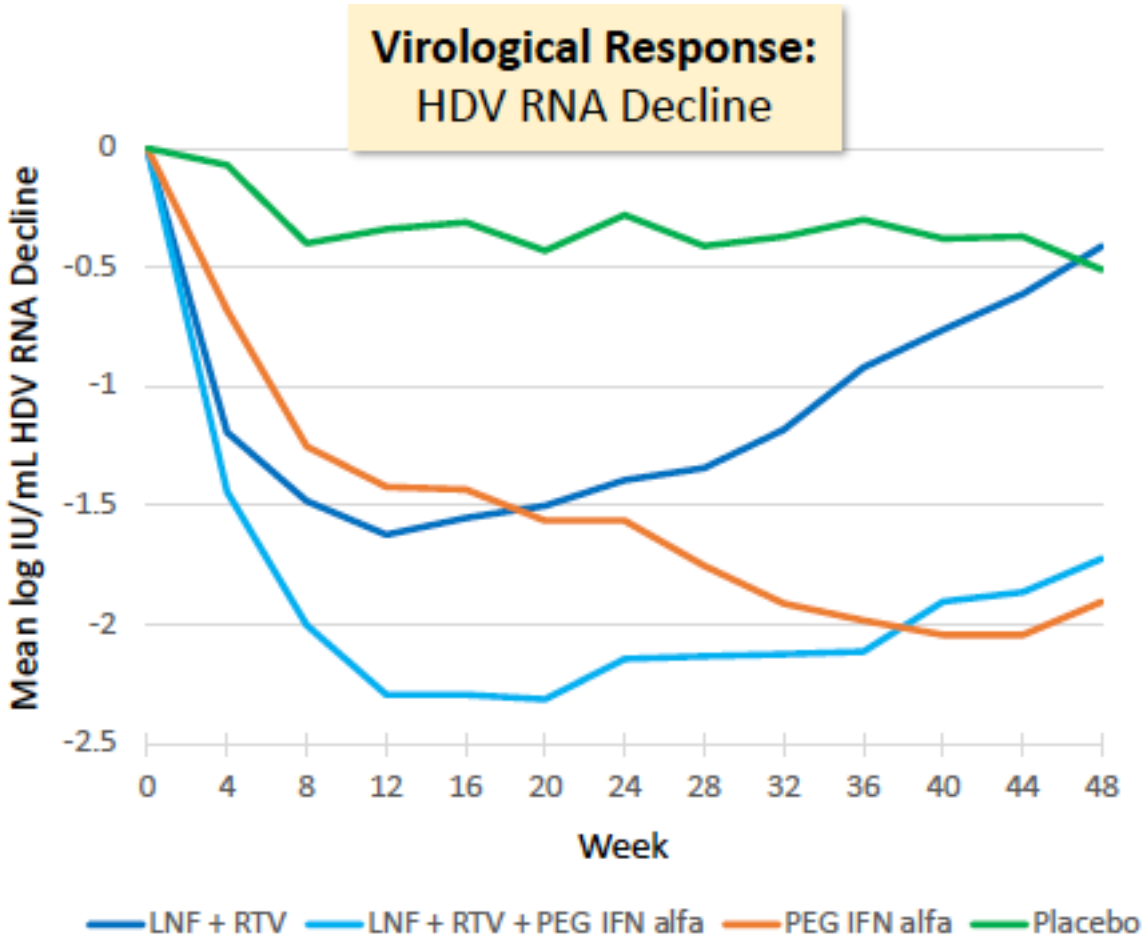


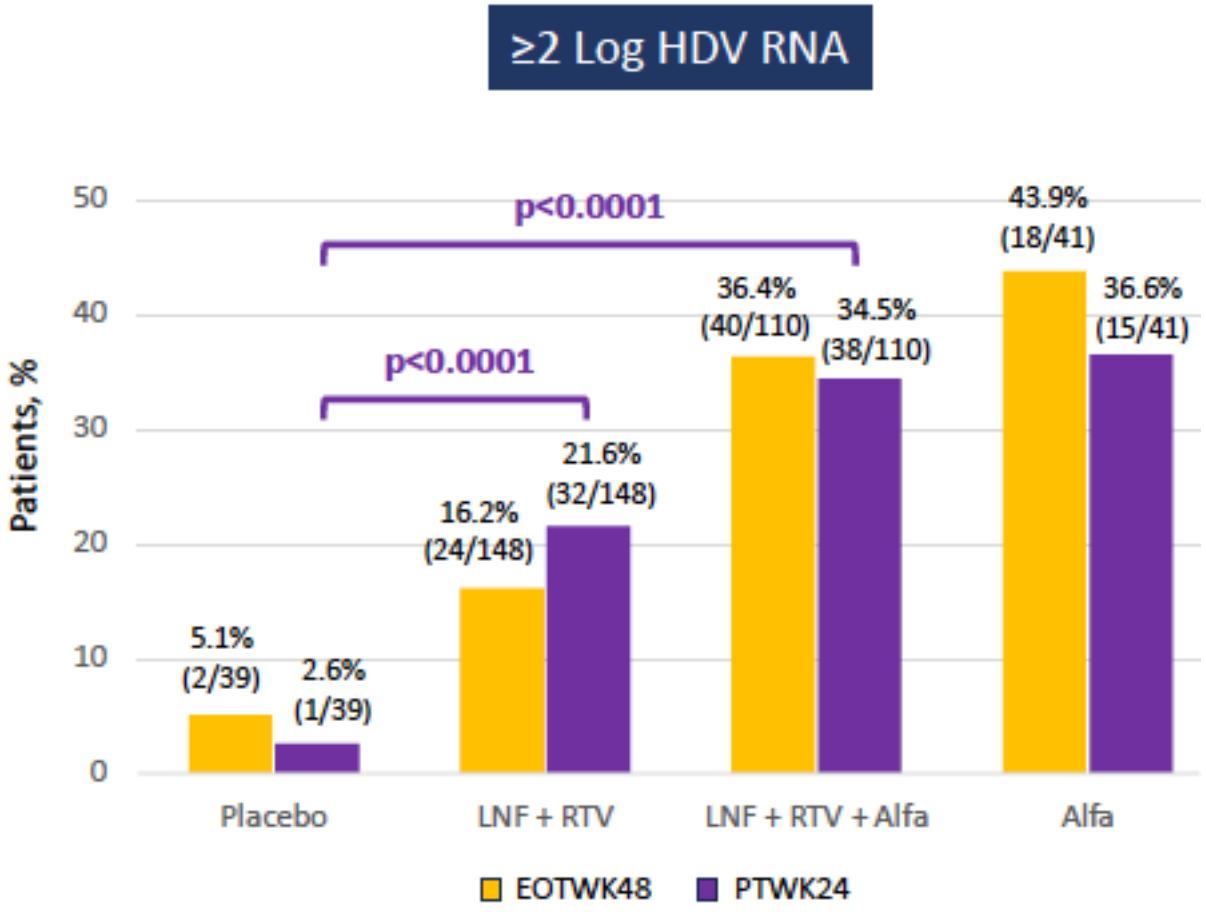
Primary Endpoint Achieved with Significance in BOTH Arms

% PATIENTS ACHIEVING COMPOSITE ≥2 LOG DECLINE IN HDV RNA + ALT NORMALIZATION AT WEEK 48



Virological Response





ORIGINAL ARTICLE

OPEN

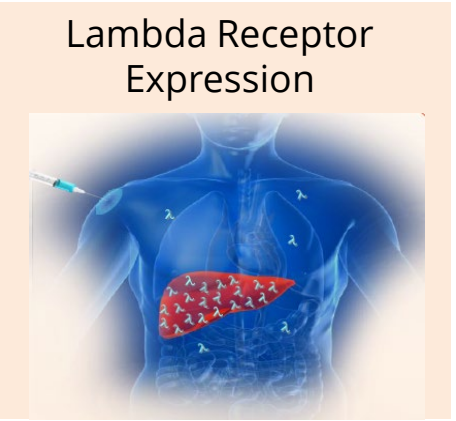
Treatment of chronic hepatitis D with peginterferon lambda—the phase 2 *LIMT-1* clinical trial

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] | Minaz Mawani[3] | Om Parkash[3] | Harel Dahari[6] | Ingrid Choong[8] | Jeffrey S. Glenn[9]

PEGYLATED INTERFERON LAMBDA

A Better Tolerated Interferon

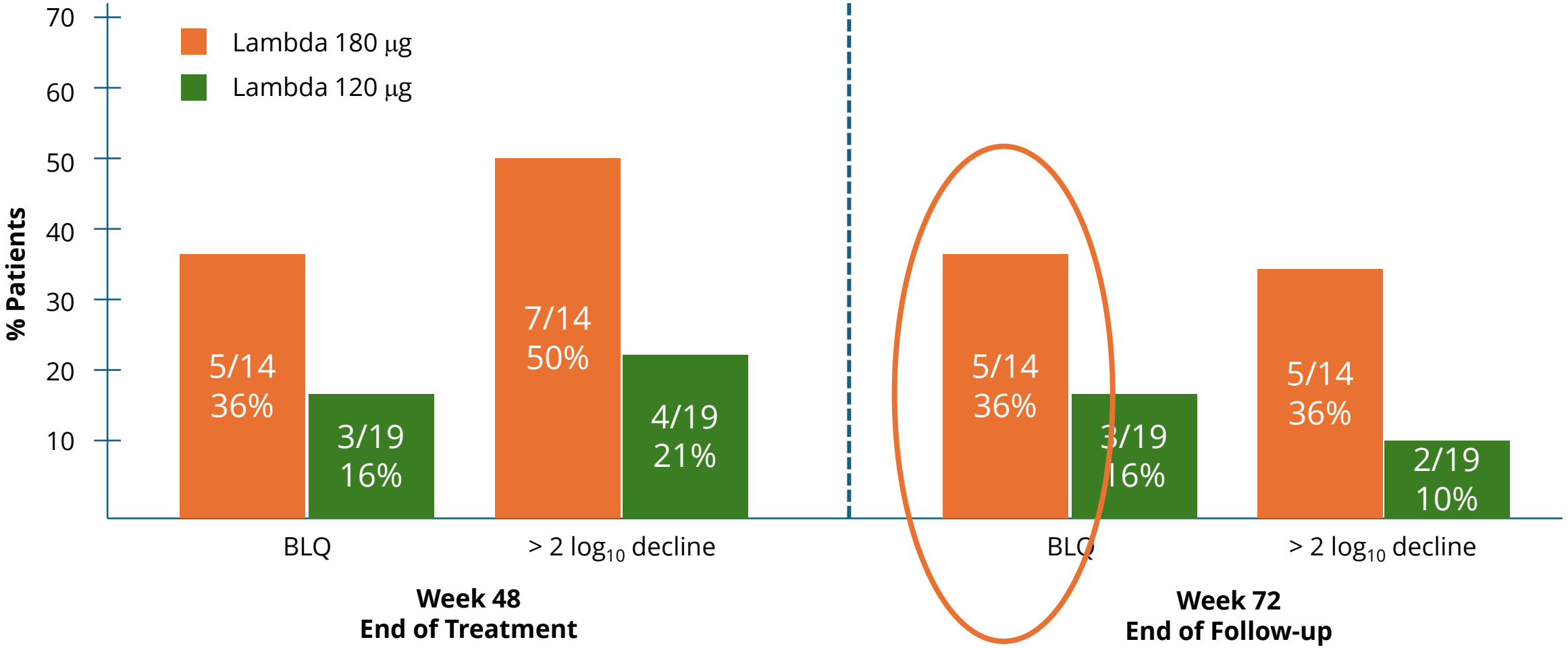
- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical trials (HCV / HBV)
- Comparable antiviral activity with less of the typical IFN alfa related side effects*



*Chan, HLY et al, J Hepatol 2016

DURABLE VIROLOGIC RESPONSE (DVR)

DVR = 36% BLQ at 24 Weeks Post-Treatment with Lambda 180 μg



Safety Profile

ADVERSE EVENTS: PREDOMINANTLY GRADE 1*

Classification	Adverse Event (AE)	Number of Patients Experiencing Grade of AE (n=33)			
		Grade 1	Grade 2	Grade 3	Grade 4
Constitutional	Fatigue	10	2	-	-
Flu-like	Pyrexia, chills, chest pain, flu-like	21	5	-	-
Neurological	Dizziness, headache	17	8	-	-
Musculoskeletal	Arthralgia, myalgia, back pain, musculoskeletal pain	18	9	-	-
Psychiatric	Depression, irritability, insomnia	1	-	-	-
Hematological	Neutrophil count depressed	-	-	-	1**
Lab Abnormalities	Bilirubin, ALT / AST / GGT increase	2	1	9	1**

- No thrombocytopenia events, no use of hematopoetic growth factors
- Elevated bilirubin and ALT levels normalized upon dose reduction or treatment discontinuation

* > 1300 weeks of treatment
** non-serious

Etzion et al, EASL **2019**

SSG Advises Eiger BioPharmaceuticals in Sale of Lonafarnib and Lambda Program Assets to Eiger InnoTherapeutics

September 13, 2024, 07:47 AM
Filed Under: Biopharmaceuticals
Related: Biopharmaceuticals, Eiger BioPharmaceuticals, Inc., SSG Capital Advisors

SSG Capital Advisors served as the investment banker to Eiger BioPharmaceuticals, Inc. in the sale of Lonafarnib and Lambda, and associated clinical assets to Eiger InnoTherapeutics, Inc. The sale was effectuated through a Chapter 11 Section 363 process in the U.S. Bankruptcy Court for the Northern District of Texas (Dallas Division). The transaction closed in September 2024.

YESTERDAY

TODAY

TOMORROW

HDV TREATMENT

HBV FUNCTIONAL CURE

IF NOT COULD BE PROBLEMATIC

THE CLINICIAN

An infectious disease specialist: “Viral hepatitis is a disease of the past”

HBV

- Effective vaccine campaign ➔ HBV much less in the young
- Effective & simple Dx

HCV

- Cure in almost 100% of pts with compensated liver disease

ID Specialist is not interested in a disease of the past

Gastroenterologist is busy doing other things

The danger is that physicians will not check for HDV

Dialog between White Hair physician and Non-White hair physician:

Physician with white hair (Old phenotype):
“So, will you be testing every HBsAg (+) patient for HDV and if positive also for HDVRNA?” Is this simple enough?
Physician without white hair (New phenotype):
“I don’t think so. This is still too complicated and don’t forget I’m not interested in HDV”
White Hair physician: !!??
White Hair physician: “Have you heard about Zager & Evans?”
Non-White hair physician: “No”
White Hair physician: “In the 60s they had a song called ‘In the year 2525’ where they said that ‘some machine doing that for you’ ” How about that?
Non-White hair physician: “Finally. You said something.”
White Hair physician explains the concept of reflex testing.

Happy End

CONCLUSION

WE ARE BETTER TODAY THAN YESTERDAY

WE NEED NOW NEW DRUGS AND NEW APPROACHES TO SERVE PTS BETTER

And there are good news also in this direction

SPECIAL THANKS TO

My co-workers in TR: Onur Keskin, Gökhan Kabaçam, A Mithat Bozdayı, Hakan Bozkaya, Ramazan Idilman, F Oğuz Önder

My former chief of Gastroenterology, Dr Ali Özden

MARIO RIZZETTO

My wife Hülya and my 2 children Özlem and Özgür