7ª Edición de Sesiones Clínicas Interhospitalarias de Hepatitis 2023

Hepatitis Delta

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A MODO DE GUIÓN

- INTRODUCCION
- EPIDEMIOLOGIA
- CLINICA Y EVOLUCION
- DIAGNOSTICO
- TRATAMIENTO
- EXPERIENCIA CON BULEVIRTIDE

GILEAD
Creating Possible

INTRODUCCION

INTRODUCCIÓN A LA HEPATITIS D

Historia del virus[1-4]

1977

Antígeno D

Identificado a mediados de la década de 1970 en Turín: una nueva reactividad inmunitaria en sujetos infectados por el VHB con enfermedad hepática grave[1]

1980

Partícula de 35-37 nm

Aislada de chimpancés HBsAg+ sobreinfectados con el suero de un paciente italiano positivo para el antígeno D[2]

1994

Virus de la hepatitis D

Clasificado como el único miembro del género Deltavirus (familia *Deltaviridae*)[3]

2020

Nueva clasificación

Junto con otros virus similares al VHD, como ***Kolmioviridae***[4]

HBsAg: antígeno de superficie de la hepatitis B (por sus siglas en inglés); **VHB/D:** virus de la hepatitis B/D.

1. Rizzetto, M et al. Gut. 1977;18:997-1003. **2.** Rizzetto, M et al. Proc Natl Acad Sci U S A. 1980;77:6124-28. **3.** Gerin, JL (1994), (Springer Japan), pp. 63-64. **4.** Hepojoki, J et al. International Committee on Taxonomy of Viruses (ICTV) 2020.

CARACTERÍSTICAS PRINCIPALES DE LA PARTÍCULA VIRAL[1-6]

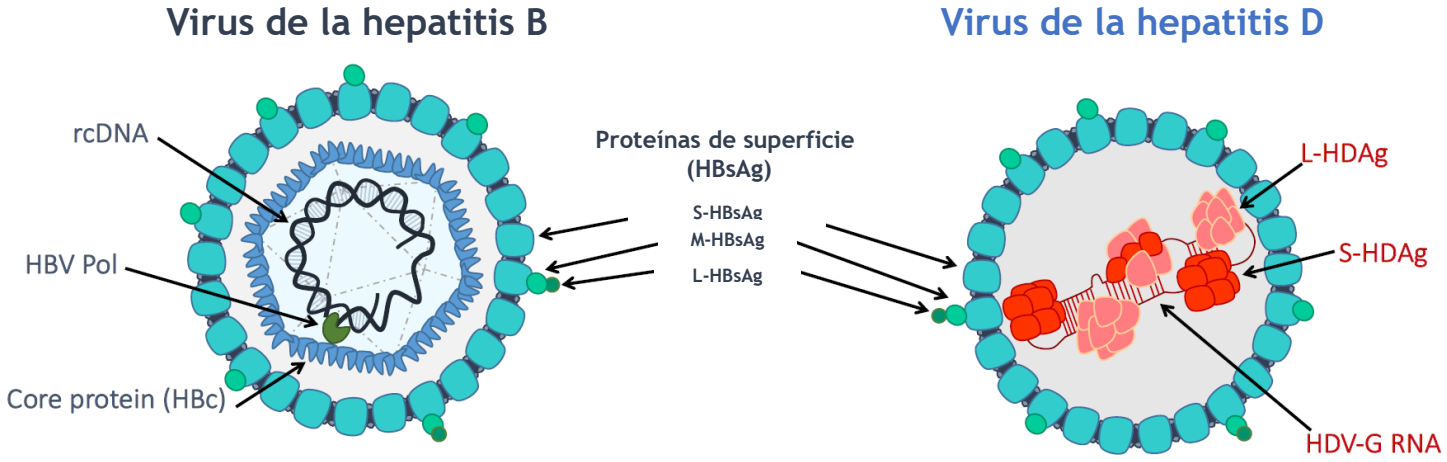
Con 36 nm, el VHD es el virus más pequeño que afecta a humanos

ENVUELTA VIRAL:

- Bicapa lipídica
- Tres proteínas de la envuelta del **VHB:**
  S-HBsAg, M-HBsAg y L-HBsAg
- **Es un virus defectivo.**

RIBONUCLEOPROTEÍNA:

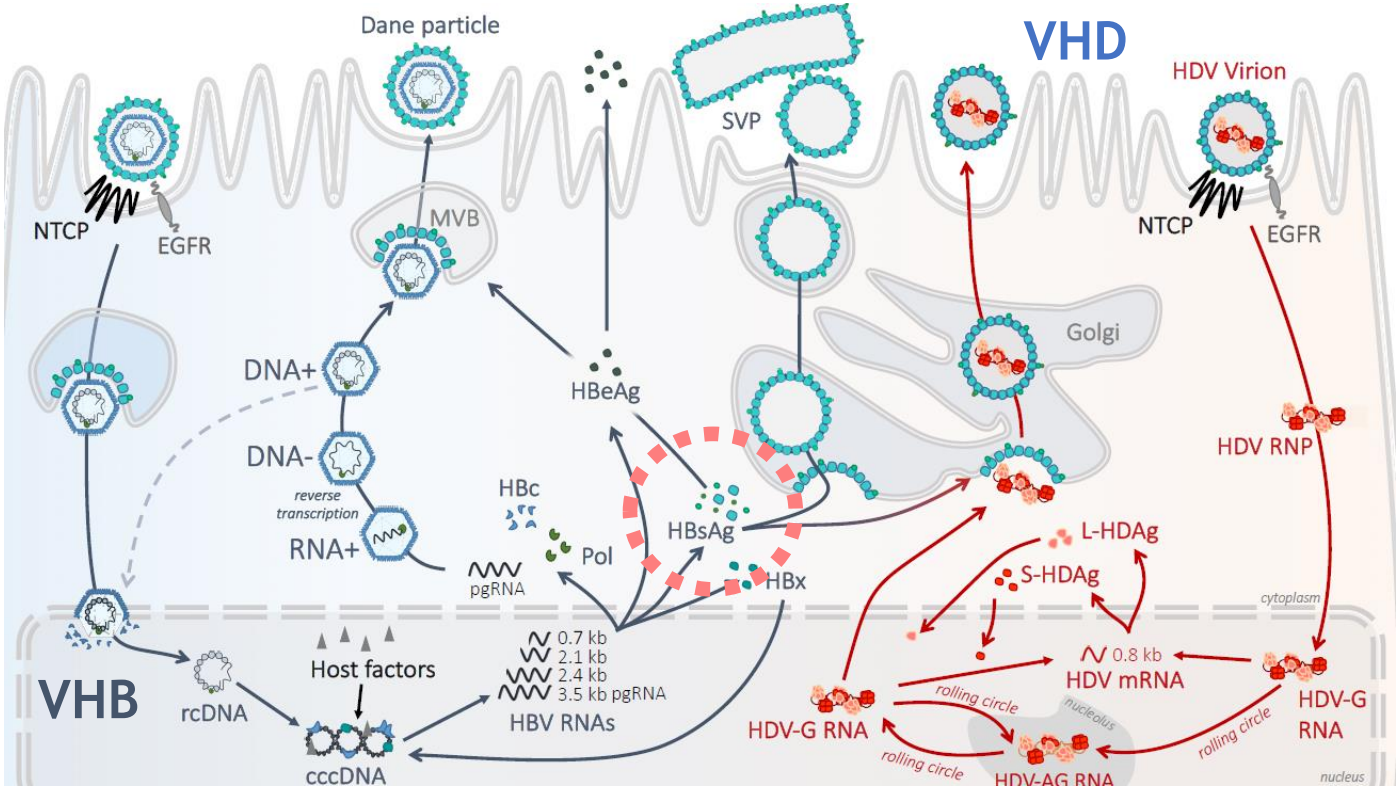
- ARN circular, monocatenario, de sentido negativo, compuesto por 1672-1697 nucleótidos según el genotipo
- Dos formas del **HDAg: S-HDAg y L-HDAg**



Adaptado de Lucifora, J et al. 2020 y Urban, S et al. 2021. **ARN:** ácido ribonucleico; **HBsAg:** antígeno de superficie de la hepatitis B*; **HDAg:** antígeno de la hepatitis D*; **L-HBsAg:** HBsAg grande*; **L-HDAg:** HDAg grande*; **M-HBsAg:** HBsAg mediano*; **rcDNA:** ADN circular relajado*; **S-HBsAg:** HBsAg pequeño*; **S-HDAg:** HDAg pequeño*; **VHB/D:** virus de la hepatitis B/D. *Por sus siglas en inglés.

1. Hughes SA, et al. Lancet 2011;378:73-85. **2.** Koh C, et al. Gastroenterology 2019;156:461-7. **3.** Stockdale AJ, et al. J Hepatol 2020;73:523-3. **4.** Lucifora, J et al. Antiviral Res. 2020;179:104812. **5.** Lempp, FA et al. Viruses. 2017;9:172. **6.** Urban, S et al. Gut. 2021;70:1782-94.

CICLO REPLICATIVO DEL VHD[1]



El VHD **depende del antígeno de superficie del VHB** para su ensamblaje, y de las proteínas celulares del huésped para su replicación

Solo los pacientes infectados por el VHB pueden contraer hepatitis D

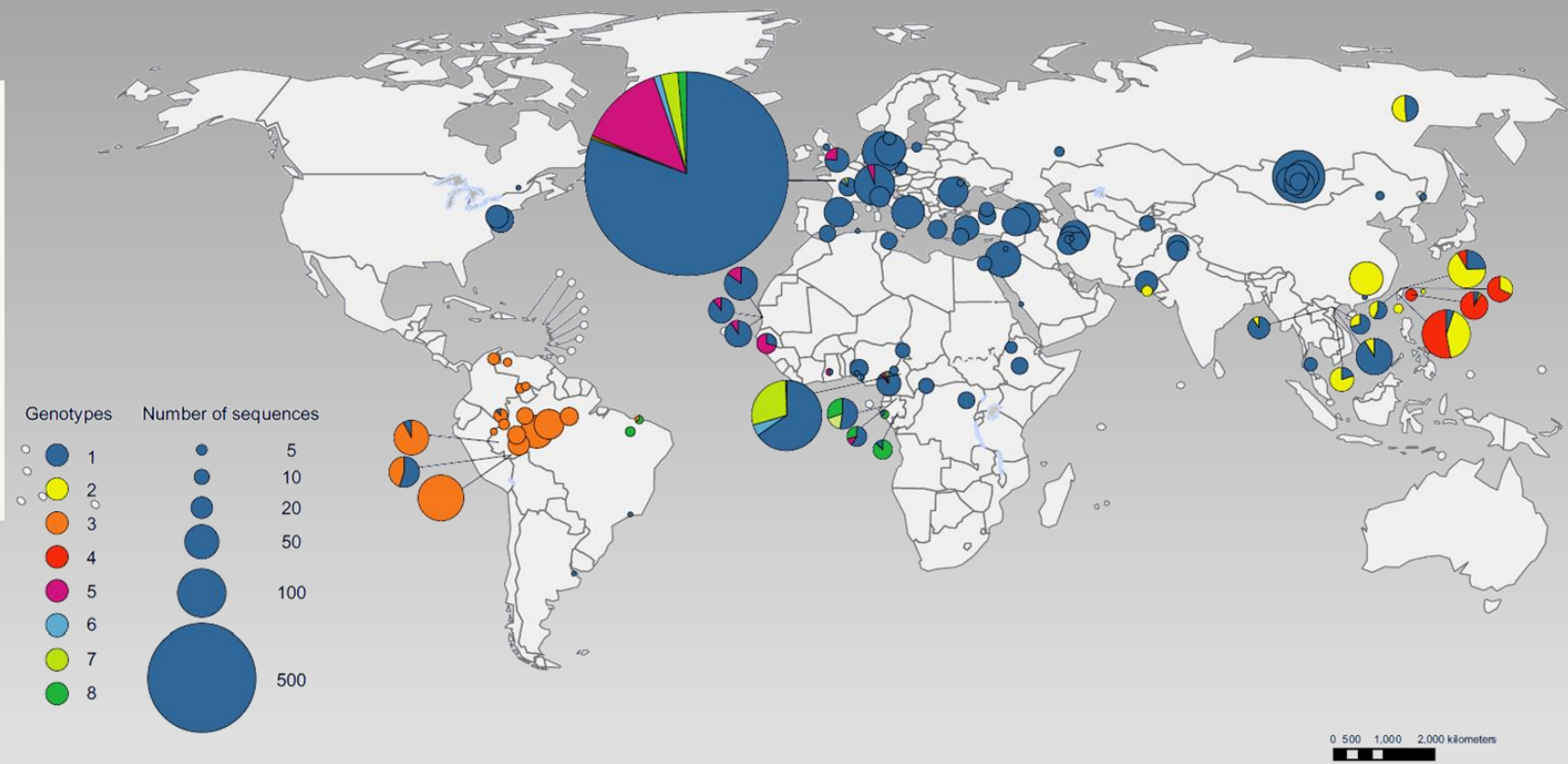
Adaptado de Lucifora, J et al. 2020. **ARNm:** ácido ribonucleico mensajero; **HBsAg:** antígeno de superficie de la hepatitis B*; **HDAg:** antígeno de la hepatitis D*; **HSPG:** proteoglicano heparán sulfato*; **L-HBsAg**: HBsAg grande*; **L-HDAg:** HDAg grande*; **M-HBsAg:** HBsAg mediano*; **NTCP:** proteína cotransportadora de taurocolato de sodio*; **RCA:** amplificación en círculo rodante*; **RNP:** ribonucleoproteína; **S-HDAg:** HDAg pequeño*. *Por sus siglas en inglés.

1. Lucifora, J et al. Antiviral Res. 2020;179:104812.

EPIDEMIOLOGIA

Epidemiologia molecular del VHD[1]

- Se han descrito ocho genotipos del VHD, con una divergencia entre genotipos del 20 %
- Globalmente, **el genotipo 1 es el más predominante**



VHD: virus de la hepatitis D.

1. Stockdale, AJ et al. J Hepatol. 2020;73:523-32.

La hepatitis D en España

Los datos epidemiológicos se ven modificados por las medidas preventivas y por el infradiagnóstico[1-5]

La prevalencia real no se conoce, pero **se estima que un 5% de los pacientes con HBsAg (+) en España son VHD-ARN+** [1-4]

Obtener estimaciones precisas de la epidemiología del VHD es un desafío[5]

- Se requieren **muestras de gran tamaño** para identificar a los pacientes HBsAg (+) antes de realizar la prueba de VHD
- Las estimaciones pueden ser muy heterogéneas debido a **patrones epidémicos variables**, así como a **variaciones en la metodología**
- Los **criterios de selección** para el diagnóstico de HBsAg y posterior VHD pueden dar lugar a un **muestreo poco representativo**

ARN: ácido ribonucleico; **VHB/D:** virus hepatitis B/D; **HBsAg:** antígeno de superficie del virus de la hepatitis B (por sus siglas en inglés).

1. Rodríguez Tajes et al. AEEH 2022 **2.** Segundo estudio de seroprevalencia en España. Ministerio Sanidad. 2020. **3.** Buti, M et al. EASL 2022. #THU384; **4.** Palom, A et al. JHEP Rep. 2022;4:100547. **5.** Stockdale AJ et al. J Hepatol. 2020; 73:523–32.

Prevalencia y características del VHD en España

Registro multicéntrico de hepatitis D en España[1,2]

Estudio de cohorte retrospectivo

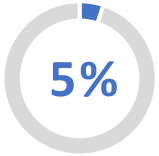
Base de datos de registros de altas hospitalarias del Sistema Nacional de Salud español

192 hospitales privados y 313 públicos (2001-2018)

Adultos diagnosticados de VHB o VHD

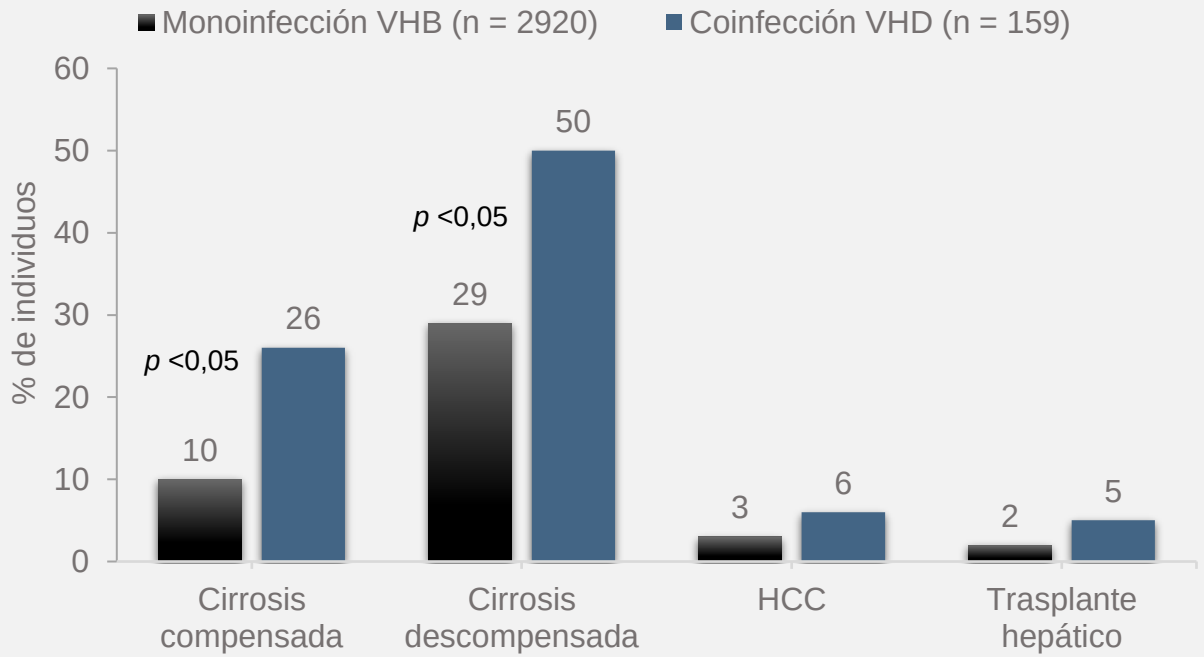
11.939

Prevalencia de VHD en adultos VHB (+)



Los individuos hospitalizados con VHD presentaban una enfermedad hepática más grave al inicio que los pacientes con VHB

Gravedad de la enfermedad hepática de base[2]



HCC: carcinoma hepatocelular (por sus siglas en inglés); **VHB/D:** virus de la hepatitis B/D.

1. Rodríguez Tajes S, et al. AEEH. 2022. **2.** Buti M, et al. EASL. 2022. #THU384.

Diagnóstico Hepatitis Delta en Andalucía:

Situación Actual

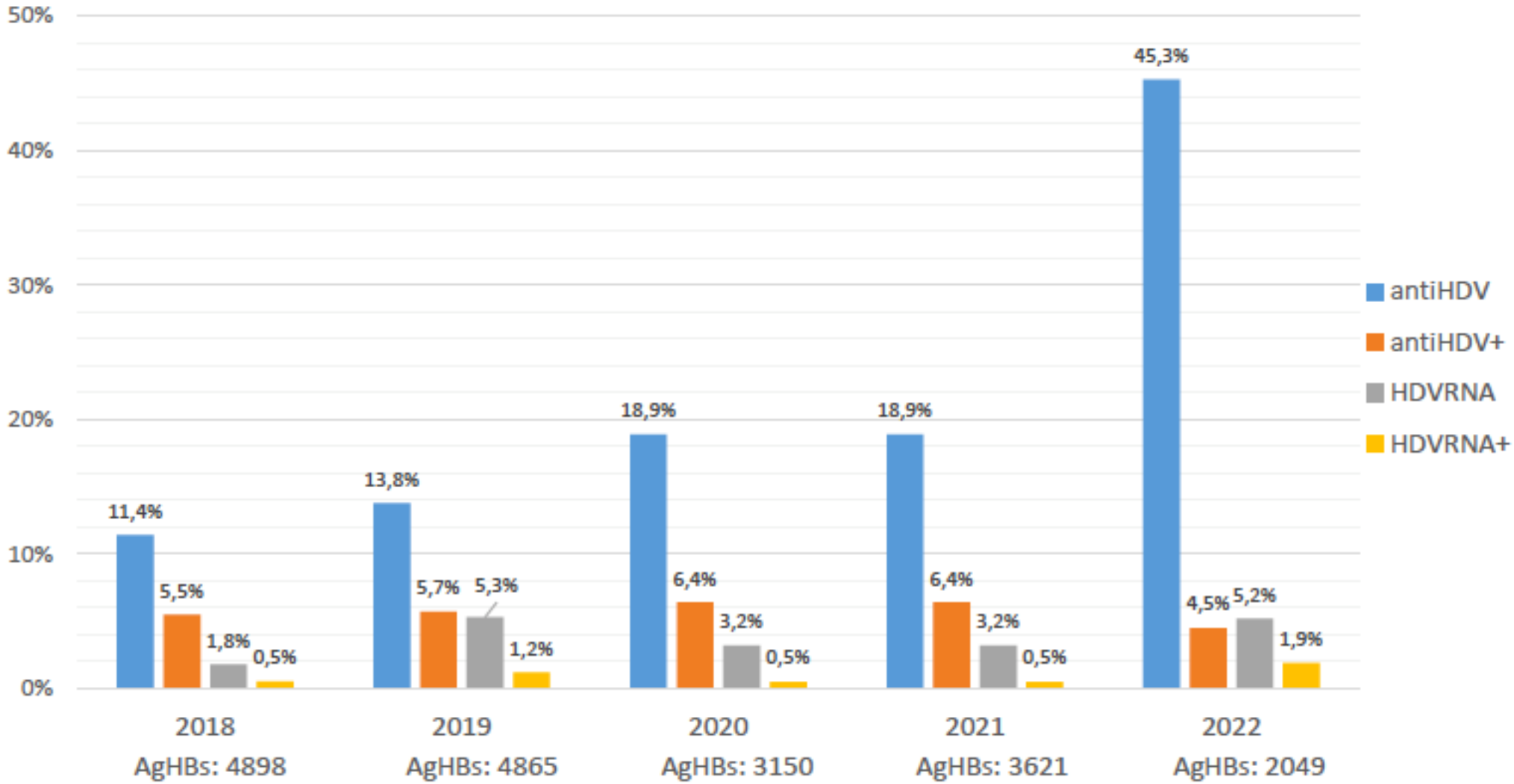
Ana Fuentes [1], Adolfo De Salazar[1], Natalia Montiel[2], Juan Carlos Alados[3], Carolina Freyre[4], Ana Belén Pérez[5], Manuel Rodríguez Maresca[6], Begoña Palop[7], Aurora García Barrionuevo[8], Fernando Fernández Sanchez[9], María Del Carmen Lozano[10], María Del Carmen Domingez[11], Encarnación Ramírez Arellano[12], Francisco Franco Álvarez De Luna[13], Alberto De La Iglesia Salgado[14], Antonio Sampedro[15], Pilar Luzón[16], Carolina Roldán[17], Fernando García[1], José María Rosales[6], Marta Casado[6], Federico García[1]

1.Hospital Universitario de San Cecilio, Granada, 2. Hospital Universitario Puerta del Mar, Cádiz, 3. Hospital del S.A.S. de Jerez de la Frontera, Jerez de la Frontera, 4. Hospital Puerto Real, Cádiz. 5. Hospital Universitario Reina Sofía, Córdoba, 6. Hospital Torrecárdenas, Almería, 7. Hospital Regional Universitario Carlos Haya, Málaga, 8. Hospital Clínico Universitario Virgen de la Victoria, Málaga, 9. Hospital Costa del Sol, Marbella, 10. Hospital Universitario Virgen del Rocío, Sevilla, 11. Hospital Universitario Nuestra Señora de Valme, Sevilla, 12. Hospital Universitario Virgen Macarena, Sevilla, 13. Hospital Juan Ramón Jiménez, Huelva, 14. Hospital Infanta Elena, Huelva, 15. Hospital Universitario Virgen de las Nieves, Granada, 16. Hospital de Poniente, Almería, 17. Hospital Universitario Ciudad de Jaén, Jaén.

XXVI Congreso Nacional de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica

Santiago de Compostela
1/3 de junio de 2023

Resultados: Cascada por años



XXVI Congreso Nacional de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
Santiago de Compostela
1/3 de junio de 2023

This study was supported by competitive grant from Gilead Sciences, S.L.U. (IN-ES-980-6335).

PREVALENCIA DE LA HEPATITIS D EN LA COMUNIDAD VALENCIANA: BÚSQUEDA ACTIVA DE CASOS

0890

Ángela Carvalho-Gomes[1], **Inmaculada Gómez González**[2], Ariadna Bono[3], Lola Gómez[4], Susana Sabater[5], Juan Carlos Rodríguez-Díaz[2], Helena Hernández-Evole[6], Antonio Palau[5], Ana Forés[5], María Rodríguez[2], Sonia Pascual[2], Martín Prieto[3], Marina Berenguer[7]

[1]CIBEREHD, Valencia; [2]Hospital General Universitario, Alicante; [3]Instituto de investigación Sanitaria La Fe, Valencia; [4]Hospital Universitario y Politécnico La Fe, Valencia; [5]Hospital General Universitario de Castellón, Castellón; [6]Hospital Clínic de Barcelona, Barcelona; [7]Universidad de Valencia, Valencia

Conclusiones

- En una región considerada históricamente de alto riesgo, alrededor del 11% de los pacientes con VHB están infectados por el virus delta. Esta cifra se mantiene estable a lo largo del tiempo y casi la mitad corresponde a individuos no nacidos en España.
- El uso de pruebas reflejas es útil para aumentar la detección de casos delta desconocidos.

Tabla 1. Seroprevalencia del VHD en pacientes VHB crónica de la C.V.

	Castellón (n=52)	Alicante (n=57)	Valencia (n=133)
Género (hombres)	78.8% (41)	77.0% (44)	60.9% (81)
Edad media	48.7	46.1	47.6
Extranjeros	46.2% (24)	Origen desconocido	42.1% (56)

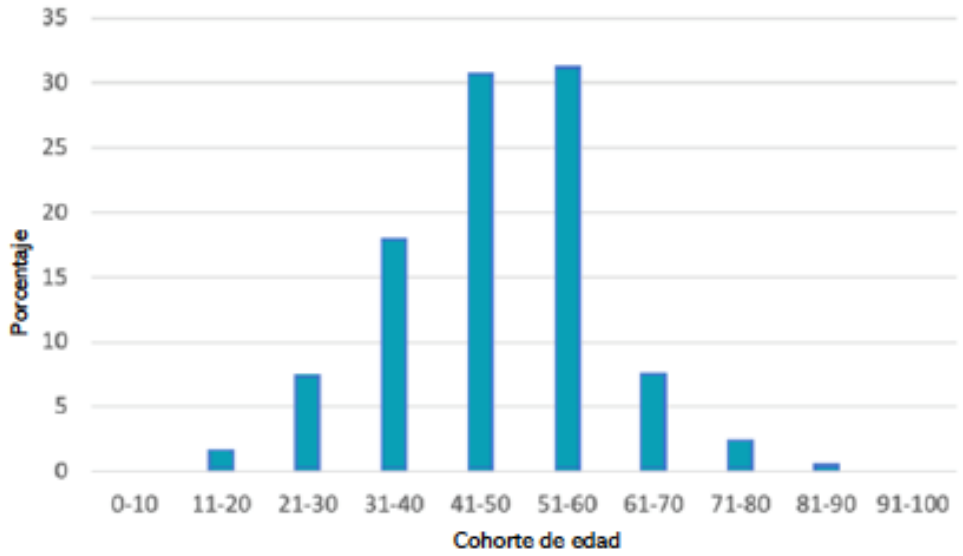


Figura 1. Nº de solicitudes de pruebas a lo largo del tiempo.

CLÍNICA Y EVOLUCIÓN

Perfil del paciente con hepatitis D

Características de pacientes extraídas del registro de la AEEH[1]

Datos nacionales que incluyen 329 pacientes anti-VHD (+)

AEEH
Asociación Española para el Estudio del Hígado

HEPATITIS DELTA REGISTRO

- **Mediana de 51 años**
  (63% de los pacientes entre 40 y 60 años)
- **59% hombres**
- **33% cirróticos**
  13% con hipertensión portal y 1% con HCC
- **47% nacidos en el extranjero**
  (24% de Europa occidental y 15% de África)
- **9%** coinfectados con **VIH**
  18% coinfectados con **VHC**
- **15% UDVP**

La proporción de nacidos en el extranjero crece año tras año, mientras que la de nacidos en España disminuye[2].

HCC: carcinoma hepatocelular (por sus siglas en inglés); **VHB/C/D:** virus de la hepatitis B/C/D; **VIH:** virus de inmunodeficiencia humana.

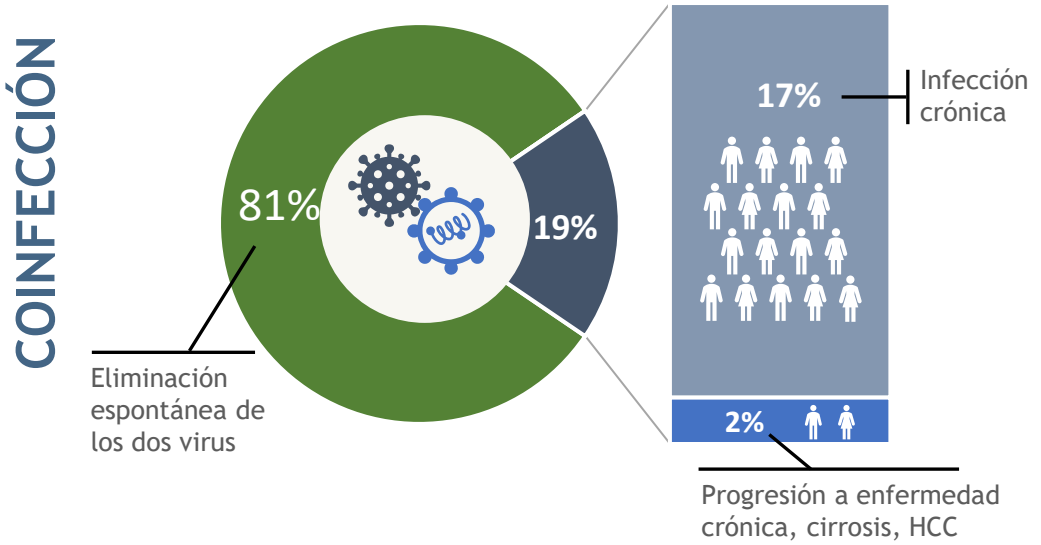
1. Rodríguez-Tajes, S et al. Characterizing chronic hepatitis delta in Spain and the gaps in its management. EASL 2023. WED-166. **2**. Ordieres C et al. Prevalence and epidemiology of hepatitis D among patients with chronic hepatitis B virus infection: a report from Northern Spain. European Journal of Gastroenterology & Hepatology 2017, 29:277–283

EVOLUCIÓN CLÍNICA SEGÚN EL MOMENTO DE INFECCIÓN

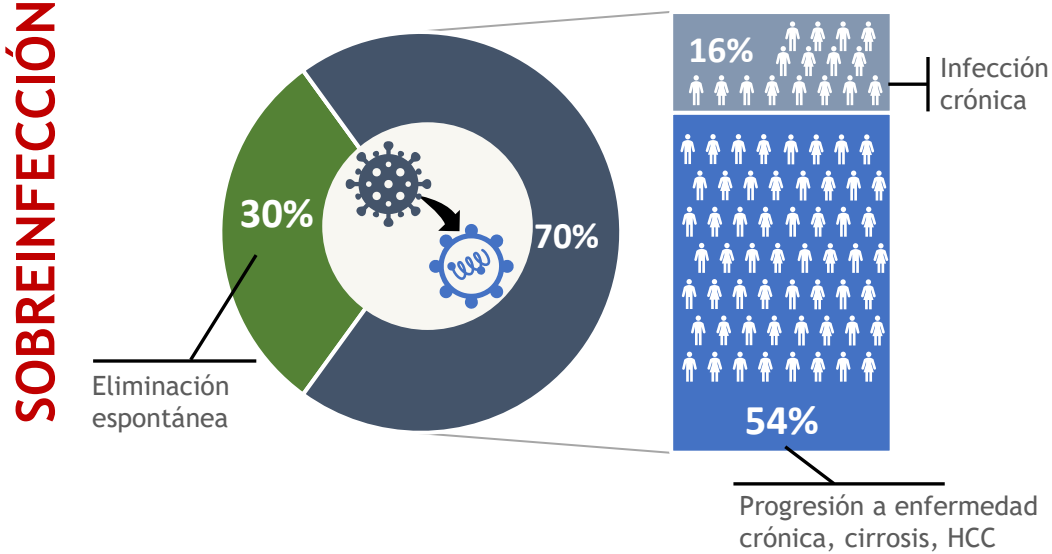
Coinfección vs. sobreinfección[1-3]

El curso clínico de la enfermedad (tanto la probabilidad de evolución a enfermedad crónica como la progresión a complicaciones a largo plazo) depende del momento de la infección por VHD

Se produce cuando una persona se infecta simultáneamente con el VHB y el VHD



Se produce cuando una persona ya infectada crónicamente por el VHB adquiere el VHD

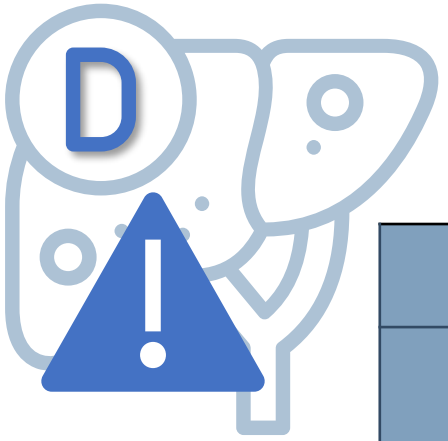


HCC: carcinoma hepatocelular (por sus siglas en inglés); **VHB/D:** virus de la hepatitis B/D.

1. Loureiro, D et al. Liver Int. 2021;41 Suppl 1:30-37. **2.** Lucifora, J et al. Antiviral Res. 2020;179:104812. **3.** Miao, Z et al. J Infect Dis. 2020;221:1677-1687.

PROGRESIÓN DE LA ENFERMEDAD

La infección por VHD produce la forma más grave de hepatitis viral[1,2]



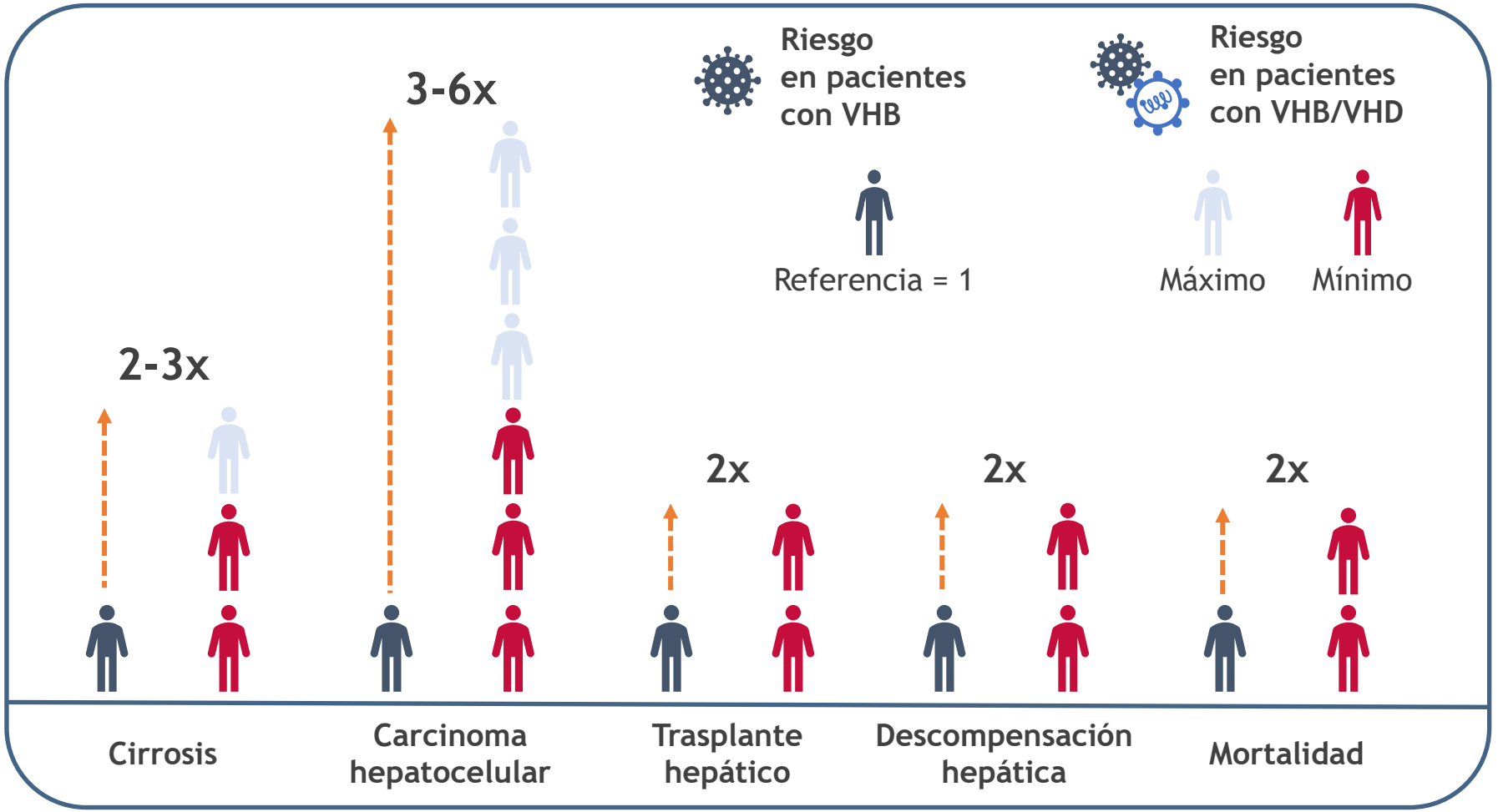
	RIESGO DE PROGRESIÓN A HEPATITIS CRÓNICA	RIESGO DE CIRROSIS O CARCINOMA HEPATOCELULAR
Hepatitis A[2]	0 %†	0 %
Hepatitis B[3]	Adultos 5 % Niños 90 %	20-30 % (de por vida)
Hepatitis C[4]	55-85 %	15-30 % (20 años)
Hepatitis D[1]	**76 %**	**Cirrosis en 5 años** **HCC en 10 años**
Hepatitis E[5]	Raramente en inmunodeprimidos	0 %

†Puede causar hepatitis fulminante en un número pequeño de pacientes. **HCC:** carcinoma hepatocelular (por sus siglas en inglés); **VHB/D:** virus de la hepatitis B/D.

1. Miao Z, et al. J Infect Dis 2020;221:1677-87. **2.** WHO. Hepatitis A fact sheet. 2022. **3.** WHO. Hepatitis B fact sheet. 2022. **4.** WHO. Hepatitis C fact sheet. 2022. **5.** WHO. Hepatitis E fact sheet. 2022.

PROGRESIÓN DE LA ENFERMEDAD

Consecuencias hepáticas a largo plazo en pacientes VHD/VHB[1,2]



Mayor riesgo de consecuencias a largo plazo de la hepatitis viral en pacientes con **VHB/VHD** frente a la monoinfección por VHB[1]

VHB/D: virus de la hepatitis B/D.

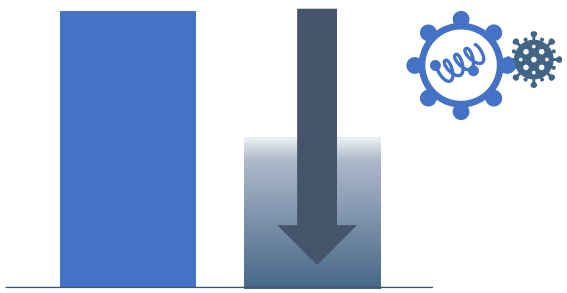
1. Da BL, et al. Gastroenterol Rep 2019;7:231-45. **2.** Miao Z, et al. J Infect Dis 2020;221:1677-87.

HEPATITIS D AGUDA Y CRÓNICA

Modelos de infección[1-4]

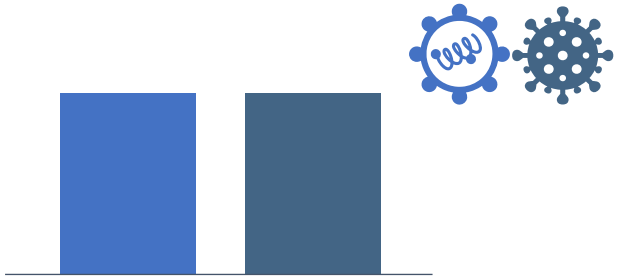
PREDOMINANTE

Replicación del **VHD**, supresión de la replicación del **VHB**



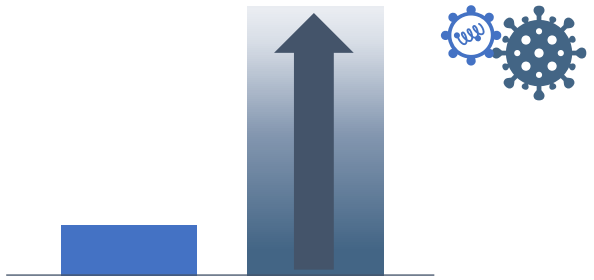
SIMILAR

Cargas virales de **VHD** y **VHB** similares



RARO

Replicación predominante del **VHB**



El VHD tiende a suprimir la replicación del VHB

Reducciones en la carga viral del VHD durante el tratamiento pueden incrementar la carga viral del VHB, dado que se reduce el efecto supresor del VHD

La carga viral del VHB no tiene impacto en la carga viral y consecuencias clínicas de la infección por VHD

El manejo del VHD con ANs debe basarse en las recomendaciones de las Guías y las decisiones clínicas individuales

El tratamiento del VHB con ANs no tiene ningún efecto sobre el VHD

ALT: alanina aminotransferasa; ANs: análogos de nucleós(t)idos; AST: aspartato aminotransferasa; VHB/D: virus de la hepatitis B/D.

1. Wedemeyer H, et al. Liver Int 2011;31(Suppl 1):140-4; 2. Da BL, et al. Gastroenterol Rep 2019;7:231-45; 3. Shah PA, et al. Gastroenterol Rep 2019;7:396-402; 4. Koh C, et al. Clin Liver Dis 2019;23:557-72.

DIAGNOSTICO

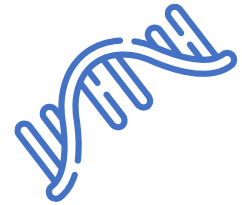
EL DIAGNÓSTICO DEL VHD

Requiere de pruebas de anticuerpos y ARN del VHD[1-3]

Anti-VHD

Prueba de cribado de primera línea

- Generalmente disponible a nivel global
- Disponibilidad limitada en países en vías de desarrollo



ARN de VHD

- Evaluado por NAT/RT-PCR
- Cualitativo y cuantitativo
- Prueba de confirmación para infecciones activas

Se requiere una amplia disponibilidad comercial

ARN: ácido ribonucleico; NAT: pruebas de amplificación de ácidos nucleicos*; RT-PCR: reacción en cadena de la polimerasa con reverso transcripción*; VHD: virus de la hepatitis D. *Por sus siglas en inglés.

1. Shah, PA et al. Gastroenterol Rep (Oxf). 2019;7:396-402. 2. Ahn, J et al. Gastroenterol Hepatol (N Y). 2014;10:647-686. 3. Cheung, A et al. Clin Liver Dis. 2020;24:405-419.

Survey to evaluate the implementation of the recommendations on the comprehensive diagnosis of viral hepatitis in a single extraction: Where are we?

J. CABEZAS[1,2], A. AGUILERA[3], M. BERENGUER[4], M. BUTI[5], M. ELIECER CANO[6], X. FORNS[7], F. GARCÍA[8], J. GARCÍA-SAMANIEGO[9], M. HERNÁNDEZ-GUERRA[10], F. JORQUERA[11], J.V. LAZARUS[12,13], S. LENS[14], E. MARTRÓ[15], J.A. PINEDA[16], M. PRIETO[17,18], F. RODRÍGUEZ-FRÍAS[19], M. RODRÍGUEZ[20], M.A. SERRA[21], J. TURNES[22], A. CASADO GÓMEZ[23], R. DOMÍNGUEZ-HERNÁNDEZ[23], N. TEJADO ALSUA[23], M.A. CASADO[23], J.L. CALLEJA[24], J. CRESPO[1,2,25]

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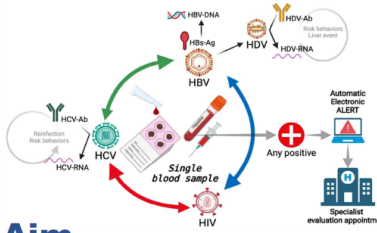
1 Introduction



The SEPD, AEEH, SEIMC, GEHEP and AEHVE agreed on a document at the beginning of 2022 to carry out a comprehensive diagnosis of viral hepatitis (B, C and D), so that the positive result in serology against the viruses of hepatitis (B, C and D), as well as HIV, would activate the analysis of the rest of the virus, including the viral load, when necessary, from the same blood extraction. This process would increase the diagnosis rate and decrease the time of access to treatment.

2 Aim

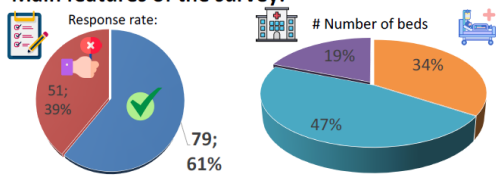
To evaluate the situation in Spain regarding the comprehensive diagnosis of viral hepatitis in a single blood draw.

3 Method

A panel of experts prepared a structured survey disseminated through the Google Forms platform to all Spanish hospitals, public or private with teaching accreditation, with 200 beds or more. The survey was sent on 20th Oct 2022 and the reception of the results closed on 1st Dec 2022.

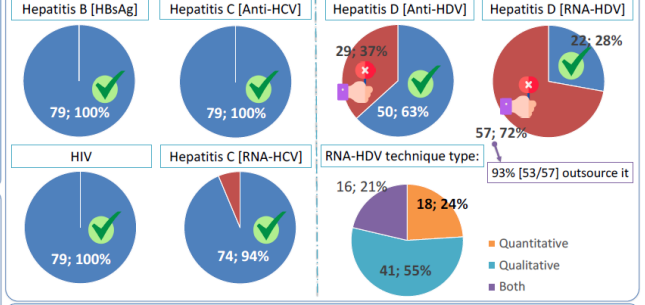
4 Results

Main features of the survey:

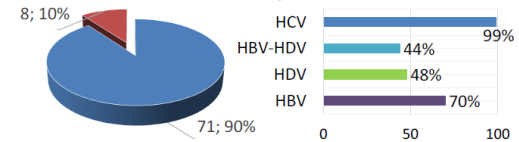


The survey was sent to 130 centers

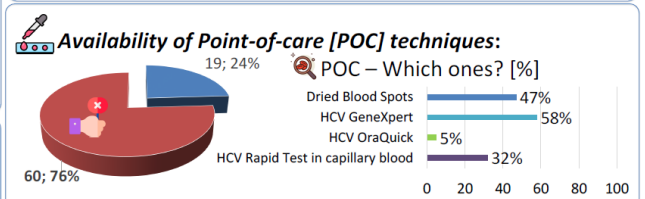
Availability of testing tools:



Reflex test evaluation:

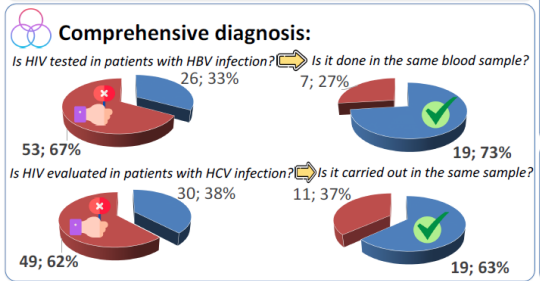


Availability of Point-of-care [POC] techniques:

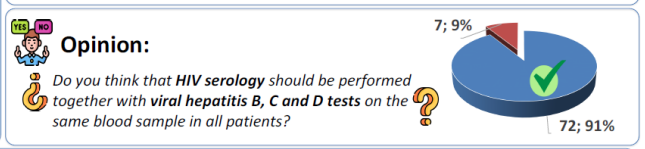


In 84% [16/19] of the centers, the POC **results are supervised by the laboratory**, and almost always (95%, 18/19) integrated into the electronic medical record.

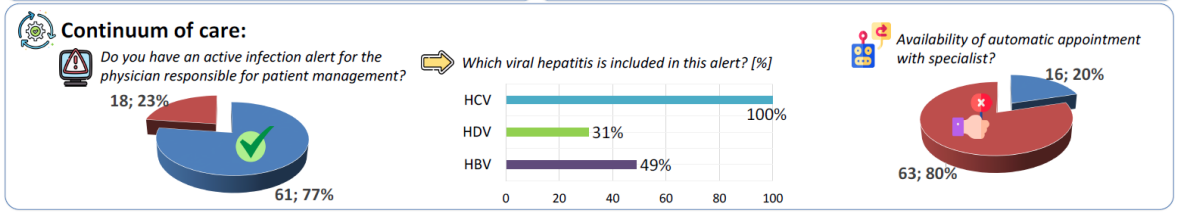
Comprehensive diagnosis:



Opinion:



Continuum of care:



5 Conclusions

Although most hospitals have the procedures to carry out a comprehensive diagnosis of viral hepatitis in a single analytical sample, this is used in less than 50% of cases for HBV/HDV. Alerts to maintain continuity of care are widely available for hepatitis C, but they need to be increased for HBV and HDV. Likewise, it is necessary to implement the devices for decentralized diagnosis.

6 Acknowledgements

This study is funded by Gilead Sciences SL

7 References

1. Crespo J, Cabezas J, Aguilera A, Berenguer M, Buti M, Forns X, et al. Recommendations for the integral diagnosis of chronic viral hepatitis in a single analytical extraction. *Gastroenterol & Hepatol. 2023;46(2):150-62.*
2. Crespo J, Calleja JL, Cabezas J, Garcia F, Aguilera A, Jorquera F, et al. A call for the comprehensive diagnosis of viral hepatitis as a key step towards its elimination. *Liver Int, 2023; doi: 10.1111/liv.15529.*

8 Contact information

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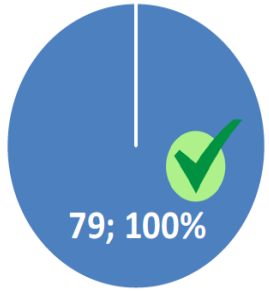
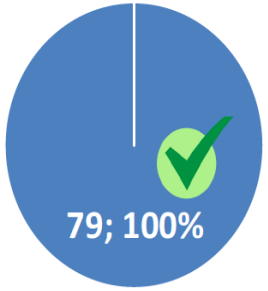
EASL CONGRESS Vienna, Austria 21–24 June 2023
DOI: 10.3252/poo.ini.EASLCONGRESS.2023
Public Health Joaquin Cabezas
FRI--188
EASL2023

Availability of testing tools:

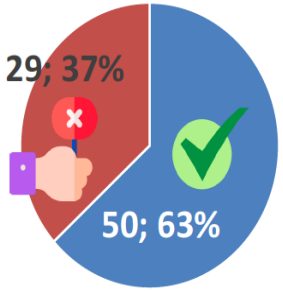
Hepatitis B [HBsAg]



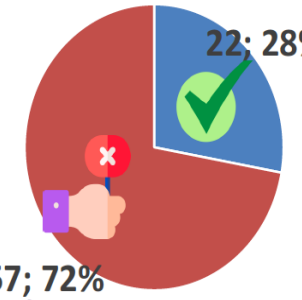
Hepatitis C [Anti-HCV]



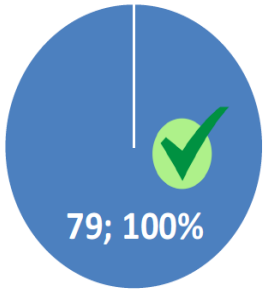
Hepatitis D [Anti-HDV]



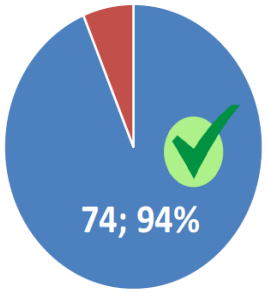
Hepatitis D [RNA-HDV]



HIV

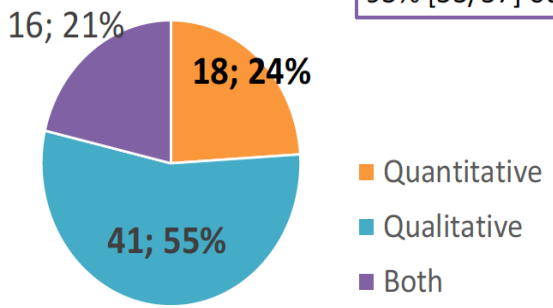


Hepatitis C [RNA-HCV]



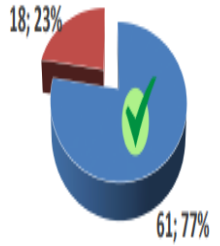
RNA-HDV technique type:

93% [53/57] outsource it

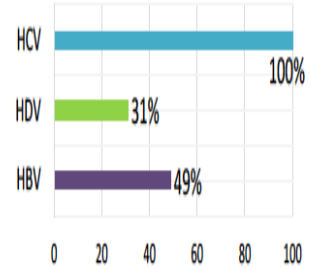


Continuum of care:

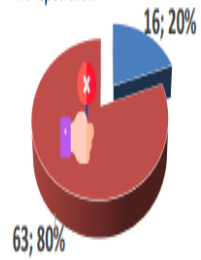
Do you have an active infection alert for the physician responsible for patient management?



Which viral hepatitis is included in this alert? (%)



Availability of automatic appointment with specialist?



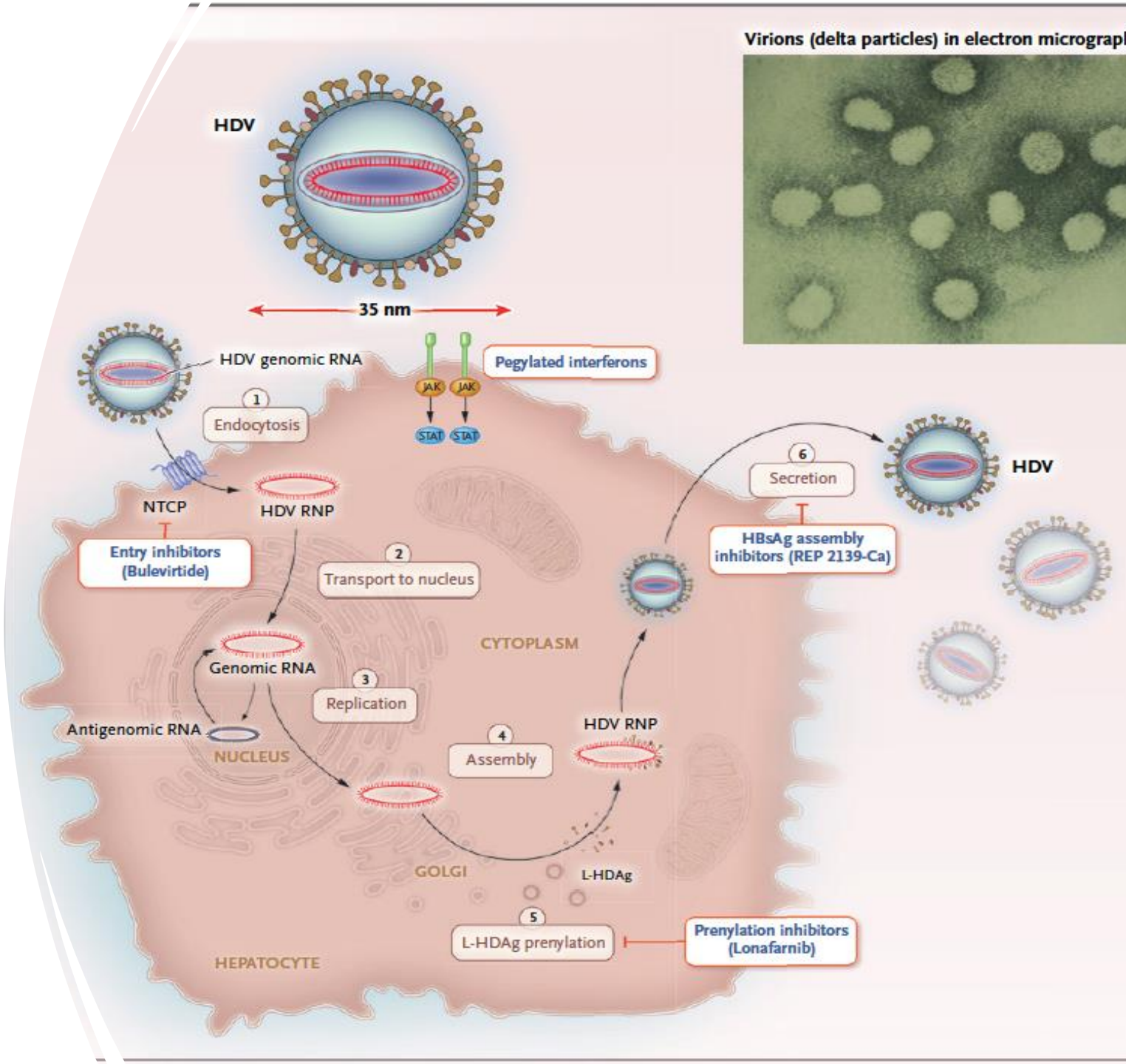
Conclusions

5

Although most hospitals have the procedures to carry out a comprehensive diagnosis of viral hepatitis in a single analytical sample, this is used in less than 50% of cases for HBV/HDV. Alerts to maintain continuity of care are widely available for hepatitis C, but they need to be increased for HBV and HDV. Likewise, it is necessary to implement the devices for decentralized diagnosis.

TRATAMIENTO

DIANAS TERAPEUTICAS



Tarik Asselah, M.D., and Mario Rizzetto, M.D.
N Engl J Med 2023; 389:58-70

Rational for treatment goals in patients with hepatitis delta

- Aim of treatment for hepatitis: prevent the development of complications[1–3]
- Surrogate endpoints should provide evidence of a decline in virological replication and liver inflammation:[4,5]

≥2 log_{10} decline in HDV RNA

Declines in HDV RNA have been associated with better outcomes in relation to disease progression[6]

Patients who were HDV RNA negative for 2 years after treatment discontinuation were less likely to:[6]

- Die due to liver disease (P=0.032)*
- Develop complications (P=0.006)*

ALT normalisation

Elevated ALT has been associated with long-term complications such as cirrhosis and HCC[7,8,9]

Patients with normal ALT levels had a lower risk of hepatic events, including HCC (P<0.001)**[10]

1. Chotiyaputti W, et al. J Viral Hepat 2010;17:675–84; 2. Feld J, et al. Hepatology 2009;49:S96–102; 3. Yurdaydin C, et al. J Hepatol 2019;70:1008–15; 4. FDA Developing Drugs for HDV. Available at: www.fda.gov/media/132137/download (accessed January 2022); 5. Cornberg M, et al. J Hepatol 2020;72:539–57; 6. Yurdaydin C, et al. J Infect Dis 2018;217:1184–82; 7. EASL. J Hepatol 2017;67:370–98; 8. Gilman C, et al. World J Gastroenterol 2019;25:4580–97; 9. Terrault N, et al. Hepatology 2018;67:1560–99; 10. Wong GLH, et al. J Hepatol 2018;69:793-802.

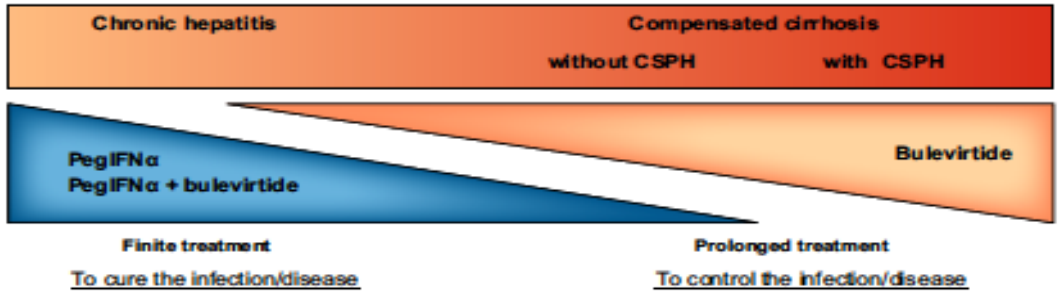
*When compared with patients without a maintained response
**In patients with CHB receiving nucleos(t)ide analogue treatment
ALT: alanine aminotransferase; CHB: chronic hepatitis B; HCC hepatocellular carcinoma.

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis delta virus☆

European Association for the Study of the Liver*



Statement

- IFNα has been used since the '90s for the treatment of CHD. Mono- and multicentre studies have been conducted with IFNα, with only two randomised phase II studies published. Nevertheless, long-term data on clinical benefit and safety are available **(LoE 2, strong consensus).**

Recommendations

- All patients with CHD and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PegIFNα **(LoE 2, strong recommendation, consensus).**
- PegIFNα for 48 weeks should be the preferred treatment schedule **(LoE 3, strong recommendation, consensus).**
- Personalised treatment durations may be considered based on HDV RNA and HBsAg kinetics and treatment tolerability **(LoE 3, weak recommendation, strong consensus).**

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

Recommendations

- All patients with CHD and compensated liver disease should be considered for treatment with BLV **(LoE 3, strong recommendation, consensus).**
- The optimal dose and duration of treatment have not yet been defined **(LoE 5, consensus).** Until further data become available, long-term treatment with BLV, 2 mg once daily, may be considered **(LoE 5, weak recommendation, consensus).**
- The combination of pegIFNα and BLV may be considered in patients without pegIFNα intolerance or contraindications **(LoE 5, weak recommendation, consensus).**

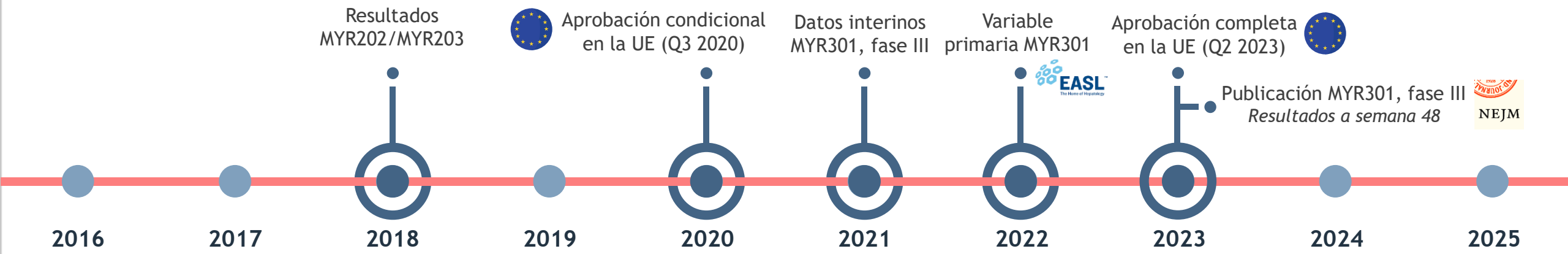
Journal of Hepatology, **August 2023**. vol. 79 | 433–460

PegIFNα no está indicado para el tratamiento de la hepatitis delta.
La combinación de bulevirtida y PegIFNα no está indicada para el tratamiento de la hepatitis delta
Bulevirtida: medicamento aprobado por la Comisión Europea y sin financiación y precio en España

EXPERIENCIA CON BULEVIRTIDA*

*Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.

Bulevirtida*: desarrollo clínico e hitos[1-9]



MYR201

MYR203
Fase II; BLV ± TDF, BLV ± PEG-INFα; 48 semanas

MYR202
Fase II; BLV ± TDF; 24 semanas

MYR204
Fase II; BLV + PEG-INFα; 96 semanas

MYR301
Fase III; BLV; 144 semanas

Terapia finita#

Terapia crónica

*Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.
#El tratamiento con BLV está indicado para el tratamiento crónico de la hepatitis delta. BLV: bulevirtida; DC: decisión de la Comisión; PEG-INFα: interferón pegilado†; TDF: fumarato de disoproxilo de tenofovir†; U.E.: Unión Europea. †Por sus siglas en inglés.

1. EPAR bulevirtida. Disponible en: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex. Fecha de acceso: Junio 2023. 2. Kang, C et al. Drugs. 2020;80:1601-1605. 3. Ensayo MYR201 (clinicaltrials.gov - NCT02637999). 4. Ensayo MYR202 (NCT03546621). 5. Ensayo MYR203 (NCT02888106). 6. Ensayo MYR204 (NCT03852433). 7. Ensayo MY301 (NCT03852719). 8. Ficha técnica bulevirtida, disponible en: https://ftgileadspain.com/filesRepositorio/68/Hepcludex_FT.pdf. Fecha de acceso: Septiembre 2023. 9. Wedemeyer H. et al. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. N Engl J Med 2023; 389:22-32 DOI: 10.1056/NEJMoa2213429

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

Heiner Wedemeyer[1], Soo Aleman[2], Maurizia Brunetto[3,4], Antje Blank[5], Pietro Andreone[6], Pavel Bogomolov[7], Vladimir Chulanov[8], Nina Mamonova[8], Natalia Geyvandova[9], Morozov Viacheslav[10], Olga Sagalova[11], Tatyana Stepanova[12], Dmitry Manuilov[13], Renee-Claude Mercier[13], Qi An[13], John F. Flaherty[13], Anu Osinusi[13], Audrey Lau[13], Julian Schulze zur Wiesch[14], Markus Cornberg[1], Stefan Zeuzem[15], Pietro Lampertico[16,17]

[1]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany, [2]Karolinska University Hospital/Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden, [3]University Hospital of Pisa , Hepatology Unit, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, Pisa, Italy, [4]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [5]Heidelberg University Hospital, Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany, [6]University of Modena and Reggio Emilia, Internal Medicine, Baggiovara Hospital, Modena, Italy, [7]State budgetary institution of health care of Moscow region “Moscow regional research clinical institute after M.F. Vladimirsky", Moscow, Russian Federation, [8]FSBI National Research Medical Center for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [9]Stavropol Regional Hospital, Stavropol, Russian Federation, [10]LLC Medical Company “Hepatolog”, Samara, Russian Federation, [11]Federal state-funded institution of higher education "Southern Ural State Madical University of Ministry of Health of the Russian Federation", Chelyabinsk, Russian Federation, [12]Limited liability company “Clinic of Modern Medicine”, Moscow, Russian Federation, [13]Gilead Sciences, Foster City, United States, [14]Universitätsklinikum Hamburg-Eppendorf , Medizinische Klinik Studienambulanz Hepatologie, Hamburg, Germany, [15]University Hospital Frankfurt, Department of Medicine, Frankfurt am Main, Germany, [16]Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, [17]CRC “A. M. and A. Migliavacca” Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy

International Liver Congress, 21–24 June 2023: Oral OS-068.

Hepatitis Delta Virus

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

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

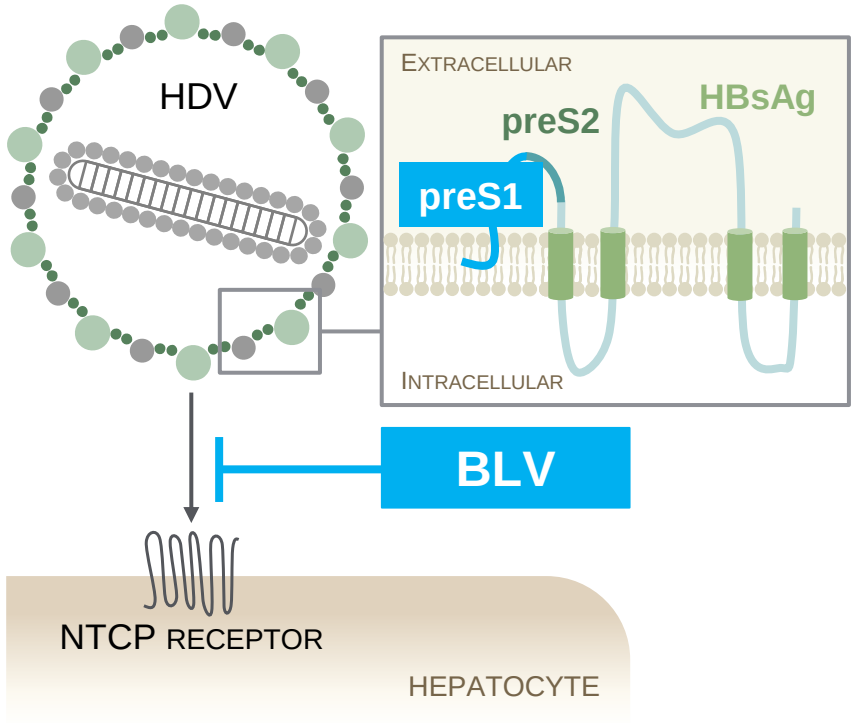
CHD, chronic hepatitis delta; HBV, hepatitis B virus; HDV, hepatitis delta virus; Pegylated interferon-alfa PegIFNα

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

Background

Bulevirtide (BLV)

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



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

1. Ni Y, et al. Gastroenterology 2014;146:1070-83; 2. Lampertico P, et al. J Hepatol 2022;77 (5):1422-30; 3. Wedemeyer H, et al. NEJM 2023;388(25)

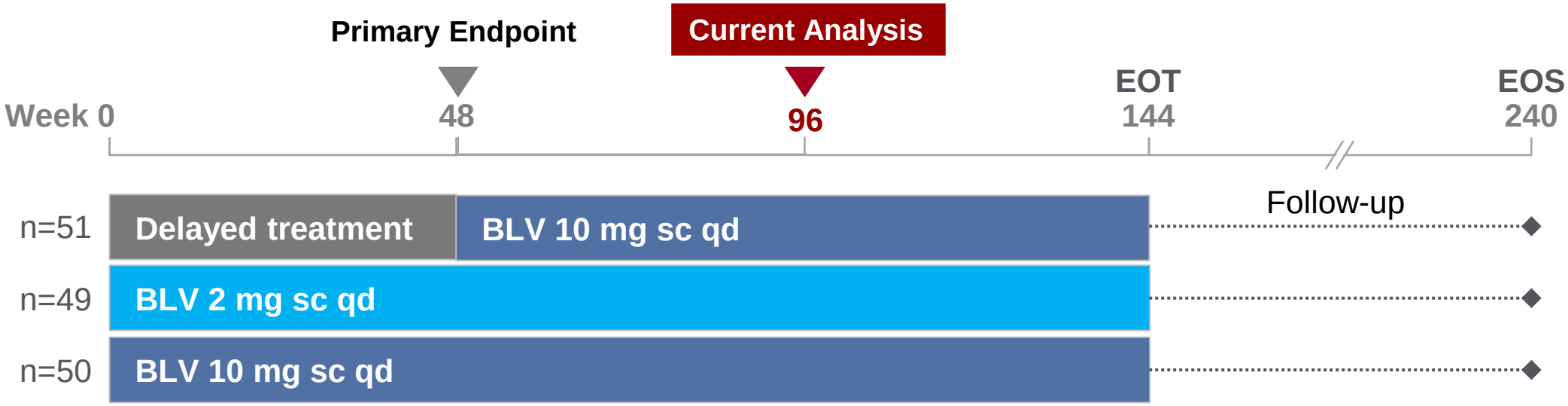
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

Study Design



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

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

Study Endpoints

Primary Study Endpoint:

The proportion of patients achieving combined response at Week 48:

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

Week 96 Analysis Endpoints:

The proportion of patients with:

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

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

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

Demographic and Disease Characteristics

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

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

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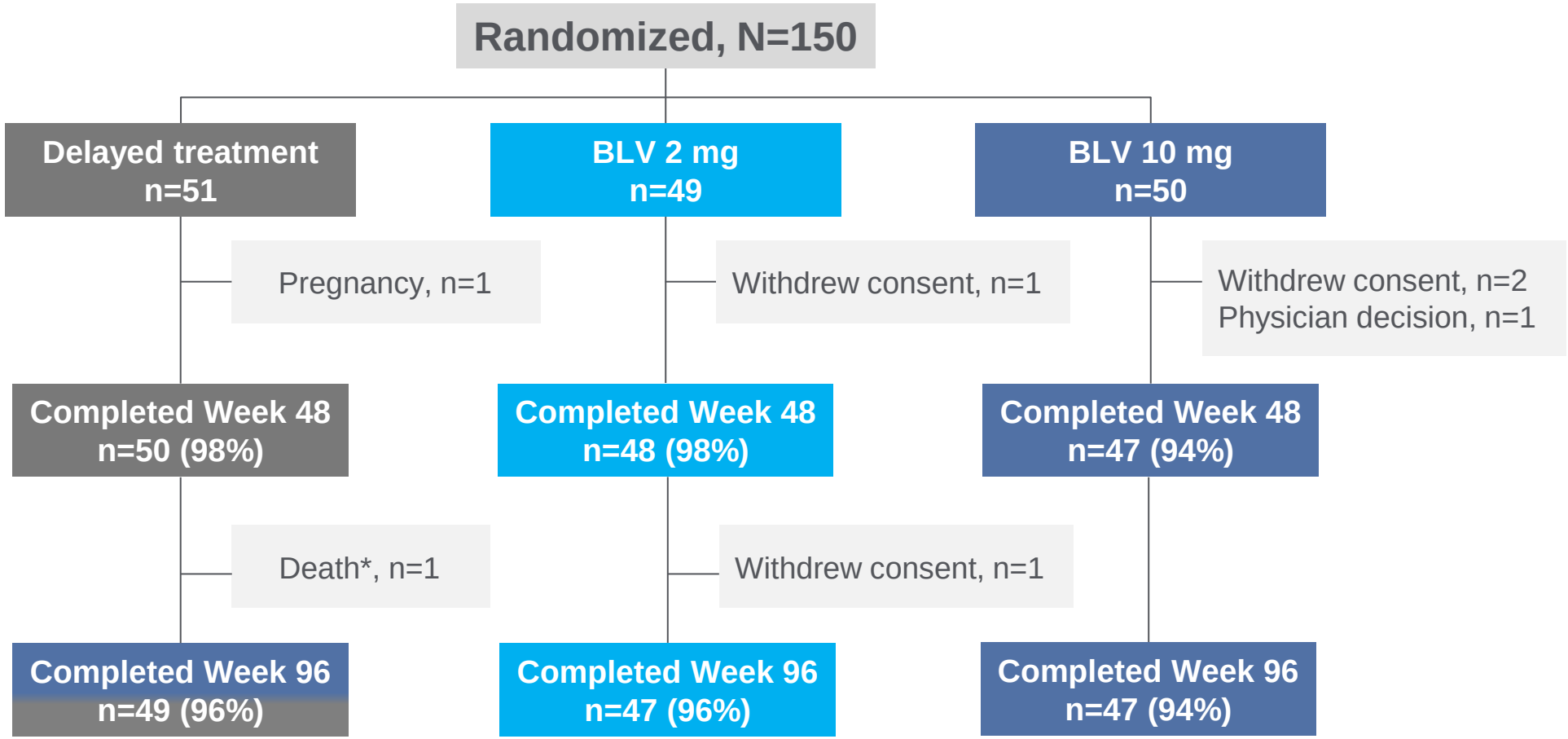
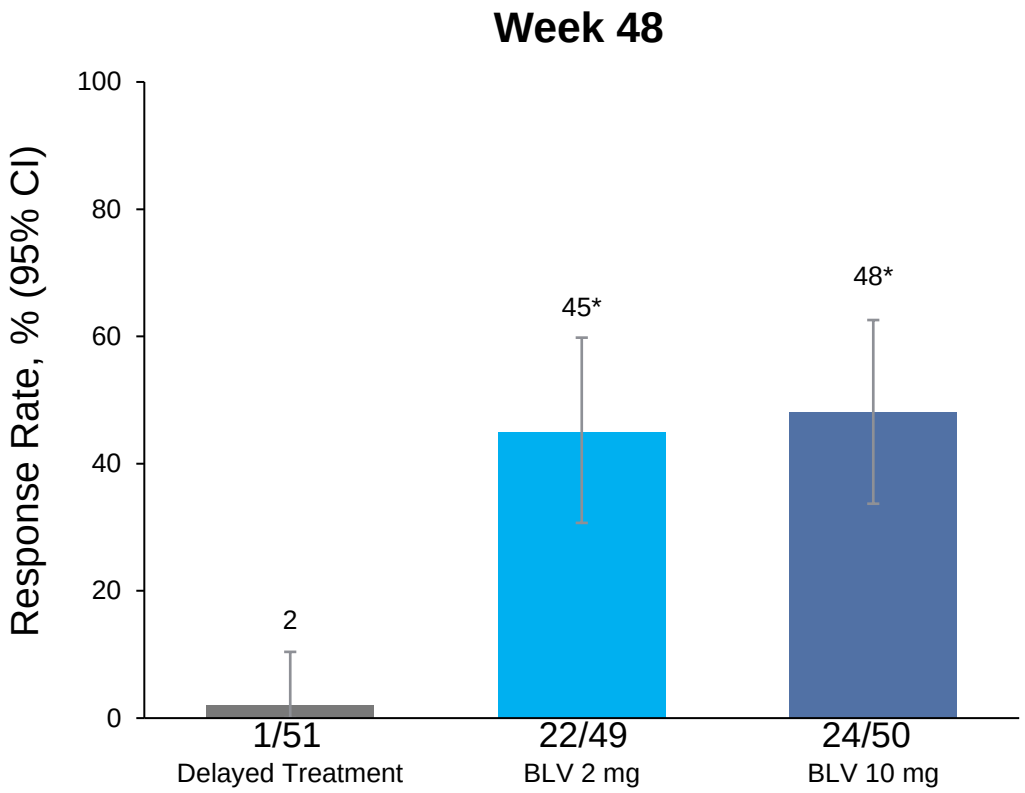
Patient Disposition



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

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

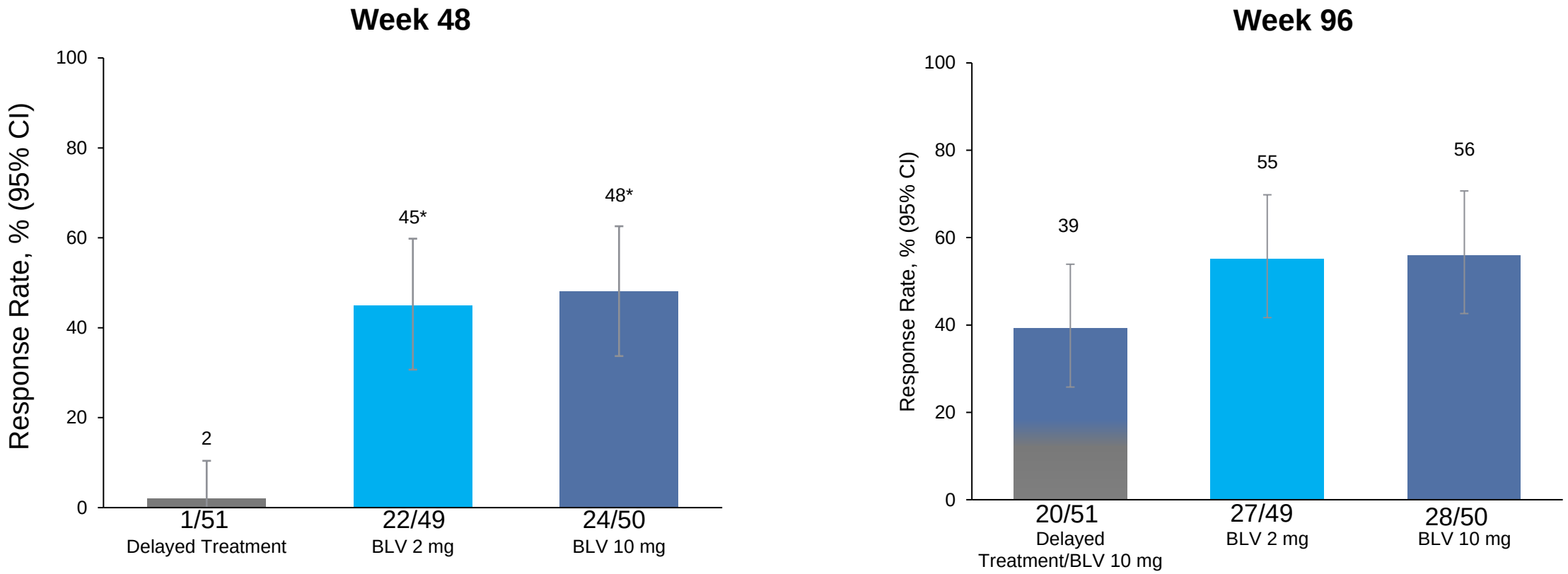
Results: Combined Response



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

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

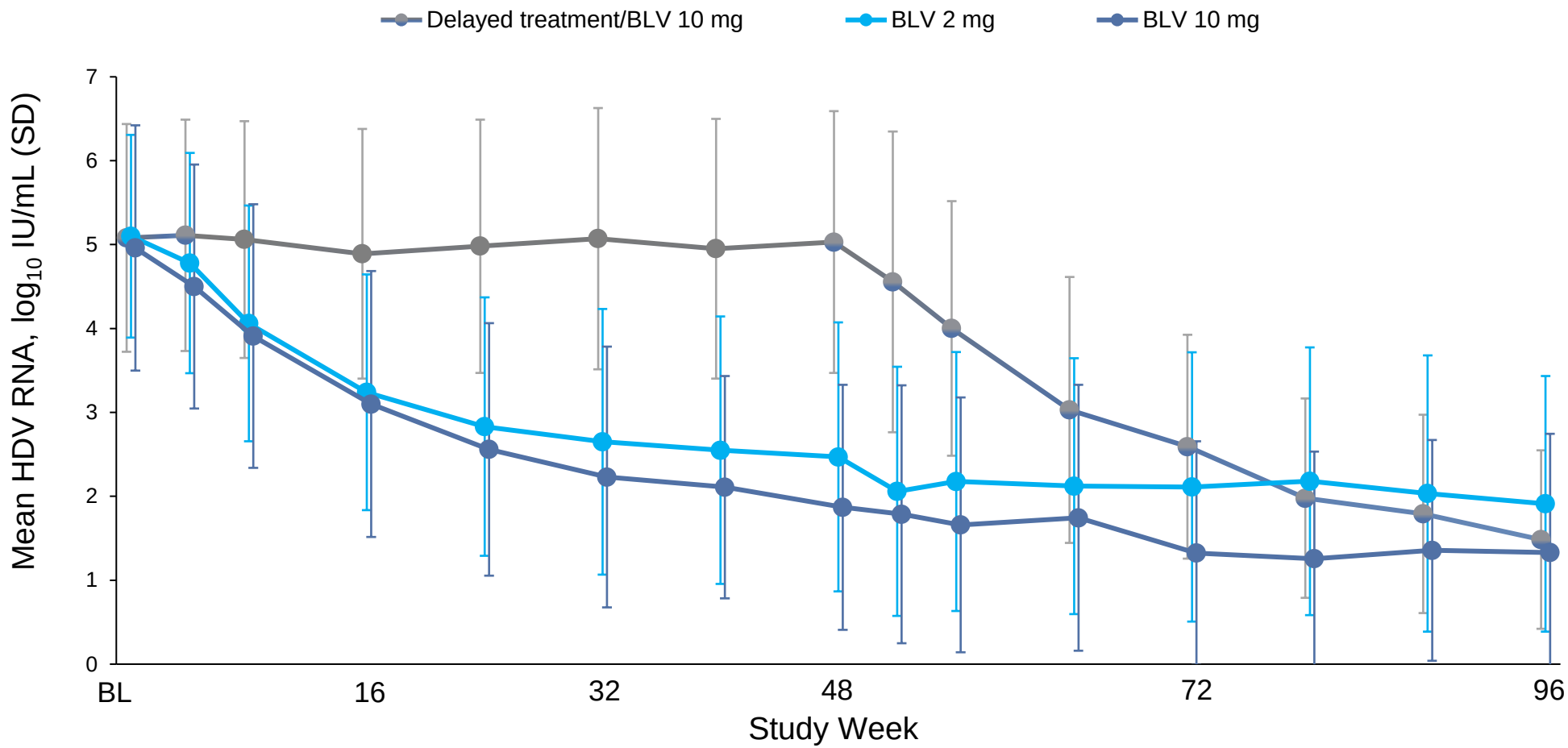
Results: Combined Response



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

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

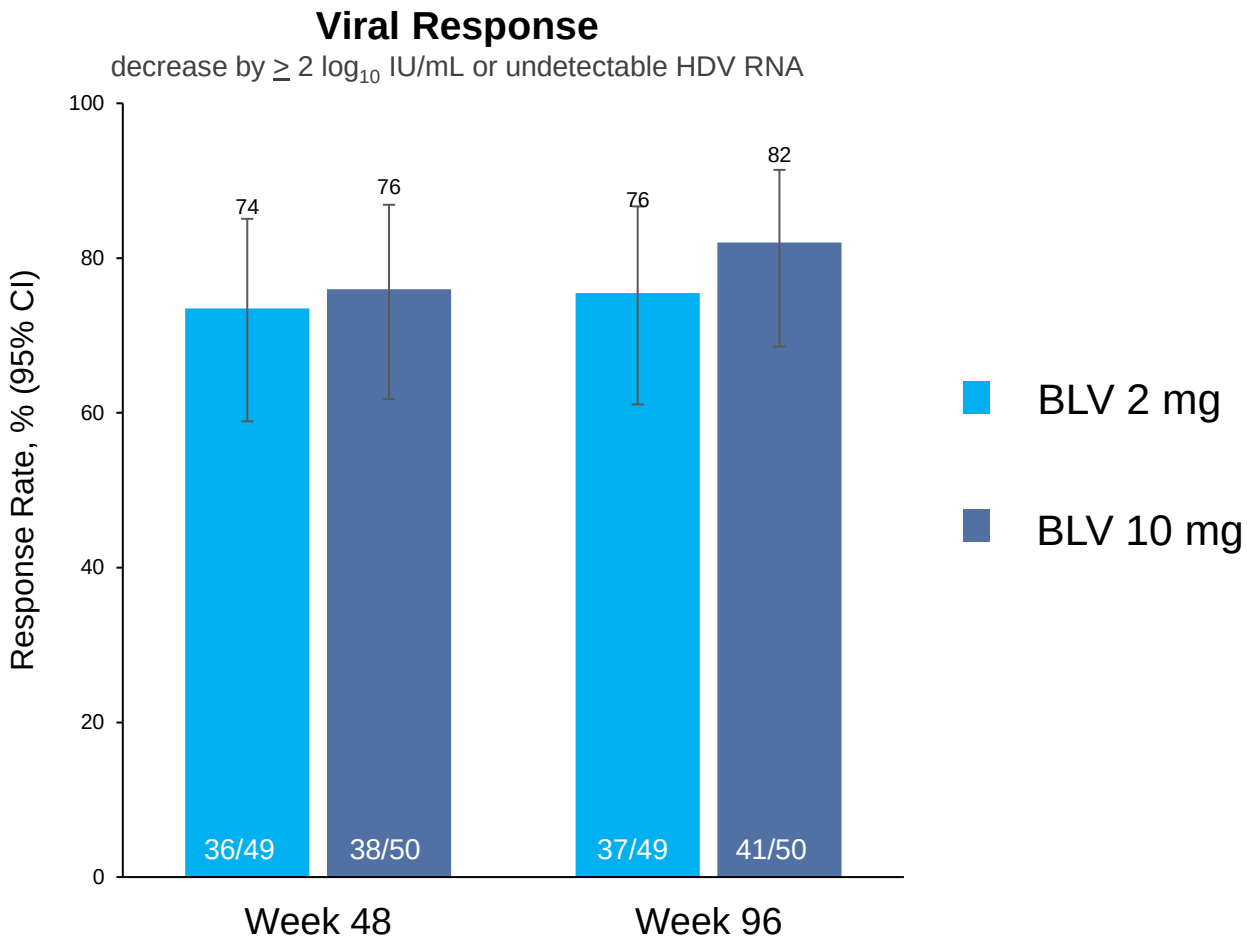
Results: HDV RNA Decline Over 96 Weeks

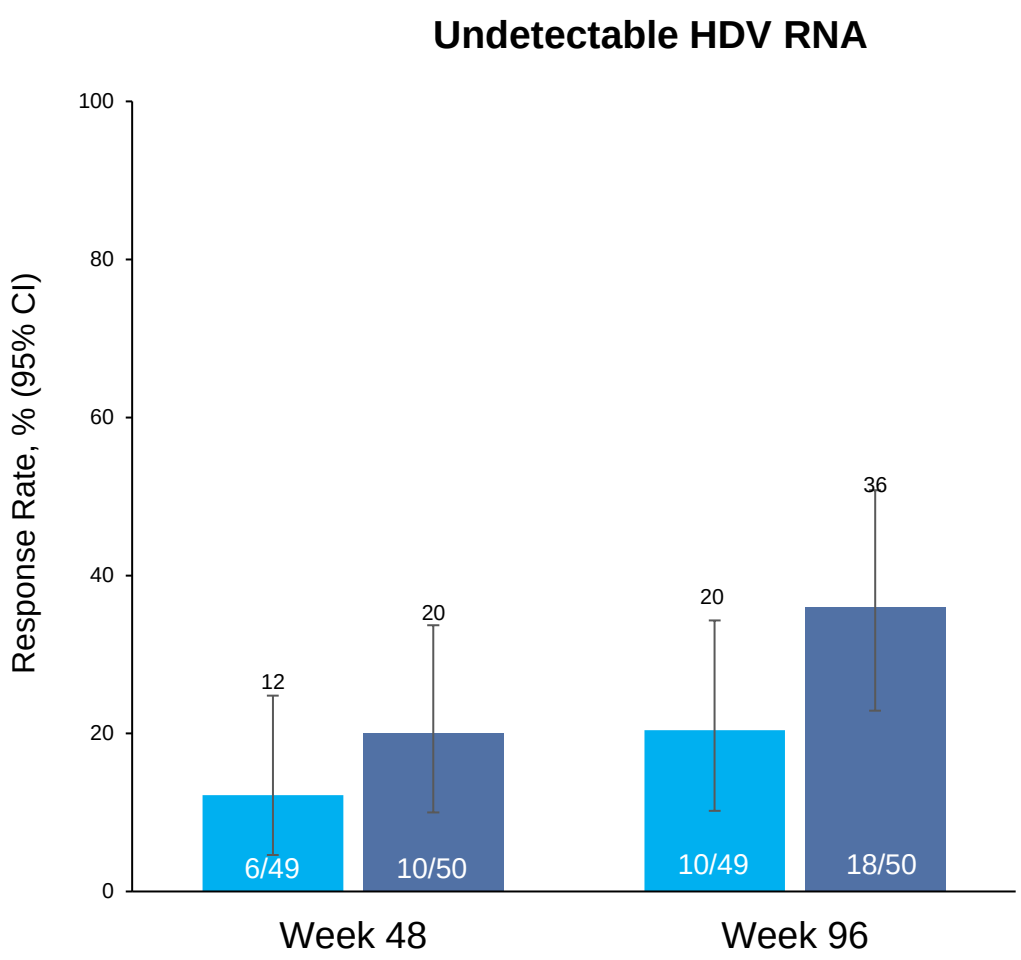


– Similar mean HDV RNA declines were seen over 96 weeks with BLV 2 mg and 10 mg

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

Results: Virologic Endpoints

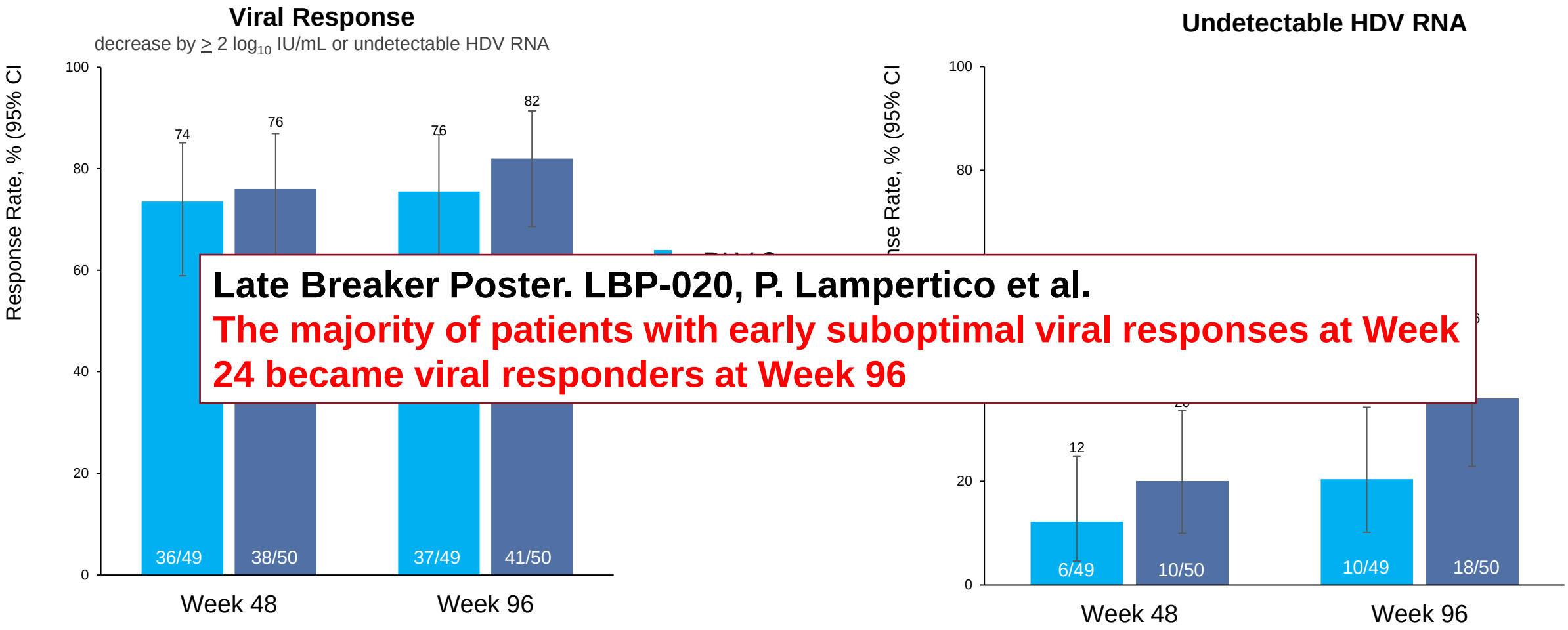




− Rates of virological response in BLV arms increased over time

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

Results: Virologic Endpoints



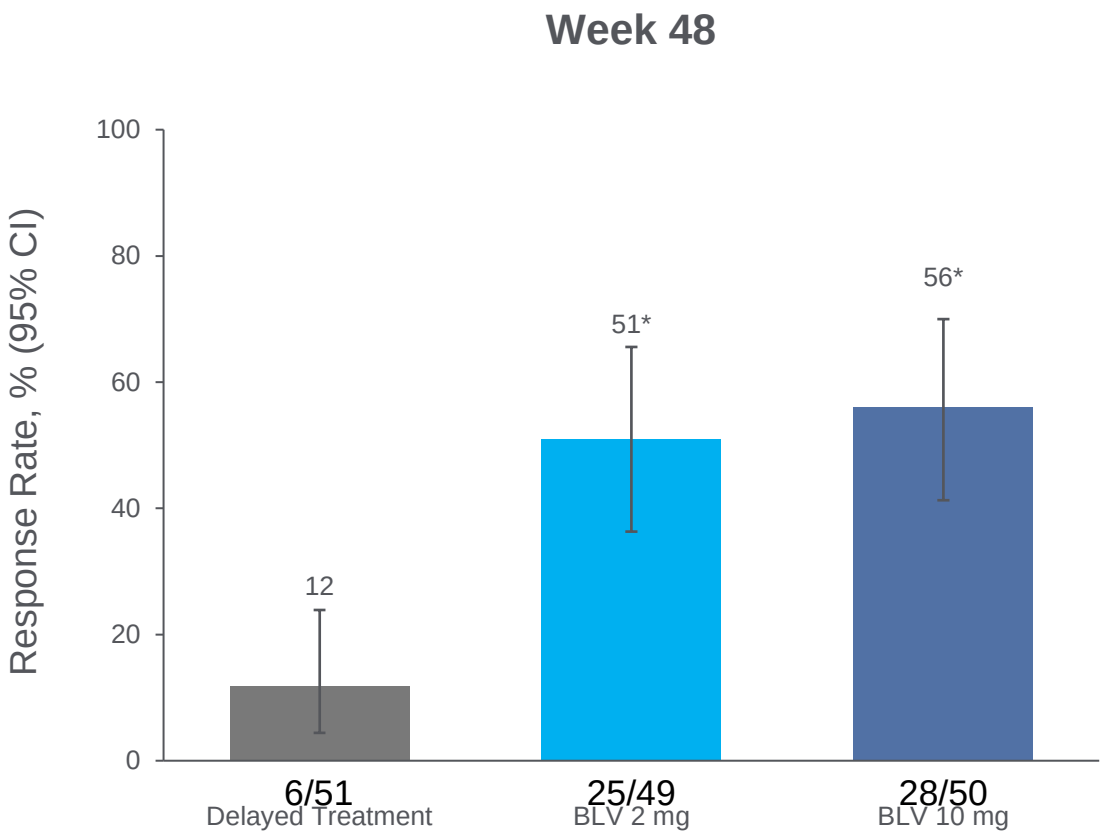
Late Breaker Poster. LBP-020, P. Lampertico et al.

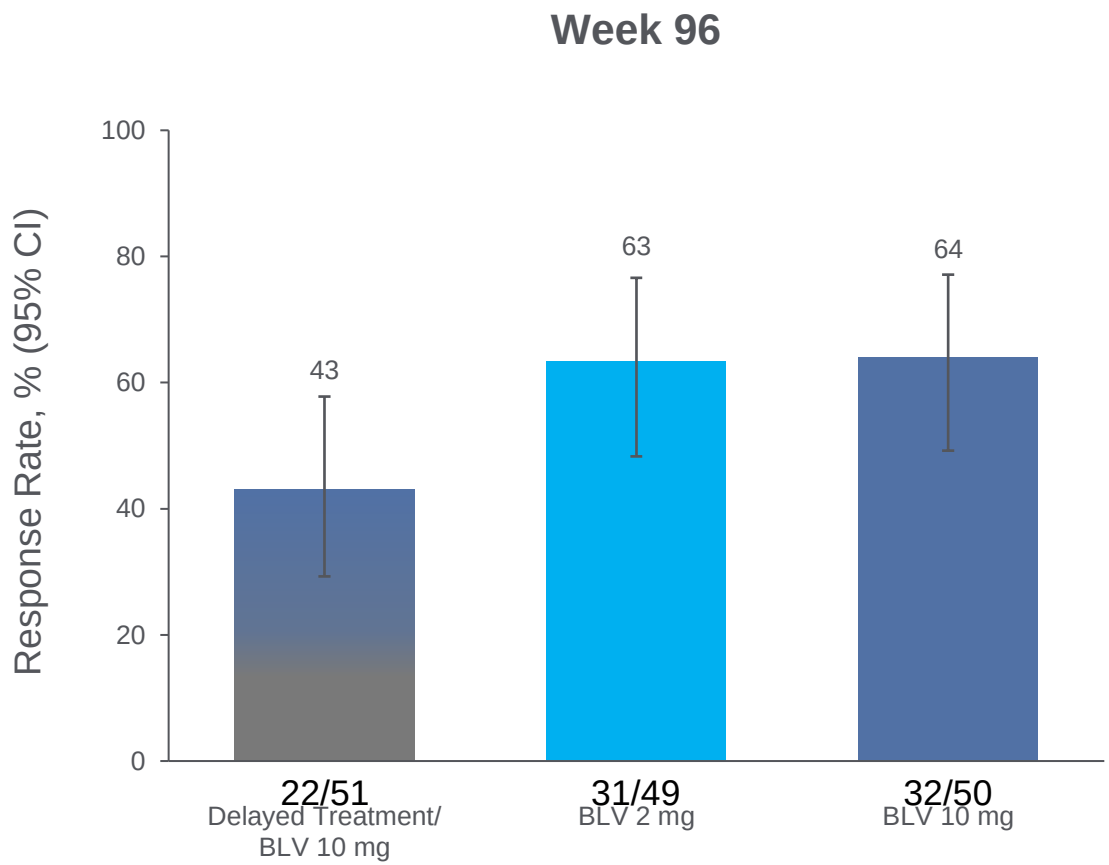
The majority of patients with early suboptimal viral responses at Week 24 became viral responders at Week 96

- Rates of virological response in BLV arms increased over time

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

Results: ALT Normalization

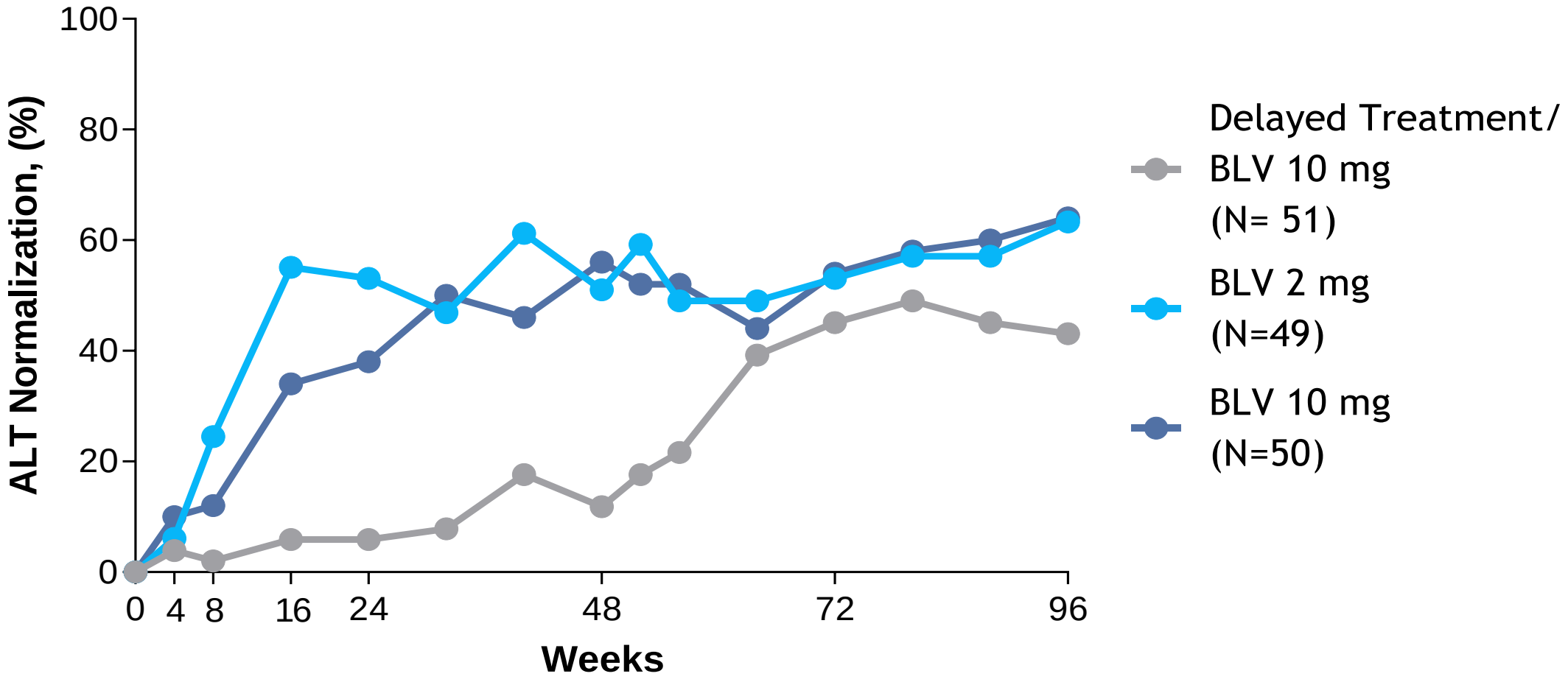




- Rates of biochemical response improved over time and were similar between doses

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

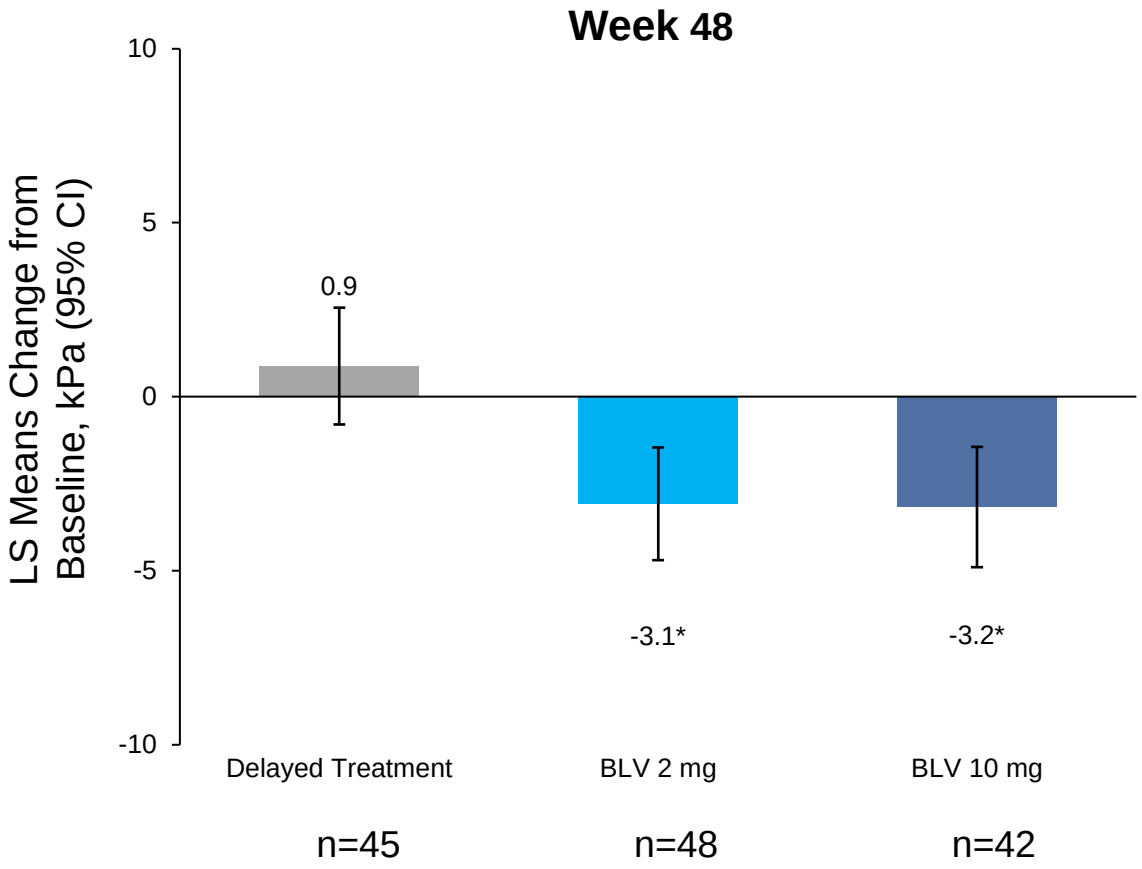
ALT Normalization Over Time

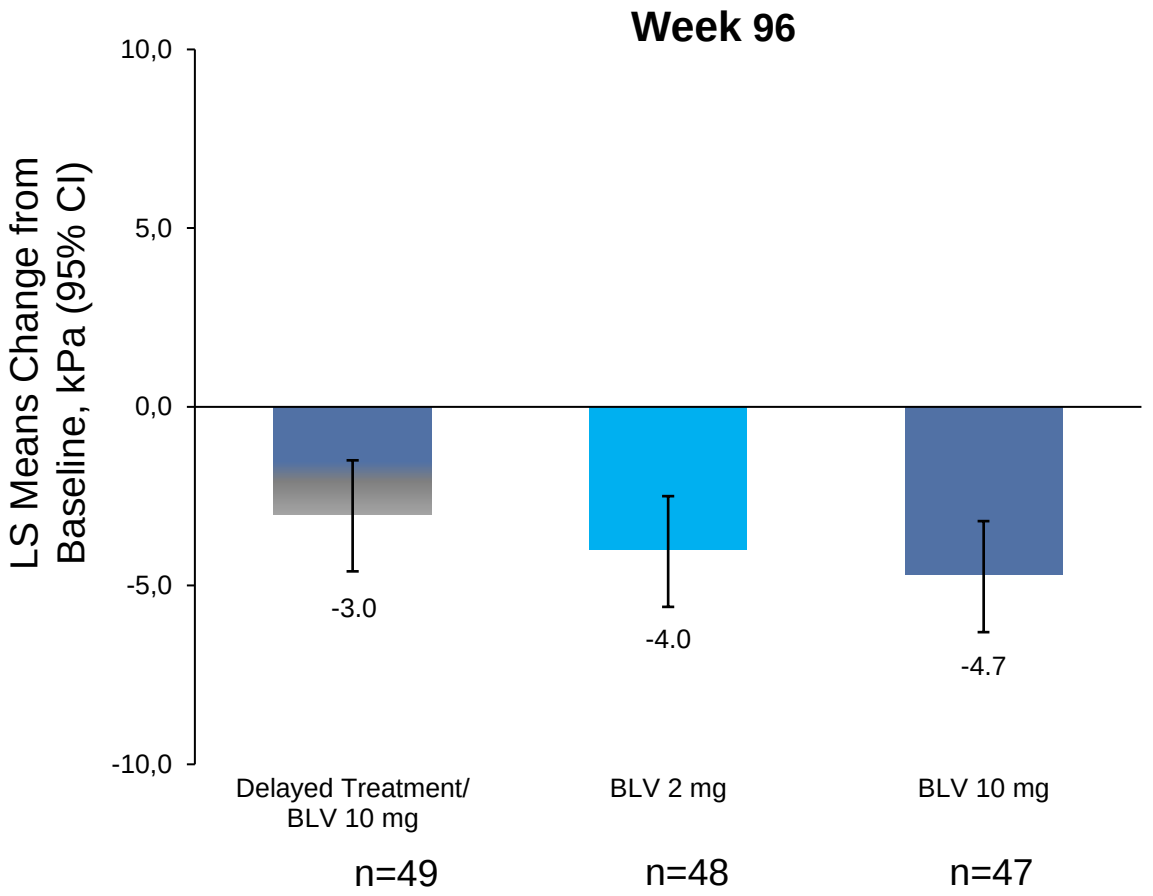


- Rates of biochemical response increased over time and were similar between doses

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

Results: Change in Liver Stiffness at Weeks 48 and 96





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

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

Results: HBV Efficacy Endpoints at Week 96

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

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

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

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		Delayed Treatment/BLV 10 mg n=51	BLV 2 mg n=49	BLV 10 mg n=50
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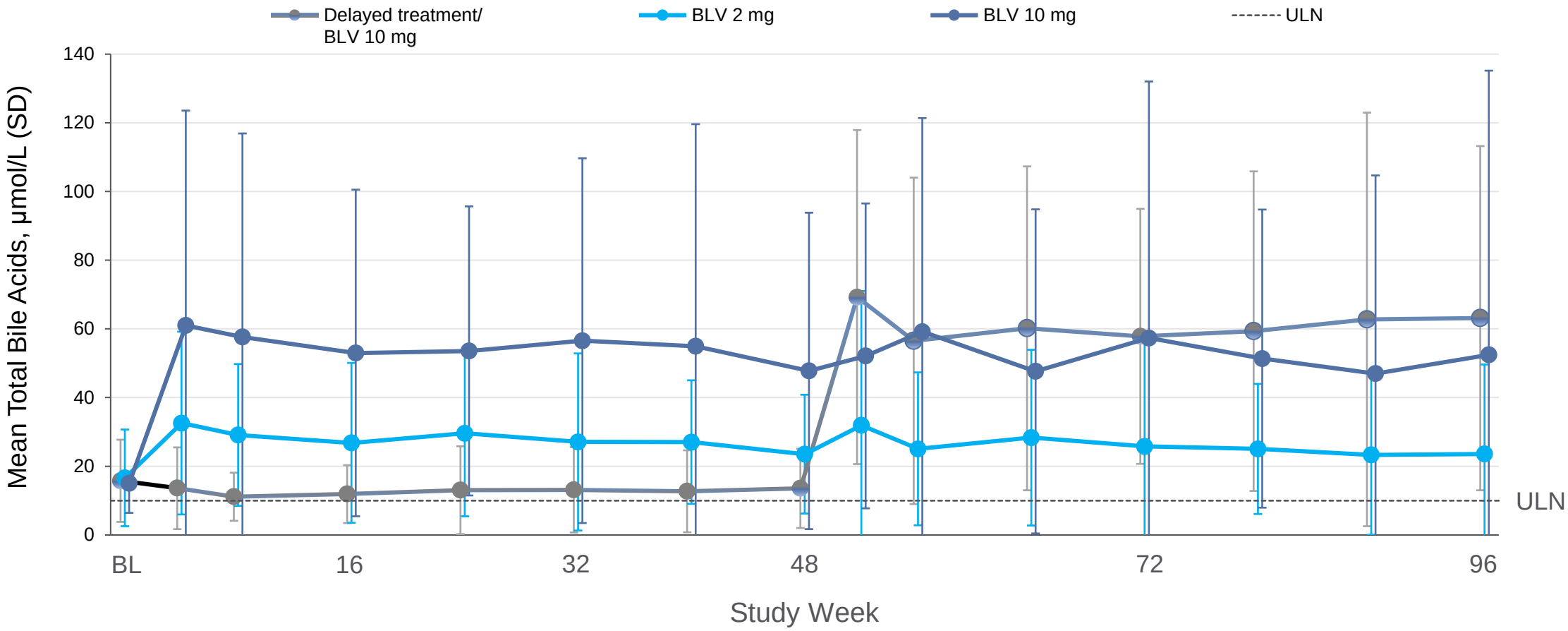
	LS mean change in HBsAg, log_{10} IU/mL (95% CI)	-0.152 (-0.277, -0.026)	-0.240 (-0.370, -0.110)	-0.139 (-0.271, -0.007)
HBV DNA	Mean change from BL in HBV DNA, log_{10} IU/mL (SD)	-0.363 (0.889)	-0.583 (1.305)	-0.599 (1.073)

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

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

Results: Total Bile Acids Levels Over 96 Weeks



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

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

Safety: Overall Summary

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

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

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

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

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

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

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

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

Safety: Serious Adverse Events

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

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Summary/Conclusions

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

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

Treatment with BLV for 96 weeks is safe and efficacious

BLV, bulevirtide; HDV, hepatitis delta virus.

Acknowledgements

We extend our thanks to the patients, their families, and all participating investigators.

This study was funded by Gilead Sciences.

Editing and production assistance were provided by Red Nucleus, New York, NY, funded by Gilead Sciences, Inc.

Bulevirtide Improves Health-Related Quality of Life Measured by EQ-5D VAS in Patients With Chronic Hepatitis Delta: An Exploratory Analysis of a Phase 3 Trial at 48 Weeks

Maria Buti[1], Heiner Wedemeyer[2], Soo Aleman[3], Vladimir Chulanov[4,5], Viacheslav Morozov[6], Olga Sagalova[7], Tatyana Stepanova[8], Robert G Gish[9], Andrew Lloyd[10], Ankita M Kaushik[11], Vithika Suri[11], Dmitry Manuilov[11], Anu O Osinusi[11], John Flaherty[11], Shubhram Pandey[12], Barinder Singh[12], Pietro Lampertico[13,14]

[1]Hospital Universitario Valle Hebron, Barcelona, Spain; [2]Medizinische Hochschule Hannover, Hannover, Germany; [3]Karolinska Universitetssjukhuset, Karolinska Institutet, Stockholm, Sweden; [4]National Medical Research Center of Tuberculosis and Infectious Diseases, Ministry of Health, Moscow, Russian Federation; [5]Sechenov University, Moscow, Russian Federation; [6]Hepatolog, LLC, Samara, Russian Federation; [7]Southern Ural State Medical University, Chelyabinsk, Russian Federation; [8]Clinic of Modern Medicine, Moscow, Russian Federation; [9]Hepatitis B Foundation, Doylestown, PA, USA; [10]Acaster Lloyd Consulting Ltd, London, UK; [11]Gilead Sciences, Inc., Foster City, CA, USA; [12]Pharmacoevidence Private Ltd, Punjab, India; [13]Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; [14]CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

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INTRODUCTION

- Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis and is associated with progression to cirrhosis, decompensation, hepatocellular carcinoma, and end-stage liver disease[1]
- In a small observational study, patients with CHD reported outcomes in several psychological and physical domains worse than those reported by patients with hepatitis B virus infection only[2]
- In 2020, the European Medicines Agency granted conditional marketing authorization to bulevirtide (BLV) 2 mg, a novel sodium taurocholate cotransporting polypeptide entry inhibitor, as the first treatment approved for CHD[3]
- The Phase 3 MYR301 trial showed that BLV administered for 48 weeks as a treatment for CHD was well tolerated and associated with significant reductions in hepatitis Delta virus (HDV) RNA and biochemical disease activity, with improvements in quality of life[4,5]

OBJECTIVE

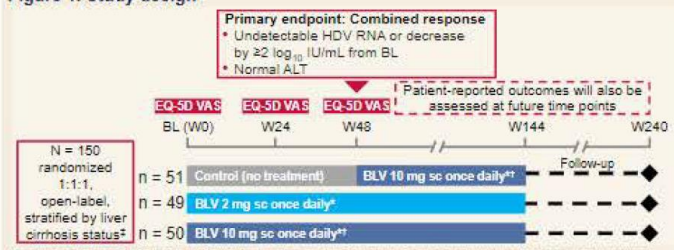
- To evaluate health-related quality of life (HRQOL) outcomes by EQ-5D visual analog scale (VAS) in patients with CHD after 48 weeks of treatment with BLV 2 and 10 mg in the ongoing MYR301 Phase 3 trial

METHODS

- MYR301 (NCT03852719; EudraCT 2019-001213-17) is a randomized, open-label, parallel-group, multicenter Phase 3 trial
  - 150 patients with CHD were assigned (1:1:1) to BLV 2 mg, BLV 10 mg, or control for up to 3 years
  - Control patients received no active anti-HDV treatment for 48 weeks, followed by 96 weeks of BLV 10 mg
- Patients completed the EQ-5D VAS at study baseline (BL), week 24, and week 48
  - The EQ-5D VAS records patients' self-rated health on a vertical VAS, the endpoints of which are labeled "the best health you can imagine" (100) and "the worst health you can imagine" (0)
  - Positive change from BL indicates improvement in patients' perception of their health
- Descriptive analyses included changes from BL to week 48 in EQ-5D VAS scores for the full analysis set
- Change from BL in EQ-5D VAS was analyzed in a mixed-effect repeated measurement model with fixed-effect factors, including treatment, region, presence of cirrhosis, and visit and treatment-by-visit interaction, with BL values as covariables

RESULTS

Figure 1. Study design



*Nucleos(t)ide analogues for treatment of underlying HDV infection were allowed if indicated by treatment guidelines. †BLV 10 mg sc once daily, a dosage that was not approved by regulators. ‡Patients with compensated liver disease up to Child-Pugh score of 7 were included. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; sc, subcutaneous; VAS, visual analog scale; W, week.

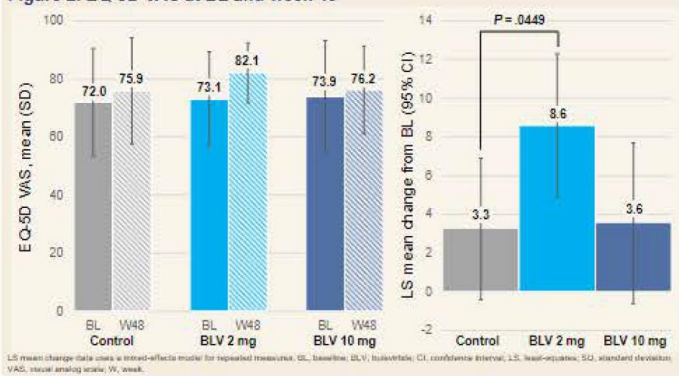
Table 1. Baseline characteristics

Baseline variables	Control n = 51	BLV 2 mg n = 49	BLV 10 mg n = 50
Age, years, mean (SD)	40.5 (7.5)	43.6 (9.0)	41.3 (8.5)
Sex, male, n (%)	26 (51)	30 (61)	30 (60)
Race, n (%)			
White	40 (78)	41 (84)	43 (86)
Asian	11 (22)	8 (16)	6 (12)
Black	0	0	1 (2)
BMI, kg/m^2, mean (SD)	25.3 (3.9)	24.4 (3.1)	25.1 (3.6)
Cirrhosis, n (%)	24 (47)	23 (47)	24 (48)
ALT, U/L, mean (SD)	101.6 (61.9)	107.9 (62.5)	123.4 (80.6)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.08 (1.36)	5.10 (1.21)	4.96 (1.46)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	0.89 (0.99)	1.28 (1.30)	1.07 (1.27)
HBeAg negative, n (%)	47 (92)	45 (92)	43 (86)
Previous IFN therapy, n (%)	29 (57)	26 (53)	29 (58)

ALT, alanine aminotransferase; BLV, bulevirtide; BMI, body mass index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; IQR, interquartile range; SD, standard deviation.

- Baseline characteristics were well balanced between groups

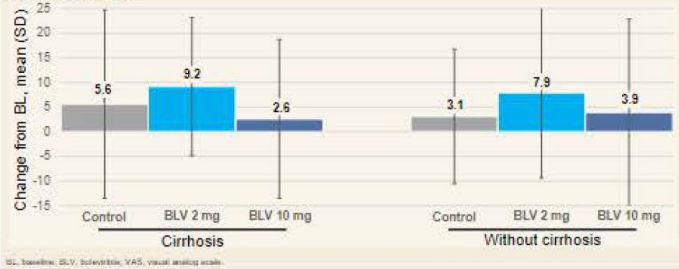
Figure 2. EQ-5D VAS at BL and week 48



LS mean change data uses a mixed-effects model for repeated measures. BL, baseline; BLV, bulevirtide; CI, confidence interval; LS, least-squares; SD, standard deviation; VAS, visual analog scale; W, week.

- Patients with CHD treated with BLV 2 mg reported statistically significant improvements from BL to week 48 in HRQOL (EQ-5D VAS)
- At week 48, change from BL was significantly greater among patients treated with 2 mg BLV compared to control (P <.05)
- Treatment with BLV 10 mg showed improvement in EQ-5D VAS scores, however, statistical significance was not reached

Figure 3. EQ-5D VAS change from BL to week 48 in patients with or without cirrhosis at BL



BL, baseline; BLV, bulevirtide; VAS, visual analog scale.

- Similar proportions of patients with and without cirrhosis showed trends toward improvement however, statistical significance was not reached

LIMITATIONS

- Limitations of this study include the open-label design and exploratory nature of this analysis

CONCLUSIONS

- Patients with CHD treated with BLV 2 mg experienced statistically significant improvements in HRQOL measured by EQ-5D VAS from BL at week 48, and this improvement was significantly greater compared to patients in the control group
- Treatment with BLV 10 mg did not show significant improvements in EQ-5D VAS scores
- The cirrhosis-specific subgroups showed similar improvement trends among patients with or without cirrhosis, however, statistical significance was not reached due to wider confidence intervals arising from the small sample size among subgroups
- Further investigation is needed to understand the long-term effects of BLV treatment

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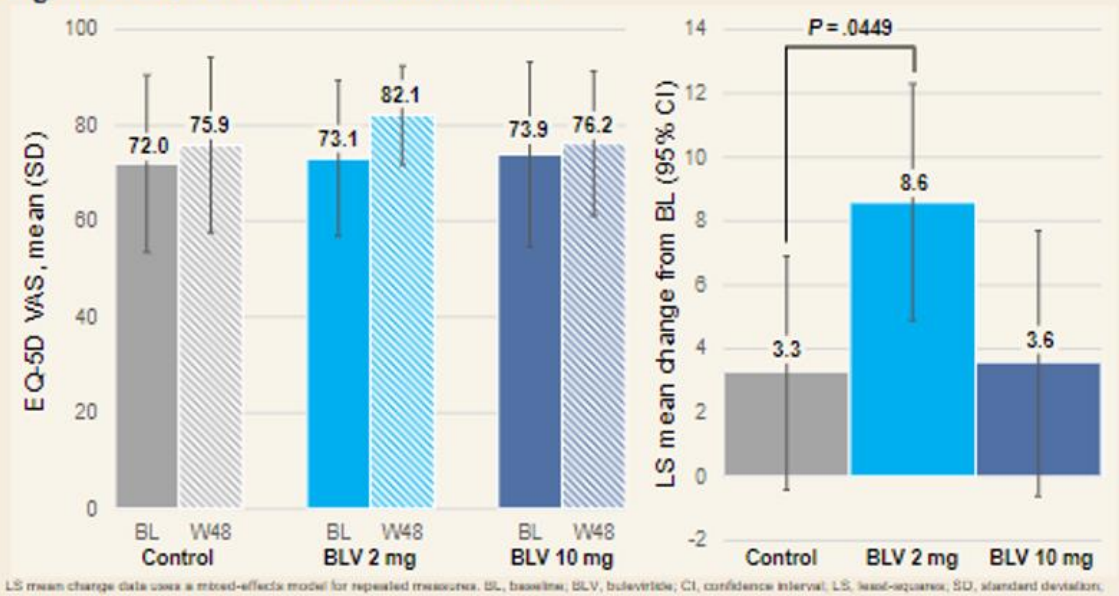
Acknowledgments: This study was funded by Gilead Sciences, Inc., Foster City, CA, USA. Medical writing and editorial support were provided by Danielle Shepherd, PhD, AlphaScientia, LLC, San Francisco, CA, USA, and funded by Gilead Sciences, Inc. Disclosures: MB declares financial relationships with Gilead Sciences, Inc., and AbbVie for speaking and teaching. HW reports Shubhra honoraria for speaking or consulting from AbbVie, BMS, Boehringer Ingelheim, Eiger, Gilead Sciences, Inc., Janssen, Merck Sharp & Dohme, MYR GmbH, Novartis, Nordic, Roche, Roche Diagnostics, Siemens, and Transgene, and research support from Abbott, BMS, Gilead Sciences, Inc., Novartis, Roche Diagnostics, and Roche. SA reports speaking honoraria from Gilead Sciences, Inc, AbbVie, Merck Sharp & Dohme, and Stiegen, and research grants from Gilead Sciences, Inc, and AbbVie. VL reports consultancy and/or speaker's bureau from Abbott, AbbVie, AstraZeneca, BMS, Gilead Sciences, Inc., GSK, Hepatera, MSD/Merck, Pharmasanclant, Roche, and Ri-Pharm. VM reports no conflicts of interest. DS reports honoraria for speaking or consulting from AbbVie, Gilead Sciences, Inc., Merck/Schering-Plough, Abbott, Pharmasanclant, and Hepatera. IS reports no conflicts of interest. MG reports grants from Gilead Sciences, Inc., consultancy and advisory for Abbott, AbbVie, Alfasigma, Antica, Arrowhead, Dynavax, Eiger, Ionis, Enyo Fibronostics, Inc., Fujifilm Wako Diagnostics, Genentech, Gentistic, Gerson Lehrman Group, Gilead Sciences, Inc., Helios, HepaLX, HepQuant, Intercept, Janssen, Merck, Pantarpeutics, Pfizer, Quest, Sonic Incytes, Topography Health, and Versatonic scientific or clinical advisory board for AbbVie, Antica, Dynavax, Enyo, Genentech, Gentistic, Gilead Sciences, Inc., Helios, HepaTX, HepQuant, Intercept, Janssen, Merck, Pfizer and Prodigy, chair clinical advisory board for Prodigy, clinical trials alliance with Topography Health, data safety monitoring board for Alfasigma, Arrowhead, CymaBay Therapeutics, Inc., and Durect, speakers bureau for AbbVie, Bristol Myers Squibb, Ionis, Genentech, Gilead Sciences, Inc., and Intercept, minor stock shareholder in HbioSciences and CoDiagstat, and stock options for AregoBiomed, Eiger, Gentistic, HepaTX, and HepQuant. AL is an employee of Acaster Lloyd Consulting Ltd, London, UK, which was contracted by sponsor for research. AK, VM, VSR, AO, and JF are employees of Gilead Sciences, Inc., and may own stock or stock options. SP and BS are employees of Pharmacoevidence and report no other conflicts of interest.

DISCLOSURES ABSTRACT COMMENT

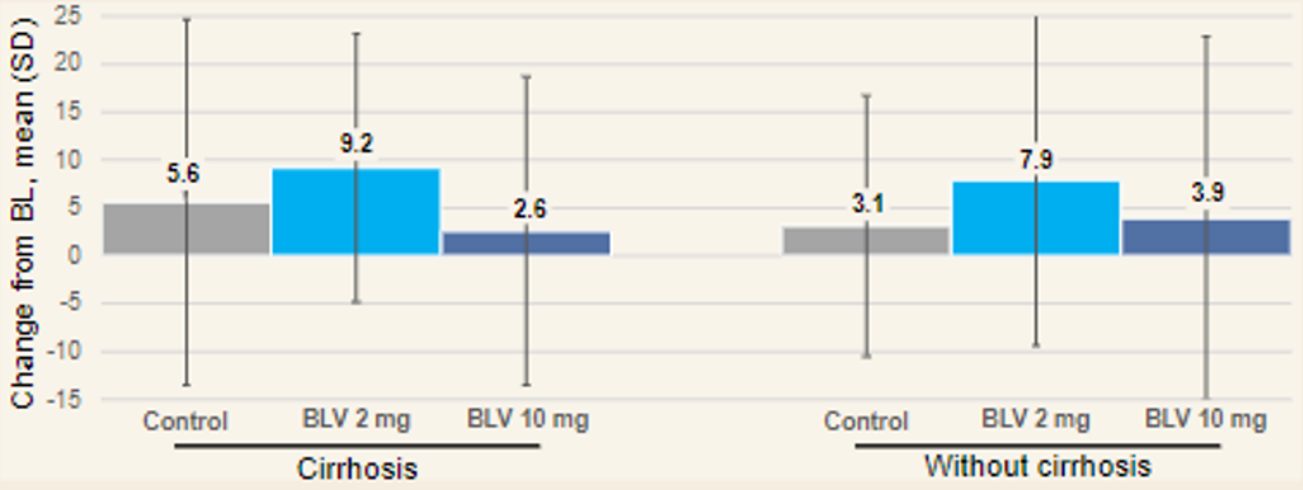
Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.

Figure 2. EQ-5D VAS at BL and week 48



LS mean change data uses a mixed-effects model for repeated measures. BL, baseline; BLV, bulevirtide; CI, confidence interval; LS, least-squares; SD, standard deviation; VAS, visual analog scale; W, week.

Figure 3. EQ-5D VAS change from BL to week 48 in patients with or without cirrhosis at BL



BL, baseline; BLV, bulevirtide; VAS, visual analog scale.

CONCLUSIONS

- Patients with CHD treated with BLV 2 mg experienced statistically significant improvements in HRQOL measured by EQ-5D VAS from BL at week 48, and this improvement was significantly greater compared to patients in the control group
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- Further investigation is needed to understand the long-term effects of BLV treatment

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EASL CONGRESS
Vienna, Austria
21–24 June 2023

VIROLOGICAL AND CLINICAL OUTCOMES OF PATIENTS WITH HDV-RELATED COMPENSATED CIRRHOSIS TREATED WITH BULEVIRTIDE MONOTHERAPY: THE RETROSPECTIVE MULTICENTER EUROPEAN STUDY (SAVE-D)

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INTRODUCTION 1

Bulevirtide (BLV) has been approved by EMA for treatment of chronic compensated hepatitis D virus (HDV) infection, however real-life data in large cohorts of cirrhotic patients are lacking.

AIM 2

To evaluate effectiveness and safety of BLV monotherapy in patients with compensated HDV-related cirrhosis treated in real-life practice.

METHOD 3

Consecutive compensated HDV cirrhotic patients starting BLV 2 mg/day since July 2019 were included in a retrospective multicenter real-life European study.

Clinical, biochemical and virological features at BLV start and during treatment were collected. Virological response (HDV RNA undetectable or ≥ 2-log decline vs. baseline), biochemical response (ALT <40 U/L), combined response (biochemical + virological) and adverse events were assessed. HDV RNA was quantified locally.

Liver-related events (hepatocellular carcinoma, decompensation, liver transplantation) were recorded.

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- Dietz-Fricke C, Tacke F, Zöllner C, et al. *Treating hepatitis D with Bulevirtide - Real-world experience from 114 patients.* JHEP Rep. 2023 doi: 10.1016/j.jhepr.2023.100686

CONCLUSIONS 6

BLV 2 mg/day monotherapy up to 96 weeks was safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses increased over time. The risk of decompensation was very low.

CONTACT INFORMATION 7

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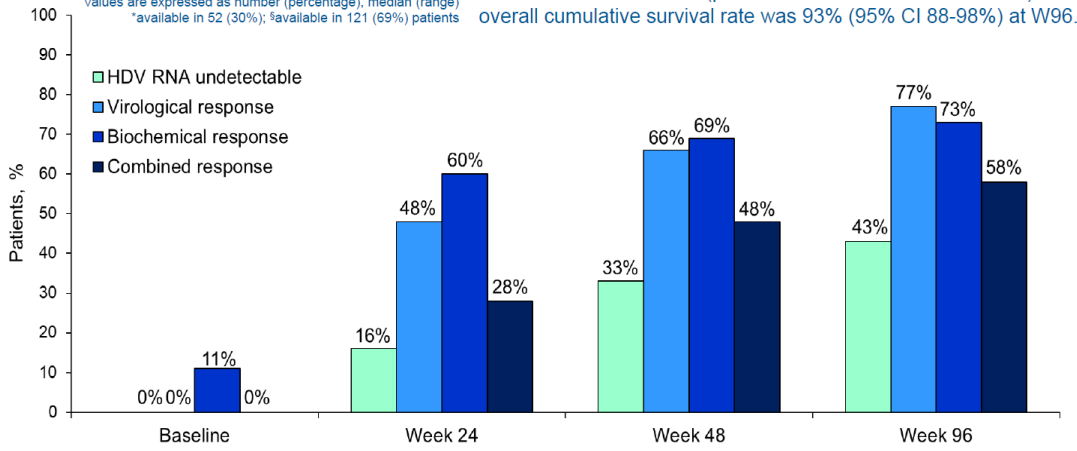
RESULTS 4

176 patients receiving BLV monotherapy up to 96 weeks [median: 48 (8-96) weeks] were included.

Variables	Overall (n=176)
Age, years	50 (19-82)
Males	104 (59%)
Caucasians	159 (90%)
HDV genotype 1*	50 (96%)
HIV-positive	15 (9%)
CPT score A	176 (100%)
Esophageal varices§	65 (54%)
Previous ascites	21 (12%)
Active HCC	11 (6%)
LSM, kPa	18.3 (6.4-75.0)
AST, U/l	78 (7-873)
ALT, U/l	77 (23-1,074)
Bilirubin, mg/dl	1.0 (0.2-4.4)
Albumin, mg/dL	3.9 (2.8-4.9)
Platelets, x10^3/mm^3	89 (17-330)
qHBsAg, LogIU/ml	3.7 (0.8-4.5)
NUC-treated	160 (91%)
HDV RNA, LogIU/ml	5.4 (1.2-8.5)

Values are expressed as number (percentage), median (range)
*available in 52 (30%); §available in 121 (69%) patients



Rates of virological, biochemical, combined response and HDV RNA undetectability are shown in **Figure 1**. Patients with <1 log HDV RNA decline *vs.* baseline declined from 25% at W24 to 18% at W48.

In the 15 HIV-positive patients, HIV-RNA persisted undetectable during treatment without significant changes in CD4 T-cell count; rates of virological response were similar to HIV-negative patients.

Bile acids significantly increased, 10% patients reported mild and transient pruritus. Injection site reactions occurred in 3% of cases; 1 patient discontinued BLV due to a grade 3 maculopapular rash with mild eosinophilia. 4 patients were lost to follow-up and 3 discontinued due to primary non response.

The W96 cumulative risk of de-novo HCC (7 cases) and decompensation (n=2 ascites, n=1 variceal bleeding) was 5.9% (95% CI 2-12%) and 2.4% (95% CI 1-5%), respectively. Six (3%) patients underwent liver transplantation (n=4 for HCC, n=2 for end-stage liver disease; BLV stopped at transplant) and 2 patients died of BLV-unrelated causes (pneumonia and intestinal infarction). The overall cumulative survival rate was 93% (95% CI 88-98%) at W96.

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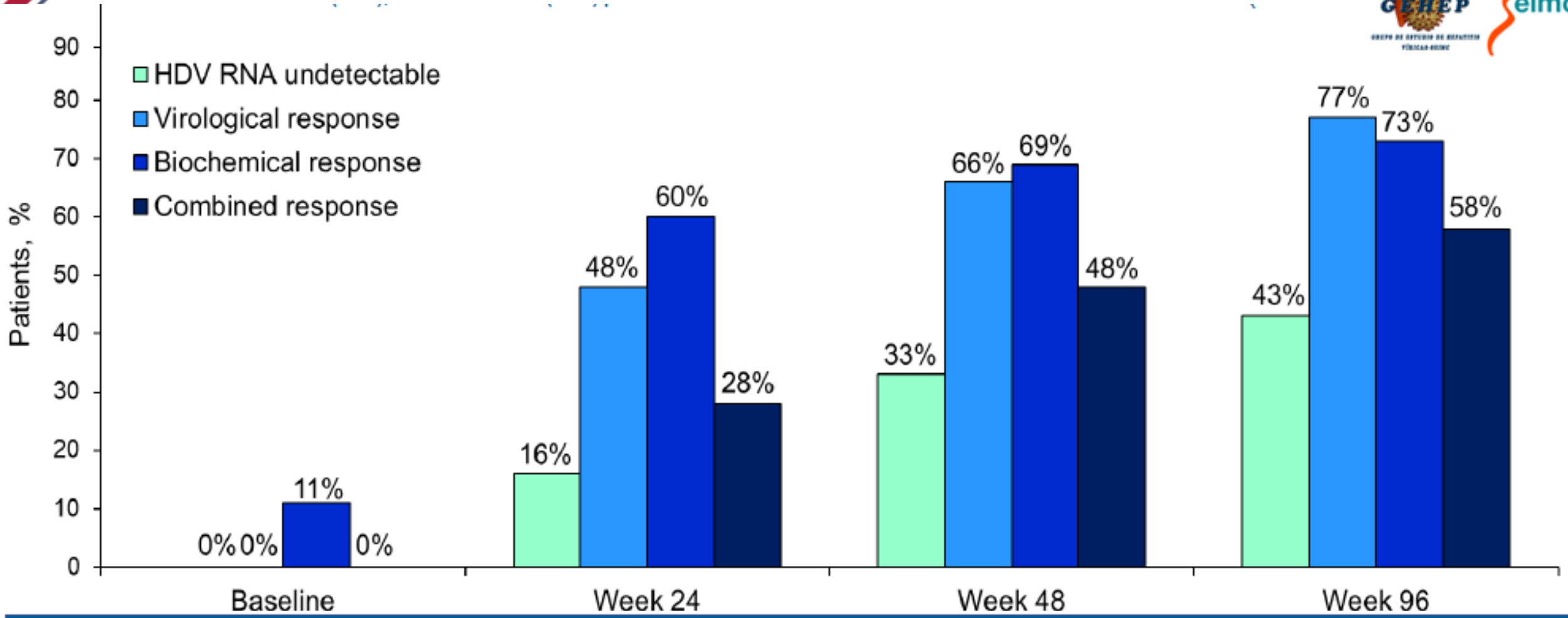

CONCLUSIONS

6

BLV 2 mg/day monotherapy up to 96 weeks was safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses increased over time. The risk of decompensation was very low.

Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.

EASL CONGRESS
Vienna, Austria
21–24 June
2023

Improvements in ALT levels during Bulevirtide treatment for hepatitis D are seen regardless of virologic response

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Hannover Medical School

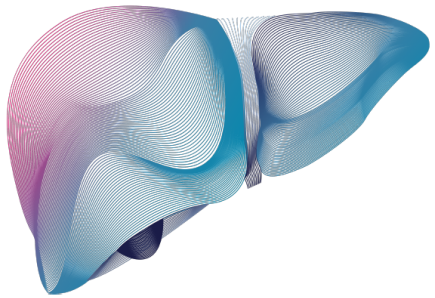
Gastroenterology
Hepatology
Infectious Diseases
Endocrinology

Key message

BLV treatment leads to an improvement in ALT levels

ALT levels also improve in cases without virologic response

Clinical benefits from BLV treatment might might be partially independent from virologic response



1 Introduction

Hepatitis D is the most debilitating form of viral hepatitis leading to liver cirrhosis and hepatocellular carcinoma. In 2020, the entry inhibitor bulevirtide (BLV) was approved for the treatment of compensated liver disease in patients with chronic hepatitis D. The conditional approval was based on promising results regarding improvements in biochemical hepatitis activity and reduction of HDV-RNA. Indeed, the FDA and EMA suggest combined endpoints of virologic and biochemical response for clinical trials. Real-world data on treatment response are critical, as patient collectives in a clinical routine setting differ from those in controlled trials.

2 Method

In a joint effort we retrospectively collected anonymized real-world data from 16 German centres treating patients with BLV for chronic hepatitis D. A total of 114 baseline cases was collected. ALT levels were considered normal when < 35 IU/l in female and < 45 IU/l in male patients. Virologic response was assumed when HDV-RNA was either undetectable, below the lower limit of quantification or had decreased by ≥ 2 log.

3 Results

We included a total of 114 patients. Viral response was reached in n=87 (76%) patients after a mean treatment duration of 23 weeks and was accompanied by a decline in ALT by 67 IU/l. In analogy to clinical trials data was analyzed in more detail at week 12 and week 24. Complete data sets were available from n=33 patients. ALT levels decreased significantly within the first 12 weeks of treatment. Interestingly, a significant decline of ALT at week 12 and 24 was also seen in cases without virologic response. Baseline ALT-levels were higher in those without virologic response at week 12 (Fig. 1a). ALT normalization was defined as a decrease below 35 IU/l for female and below 45 IU/l for male patients. Elevated ALT levels at baseline were measured in 26/33 patients. At week 12 and 24, ALT had normalized in 9/26 and 5/26, respectively. When separating cases with viral non-response at week 24 (n=5) we could show that even in these cases ALT levels improved significantly (Fig. 2). Interestingly, declines in ALT levels were accompanied by a decline in serum IgG-levels.

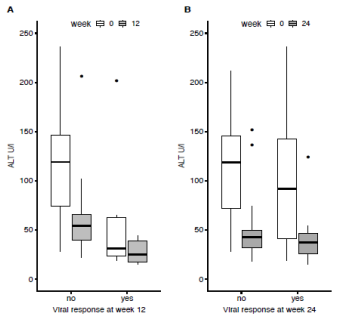


Figure 1. ALT levels at baseline and follow-up weeks grouped by viral response
Boxplots represent ALT levels at week 0 (white), week 12 (grey) and week 24 (dark grey). Outlying data points are visualized by dots. Wilcoxon signed-rank tests were used for comparison of ALT at week 0 and 12 or 24 showing a significant decline of ALT regardless of viral response.

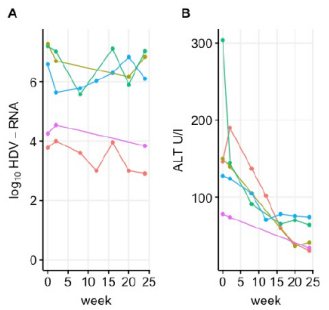


Figure 2. Improvement of ALT levels (B) in n=5 patients with viral non-response (A)
Dots and lines represent individual courses of viral load and ALT levels of patients with viral non-response defined as HDV-RNA decline < 1 log. ALT levels decrease in all of the n=5 patients.

4 Conclusions

- Improvements in biochemical hepatitis activity occur frequently under treatment with BLV
- ALT declines can be seen regardless of virologic response and can even be found in patients with virologic non-response
- Anti-inflammatory effects of BLV mediated through NTCP-blockage and protection of hepatocytes from bile acids can be discussed
- Elevated serum bile acids can influence immune cells and mediate anti-inflammatory effects
- Long-term effects of ALT improvements of clinical endpoints such as fibrosis regression need to be evaluated

5 Acknowledgements

We thank all participating institutions contributing data to this real world project.

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EASL CONGRESS 2023 Vienna, Austria 21–24 June
DOI: 10.3252/pso.eu.EASLCONGRESS.2023
Viral Hepatitis
Katja Deterding
SAT–156
EASL2023

Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.

3 Results

We included a total of 114 patients. Viral response was reached in n=87 (76%) patients after a mean treatment duration of 23 weeks and was accompanied by a decline in ALT by 67 IU/l. In analogy to clinical trials data was analyzed in more detail at week 12 and week 24. Complete data sets were available from n=33 patients. ALT levels decreased significantly within the first 12 weeks of treatment. Interestingly, a significant decline of ALT at week 12 and 24 was also seen in cases without virologic response. Baseline ALT-levels were higher in those without virologic response at week 12 (Fig. 1a). ALT normalization was defined as a decrease below 35 IU/l for female and below 45 IU/l for male patients. Elevated ALT levels at baseline were measured in 26/33 patients. At week 12 and 24, ALT had normalized in 9/26 and 5/26, respectively. When separating cases with viral non-response at week 24 (n=5) we could show that even in these cases ALT levels improved significantly (Fig. 2). Interestingly, declines in ALT levels were accompanied by a decline in serum IgG-levels.

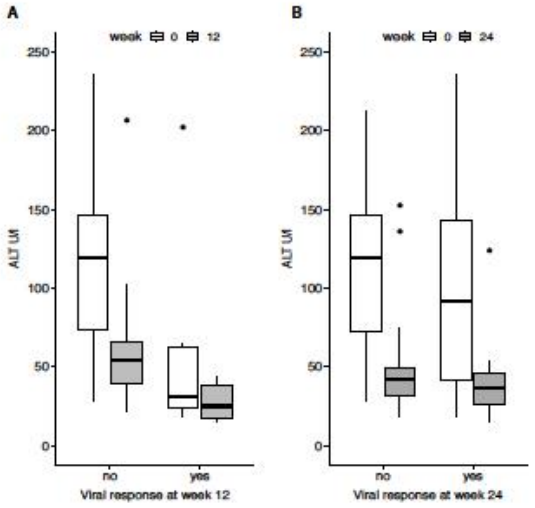
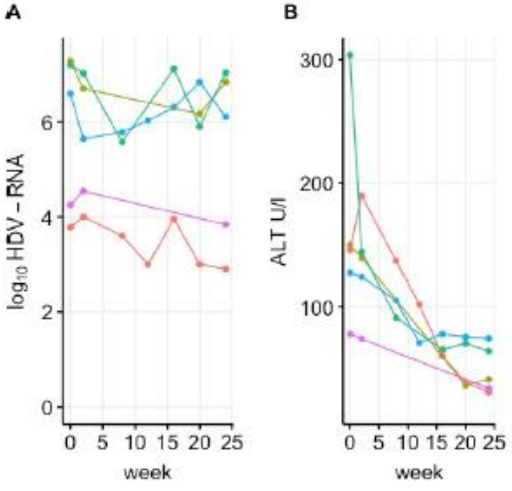


Figure 1. ALT levels at baseline and follow-up weeks grouped by viral response
Boxplots represent ALT levels at week 0 (white), week 12 (grey) and week 24 (dark grey). Outlying data points are visualized by dots. Wilcoxon signed-rank tests were used for comparison of ALT at week 0 and 12 or 24 showing a significant decline of ALT regardless of viral response.



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Continued Treatment of Early Nonresponders or Partial Virologic Responders With Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta Through Week 96 Leads to Improvement in Virologic and Biochemical Responses

LBP-020

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Key Findings

- At W24, suboptimal virologic response (NR or PR) occurred in approximately one-third of patients receiving BLV
- Of those with PR at W24, 82% (18 of 22) progressed to VR, and 77% (17 of 22) of W24 PR had biochemical response at W96 with continued BLV monotherapy
- Of those with NR at W24, 43% (6 of 14) progressed to VR at W96, and 29% (4 of 14) had biochemical response at W96 with continued BLV monotherapy

Conclusions

In CHD patients showing a suboptimal early response to BLV at W24, the majority showed progressive improvement with treatment through W96, supporting ongoing treatment with BLV

Partial virologic responders at W24 were more likely than nonresponders to achieve virologic response by W96

References: 1. Stockdale AJ, et al. *J Hepatol* 2020;73:523-532. 2. Hepcludex. European Medicines Agency SmPC. 3. Yurdaydin C, et al. *J Hepatol* 2019;70:1008-1015.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators and their corresponding site staff. This study was funded by Gilead Sciences, Inc. Writing and editorial support was provided by Danielle Shepherd, PhD, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: **PL** reports speaking and teaching fees from and participation in advisory committees or review panels for AbbVie; Aligos; Alnylam; Antios; Arrowhead; Bristol Myers Squibb; Eiger; Gilead Sciences, Inc.; GSK; Janssen; Merck Sharp & Dohme; MYR GmbH; Roche; and Spring Bank Pharmaceuticals. **HW** reports honoraria for speaking or consulting from Abbott; AbbVie; Bristol Myers Squibb; Boehringer Ingelheim; Eiger; Gilead Sciences, Inc.; Janssen; Merck Sharp & Dohme; MYR GmbH; Novartis; Novira; Roche; Roche Diagnostics; Siemens; and Transgene; and research support from Abbott; Bristol Myers Squibb; and Gilead Sciences, Inc. **MRB** declares financial relationships with Gilead Sciences, Inc., and AbbVie for speaking and teaching. **PB, TS, SZ,** and **AB** report nothing to disclose. **SC** reports speaking for Euroimmune, consultant work for Novartis, and research support from Roche and MYR GmbH. **DM, QA, AHL, BLD, JF,** and **RCM** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **MC** received honoraria from AbbVie; Falk; Gilead Sciences, Inc.; GSK; Janssen-Cilag; Merck Sharp & Dohme, Novartis, Roche, Spring Bank Pharmaceuticals, and Swedish Orphan Biovitrum. **MB** recieved research support, speaker fees, and consulting fees from AbbVie, Gilead Sciences, Inc., and Janssen. **SA** has received honoraria for lectures and educational events from Gilead Sciences, Inc., AbbVie, Merck Sharp & Dohme, and Biogen and reports grants from Gilead Sciences, Inc. and AbbVie.

Introduction

- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is conditionally approved in the EU at 2 mg/day for the treatment of chronic hepatitis delta (CHD) with compensated liver disease[2]
- In clinical studies, on-treatment virologic response (VR) to HDV therapy is defined as achieving undetectability or a ≥2 log_{10} IU/mL decline in HDV RNA from baseline (BL)[3]
- The extent of benefit from continued therapy for patients with suboptimal early virologic response requires further investigation

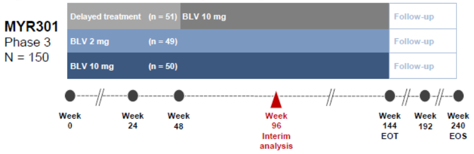
Objective

- This study aimed to evaluate whether continued therapy up to W96 results in improvement in virologic and biochemical responses among patients not achieving early VR at W24

Methods

- MYR 301 (NCT03852719) is an ongoing randomized study evaluating 3 cohorts: BLV 2 mg (Arm B) and BLV 10 mg (Arm C) to W144 and a delayed treatment arm receiving no anti-HDV therapy to W48 followed by BLV 10 mg (Arm A)
- Data from patients in Arms B and C who remained on study treatment at W96 are included in the present analysis
- No formal stopping rules were included for early nonresponse

Figure 1. MYR301 Study Design



BLV, bulevirtide; EOS, end of study; EOT, end of treatment.

- Virologic response groups were defined as follows:
  - Virologic nonresponders (NR) were defined as having an HDV RNA decline of <1 log_{10} IU/mL from BL
  - Virologic partial responders (PR) were defined as having an HDV RNA decline of ≥1 but <2 log_{10} IU/mL from BL
  - Suboptimal early virologic response was defined as NR or PR at W24
- Alanine aminotransferase (ALT) upper limit of normal: ≤31 U/L for females and ≤41 U/L for males (Russian sites) and ≤34 U/L for females and ≤49 U/L for males (all other sites)
- HDV RNA levels determined by RT-qPCR using RoboGene® HDV RNA Quantification Kit 2.0 (lower limit of quantification 50 IU/mL, lower limit of detection 6 IU/mL)
- Biochemical response (ALT within normal limits [WNL]) and change in ALT from BL were compared by response group

Results

- BL demographics and characteristics are shown in **Table 1**
- The virologic response progression for all virologic response groups at W24 (separated by BLV dose) through W48 and W96 is shown in **Table 2**
  - The proportion of PR and NR decreased over time in both BLV dosage groups
  - 38% (36 of 94) of patients included in the analysis were NR or PR at W24
  - At W96, 17% (16 of 94) of patients were NR (N = 6) or PR (N = 10)
- The virologic response progression of NR and PR (separated by BLV dose) at W24 through W48 and W96 is shown in **Figure 2**
- The mean levels and change from BL in HDV RNA and ALT by W96 among NR or PR at W24 are shown in **Table 3**

Table 1. Demographics and Baseline Characteristics by BLV Dosage

	BLV 2 mg (N = 47)	BLV 10 mg (N = 47)	Total (N = 94)
Male sex, n (%)	28 (60)	30 (64)	58 (62)
Race, n (%)			
White	39 (83)	41 (87)	80 (85)
Asian	8 (17)	5 (11)	13 (14)
Black or African American	0	1 (2)	1 (1)
Cirrhosis present, n (%)	23 (49)	22 (47)	45 (48)
HBeAg-positive, n (%)	4 (9)	7 (15)	11 (12)
Concomitant NA therapy, n (%)	32 (68)	25 (53)	57 (61)
Prior IFN therapy, n (%)	25 (53)	27 (58)	52 (55)
Genotype HDV-1, n (%)	47 (100)	45 (96)	92 (98)
HDV RNA, log_{10} IU/mL, mean (SD)	5.1 (1.2)	4.9 (1.5)	5.0 (1.3)
ALT, U/L, mean (SD)	108 (64)	128 (81)	118 (73)

ALT, alanine aminotransferase; BLV, bulevirtide; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue.

- Demographics and BL characteristics were well matched between the 2 BLV dosage groups

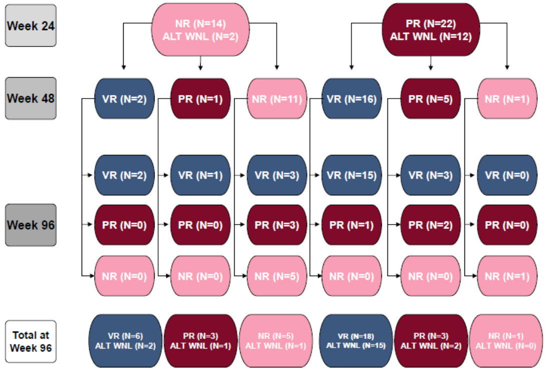
Table 2. Changes in HDV RNA Response Through W96 by BLV Dose

		BLV 2 mg (N = 47)			BLV 10 mg (N = 47)			Total (N = 94)		
		W24			W24			W24		
		NR	PR	VR	NR	PR	VR	NR	PR	VR
		N = 10	N = 12	N = 25	N = 4	N = 10	N = 33	N = 14	N = 22	N = 58
W48	NR	8 (80)	1 (8)	0 (0)	3 (75)	0 (0)	0 (0)	11 (79)	1 (5)	0 (0)
	PR	1 (10)	0 (0)	2 (8)	0 (0)	5 (50)	1 (3)	1 (7)	5 (23)	3 (5)
	VR	1 (10)	11 (92)	23 (92)	1 (25)	5 (50)	32 (97)	2 (14)	16 (73)	55 (95)
W96	NR	4 (40)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	5 (36)	1 (5)	0 (0)
	PR	3 (30)	0 (0)	2 (8)	0 (0)	3 (30)	2 (6)	3 (21)	3 (14)	4 (7)
	VR	3 (30)	11 (92)	23 (92)	3 (75)	7 (70)	31 (94)	6 (43)	18 (82)	54 (93)

Values expressed as n (%).
BLV, bulevirtide; HDV, hepatitis delta virus; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week.

- Overall, the proportion of PR and NR decreased over time in both BLV dosage groups

Figure 2. Progression of Suboptimal Responders (NR and PR) at W24 Through W48 and W96



ALT, alanine aminotransferase; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week; WNL, within normal limits.

- 43% (6 of 14) of NR at W24 and 82% (18 of 22) of PR at W24 progressed to VR at W96
- 35% (5 of 14) of NR at W24 and 5% (1 of 22) of PR at W24 were NR at W96
- 29% (4 of 14) of NR at W24 and 77% (17 of 22) of PR at W24 achieved ALT WNL at W96

Table 3. Change in Mean ALT and HDV RNA by W96 Among NR or PR at W24

	Time Point	Virologic Response Group at W24: NR (N = 14)	PR (N = 22)
HDV RNA, log_{10} IU/mL, mean (SD)	Baseline	4.4 (2.0)	5.3 (1.4)
	W24	3.8 (1.8)	3.7 (1.4)
	W48	3.6 (2.1)	2.6 (1.5)
	W96	2.8 (2.1)	1.9 (1.3)
	Change at W96	−1.6 (1.7)	−3.4 (1.3)
ALT, U/L, mean (SD)	Baseline	112 (59)	98 (64)
	W24	71 (37)	44 (26)
	W48	67 (42)	36 (14)
	W96	89 (123)	35 (24)
	Change at W96	−24 (119)	−64 (61)

ALT, alanine aminotransferase; HDV, hepatitis delta virus; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week.

- HDV RNA and ALT declines were seen by W96 among NR or PR at W24 with numerically higher declines in the PR compared to the NR subgroup
- ALT declined by >50% from BL in 5 of the 6 who remained a NR at W96, 1 ALT WNL (data not shown)

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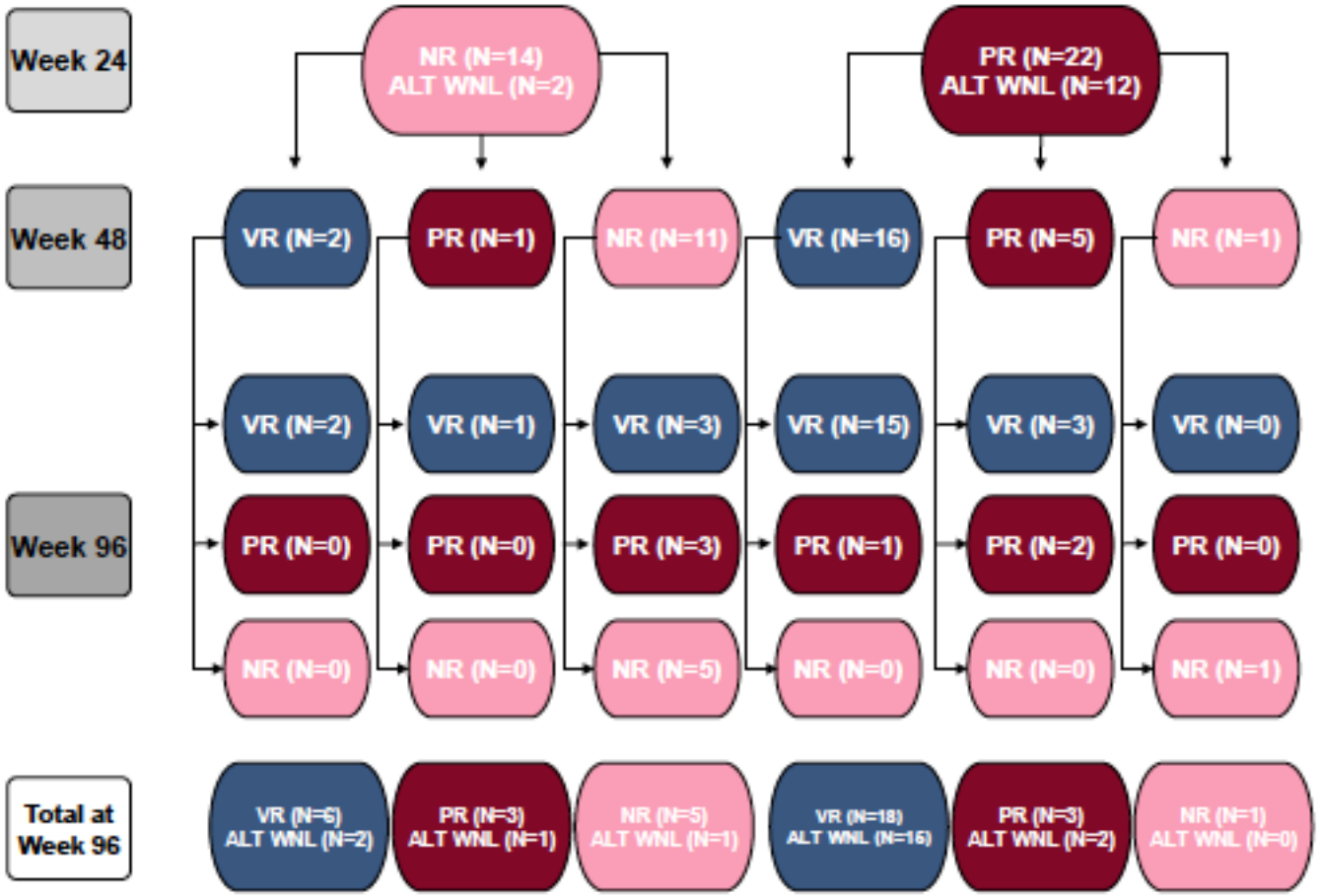

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Conclusions

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Partial virologic responders at W24 were more likely than nonresponders to achieve virologic response by W96

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Estudios en Vida Real VIH: Bulevirtide (72 semanas)

Victor de Lédinghen[1], Anne Gervais[2], Marie-Noëlle Hilleret[3], Karine Lacombe[2], Patrick Miailhes[4], Bruno Roche[2], Louis d'Alteroche[5], Jean-Pierre Arpurt[6], Isabelle Rosa[7], Antonia Le Gruyer[8], Marc-Antoine Valantin[2], Hélène Regnault[2], Véronique Loustaud-Ratti[9], Christiane Stern[2], Tarik Asselah[2], Nathalie Ganne[2], Stanislas Pol[2], Juliette Foucher[1]

[1]CHU Bordeaux, France, [2]APHP, Paris, France, [3]CHU Grenoble, France, [4]CHG Bourg en Bresse, France, [5]CHU Tours, France, [6]CHG Avignon, France, [7]CHIC Créteil, France, [8]CHG Saint-Brieuc, France, [9]CHU Limoges, France,

BACKGROUND

- Bulevirtide (BLV) is a lipopeptide inhibiting the HBV/HDV entry into the hepatocytes. Significant HDV RNA decline was observed in HBV/HDV patients who received 48 weeks of BLV in monotherapy or in combination with PEG-interferon α 2a (PEG-IFNα).
- Until now, no data has been presented in HIV/HBV/HDV co-infected patients treated with BLV.
- The aim of this analysis was to evaluate the efficacy and safety of BLV 2mg daily with or without PEG-IFN2a for 12 months in HIV co-infected patients treated in the French BLV early access program.

METHODS

- 21 patients with HIV/HBV/HDV in BLV early access program
  - compensated cirrhosis/severe fibrosis or
  - moderate fibrosis with elevated ALT levels
- Patients received BLV 2mg QD SC alone (N=14) or in combination with PEG-IFNα once weekly (N=7) according to physician's choice.
- HIV drugs regimen were TAF/FTC (in 100% of patients), and either rilpivirine (n=8), bictegravir (n=4), elvitegravir (n=4), raltegravir (n=2), darunavir (n=2) or dolutegravir (n=1).
- Per protocol (PP) analysis: Patients receiving treatment at evaluation. Intent To Treat (ITT) analysis: All patients (missing value = no response)

RESULTS

- Characteristics of patients were as follows: male 71%, mean age 48 years, cirrhosis 52%, median HDV-RNA 6.09 log10 IU/mL, median HIV-RNA 0 cp/mL (three patients had detectable HIV-RNA at day 0, all < 100 cp/mL), median CD4 558/mm3
- No specific adverse events related to BLV were reported and no HIV drug modification was needed (median CD4 at M12: 540/mm3). Only one patient had detectable HIV-RNA at M12 (31 cp/mL at baseline and 54 cp/mL at M12).
- 8 patients (38%) stopped treatment before M12: 2 adverse events unrelated to BLV (variceal bleeding, rectal cancer), 3 lost to follow-up or patient decision, 3 no response according to the physician).
- From baseline, mean HDV RNA (log10 IU/mL) declined overtime: M3 -2.25, M6 -4.09, M9 –3.37, and M12 -4.19.

RESULTS

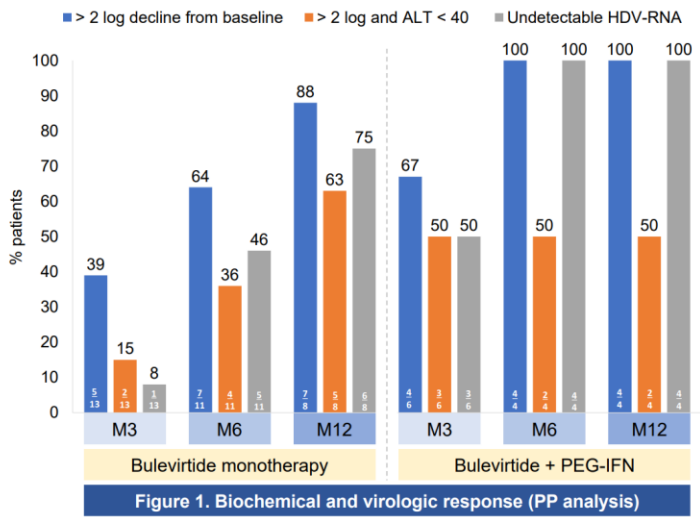

Figure 1. Biochemical and virologic response (PP analysis)

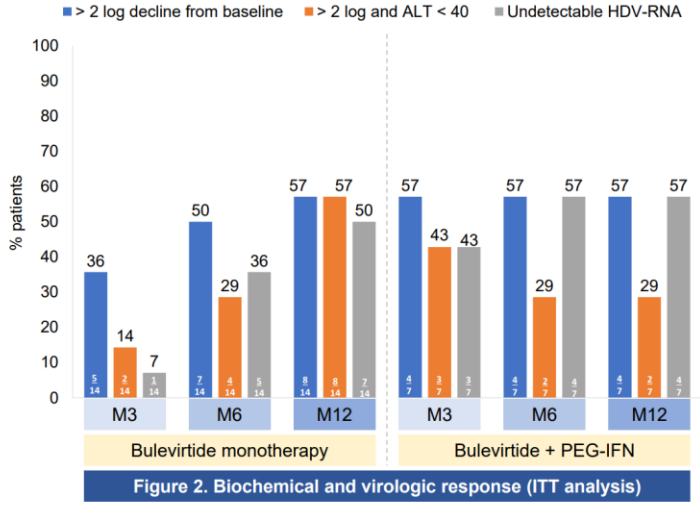

Figure 2. Biochemical and virologic response (ITT analysis)

Biochemical and virological responses gradually increased over time in patients treated by bulevirtide monotherapy.

CONCLUSIONS

- In this first real-world cohort of HIV/HBV/HDV patients, daily administration of BLV 2 mg for 12 months was safe and well tolerated with no impact on CD4, HIV viral suppression or HIV treatment regimen
- Strong HDV antiviral and biochemical responses were observed in real-life irrespective of the BLV regimen administered.

ADDITIONAL KEY INFORMATION

- Gilead collaborative study

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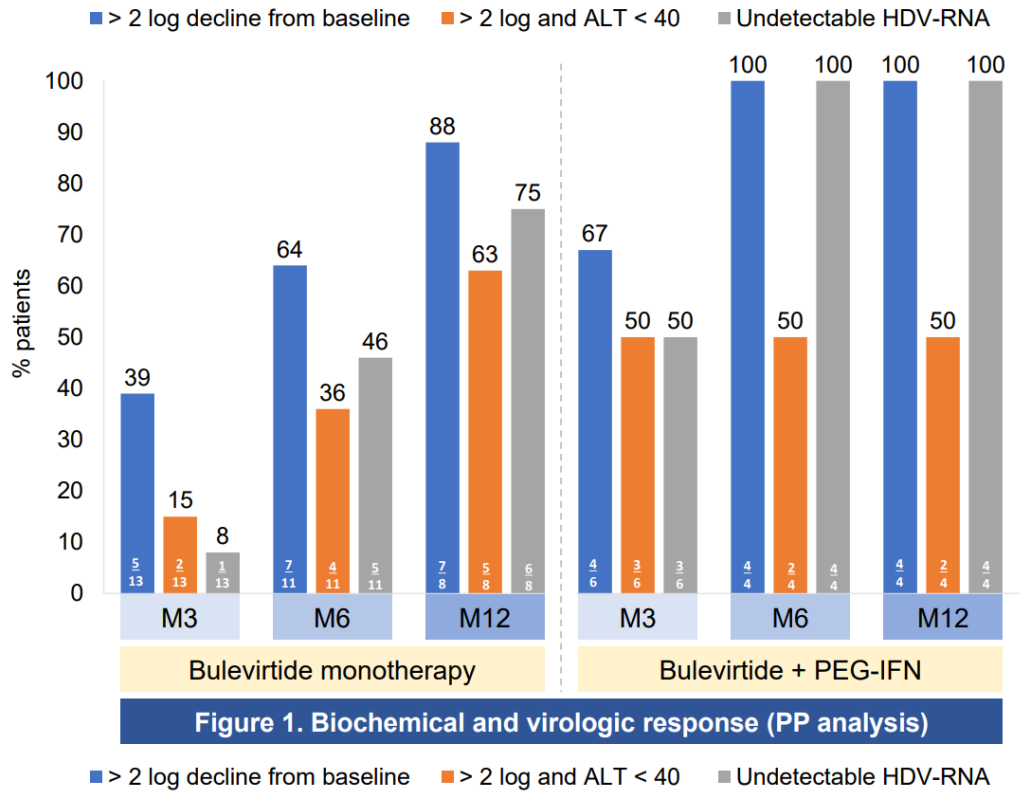
Estudios en Vida Real VIH: Bulevirtida (72 semanas)



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48 CONGRESO ANUAL ASOCIACIÓN ESPAÑOLA PARA EL ESTUDIO DEL HÍGADO
MARZO 2023 15|16|17 MADRID

Experiencia inicial en práctica clínica con Bulevirtide en pacientes con hepatitis crónica D en España

M Buti (1,2) | M Ballester (3) | MJ Devesa (4) | J Flores (5) | M García-Eliz (6) | M Pérez (7) | M Ríos (5) | A Sardiña (8) | M Siles (9) | C Vinaixa (6) | M Berenguer-Haym (2,6)

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Introducción y Objetivos

La hepatitis crónica D en nuestro país afecta a aproximadamente el 6% de los portadores del HBsAg y se asocia a una elevada progresión a cirrosis hepática y cáncer hepático. El Bulevirtide (BLV) es un inhibidor de la entrada del VHB y el VHD, y fue condicionalmente aprobado por la EMA en Julio del 2020.

Objetivo: analizar los primeros casos de hepatitis delta tratada con BLV en nuestro país desde que está disponible en algunos hospitales.

Métodos

En total se han incluido 9 pacientes con hepatitis crónica D tratados con BLV 2 mg al día durante más de 6 meses. Se analizaron distintas respuestas al tratamiento:

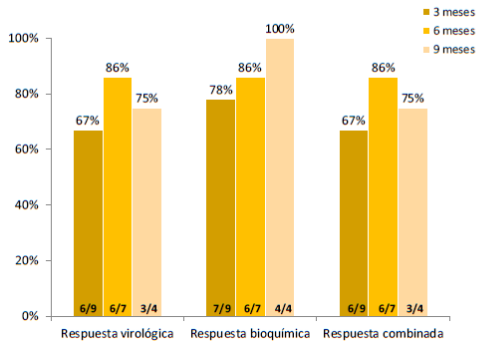
- Respuesta virológica, definida por la caída de ≥2 log en los valores de ARN-VHD o por debajo del límite de cuantificación o de detección
- Respuesta bioquímica, definida por valores normales de ALT
- Respuesta combinada, definida por la asociación de las dos anteriores

Resultados

Nueve pacientes se incluyeron en total, y la duración media de tratamiento con Bulevirtide 2mg fue de 8.7 meses.

Tabla 1. Características basales al inicio del tratamiento con BLV

Mujeres, n(%)	6 (66%)
Caucásicos, n(%)	6 (66%)
Edad media, años	54.77
ALT elevadas, n(%)	9 (100%)
Cirrosis hepática, n(%)	9 (100%)
Tratados previamente con IFN, n(%)	7 (78%)
Tratados con NUC, n(%)	7 (78%)
ADN-VHB detectable, n(%)	0 (0%)
ARN-VHD detectable, n(%)*	9 (100%)



En un paciente que continuaba con ALT y valores de ARN-VHD elevados se interrumpió el tratamiento por falta de respuesta a los 9 meses.

La tolerancia fue buena y no se observaron descompensaciones de la enfermedad hepática ni desarrollo de carcinoma hepatocelular.

Limitaciones: La determinación de ARN-VHD fue cualitativa en 5 casos y cuantitativa en 4 casos, por distintas técnicas in-house PCR. La utilización de diferentes técnicas cuantitativas y cualitativas no permite un análisis más exhaustivo de los resultados.

Conclusiones

Los resultados preliminares en pacientes con hepatitis D y cirrosis hepática compensada muestran que el tratamiento con BLV fue bien tolerado y la eficacia fue similar a la reportada en estudios de otros países europeos.

Medicamento aprobado por la Comisión Europea y sin financiación y precio en España.

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48 CONGRESO ANUAL
ASOCIACIÓN ESPAÑOLA PARA EL ESTUDIO DEL HÍGADO

MARZO 2023
15 | 16 | 17
MADRID

FEEH AEEH

Experiencia inicial en práctica clínica con Bulevirtide en pacientes con hepatitis crónica D en España

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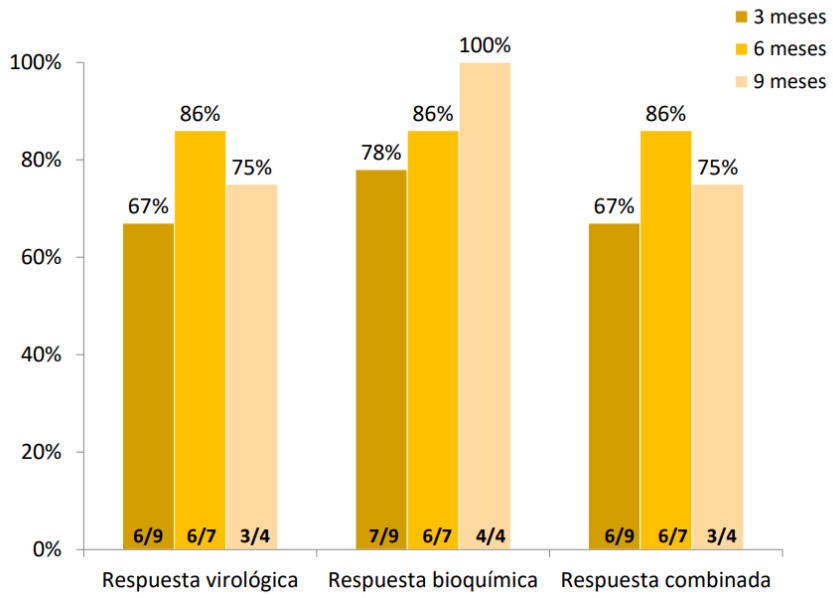
Nueve pacientes se incluyeron en total, y la duración media de tratamiento con Bulevirtide 2mg fue de 8.7 meses.

Tabla 1. Características basales al inicio del tratamiento con BLV	
Mujeres, n(%)	6 (66%)
Caucásicos, n(%)	6 (66%)
Edad media, años	54.77
ALT elevadas, n(%)	9 (100%)
Cirrosis hepática, n(%)	9 (100%)
Tratados previamente con IFN, n(%)	7 (78%)
Tratados con NUC, n(%)	7 (78%)
ADN-VHB detectable, n(%)	0 (0%)
ARN-VHD detectable, n(%)*	9 (100%)



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Los resultados preliminares en pacientes con hepatitis D y cirrosis hepática compensada muestran que el tratamiento con BLV fue bien tolerado y la eficacia fue similar a la reportada en estudios de otros países europeos

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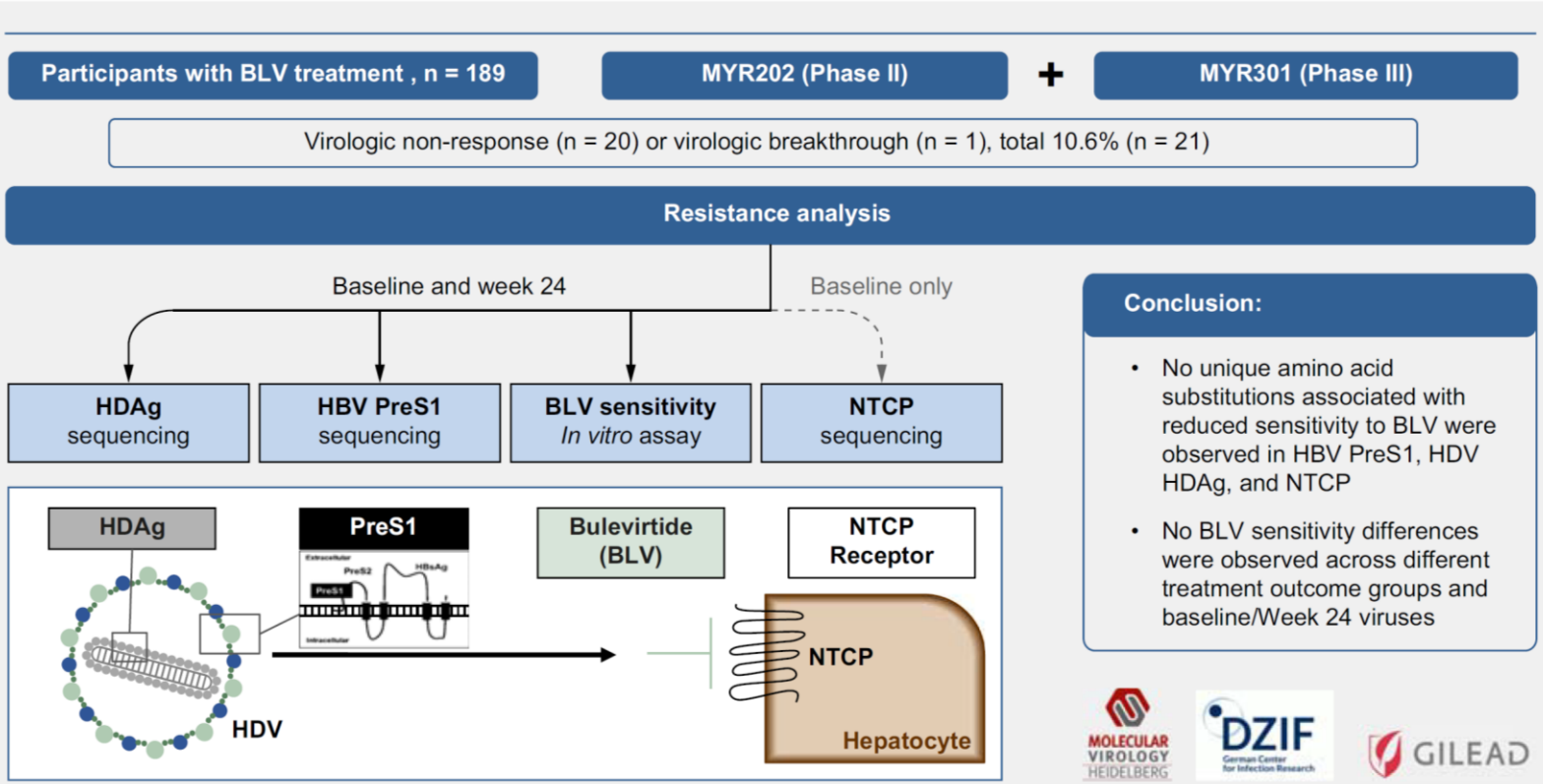
Resistencia a Bulevirtida

Graphical abstract



Highlights

- Baseline variants in HBsAg, HDAg, or *NTCP* are not associated with treatment outcome.
- Treatment-emergent variants are rare and not associated with bulevirtide resistance.
- Clinical isolates from non-responders are sensitive to bulevirtide *in vitro*.

Impact and Implications

This is the first study investigating the development of resistance in patients treated with BLV. Excluding resistance to BLV as an explanation for an insufficient decrease in HDV-RNA levels during BLV therapy is an important finding for patients, clinicians, and researchers. It demonstrates that BLV has a high barrier to resistance, indicating it is safe and suitable for long-term treatment, although long-term surveillance for resistance should be performed. Our results hint at other still unknown mechanisms as an explanation for the persistence of serum HDV-RNA during inhibition of viral entry.

Journal of Hepatology 2023. vol. 79 j 657–665

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CONCLUSIONES

- Es necesario conocer la incidencia real de Hepatitis delta en nuestro país.
- El curso de la hepatitis delta, es muy agresivo con desarrollo de cirrosis, hepatocarcinoma e incluso trasplante hepático, lo que hace necesario un diagnóstico temprano.
- Se debe realizar el diagnostico en un solo paso como ocurre en la hepatitis C.
- El único tratamiento autorizado para el tratamiento de la Hepatitis delta es la bulevirtida.
- Se hace necesario explorar los nuevos tratamientos que están en marcha con ensayos clínicos, para la Hepatitis delta


GRACIAS!!!