Nuevos tratamientos para la hepatitis B y Delta.

Dra. María Buti.

Servicio de Hepatología. Hospital Universitario Vall d'Hebron. Barcelona.

What does HBV cure mean?

Functional Cure

Clinical resolution sustained off therapy

- No inflammation: normal ALT and liver biopsy
- HBsAg loss
- HBsAb gain

Currently achievable in only a few patients

Complete Cure

Virological cure

- Clinical resolution sustained off therapy

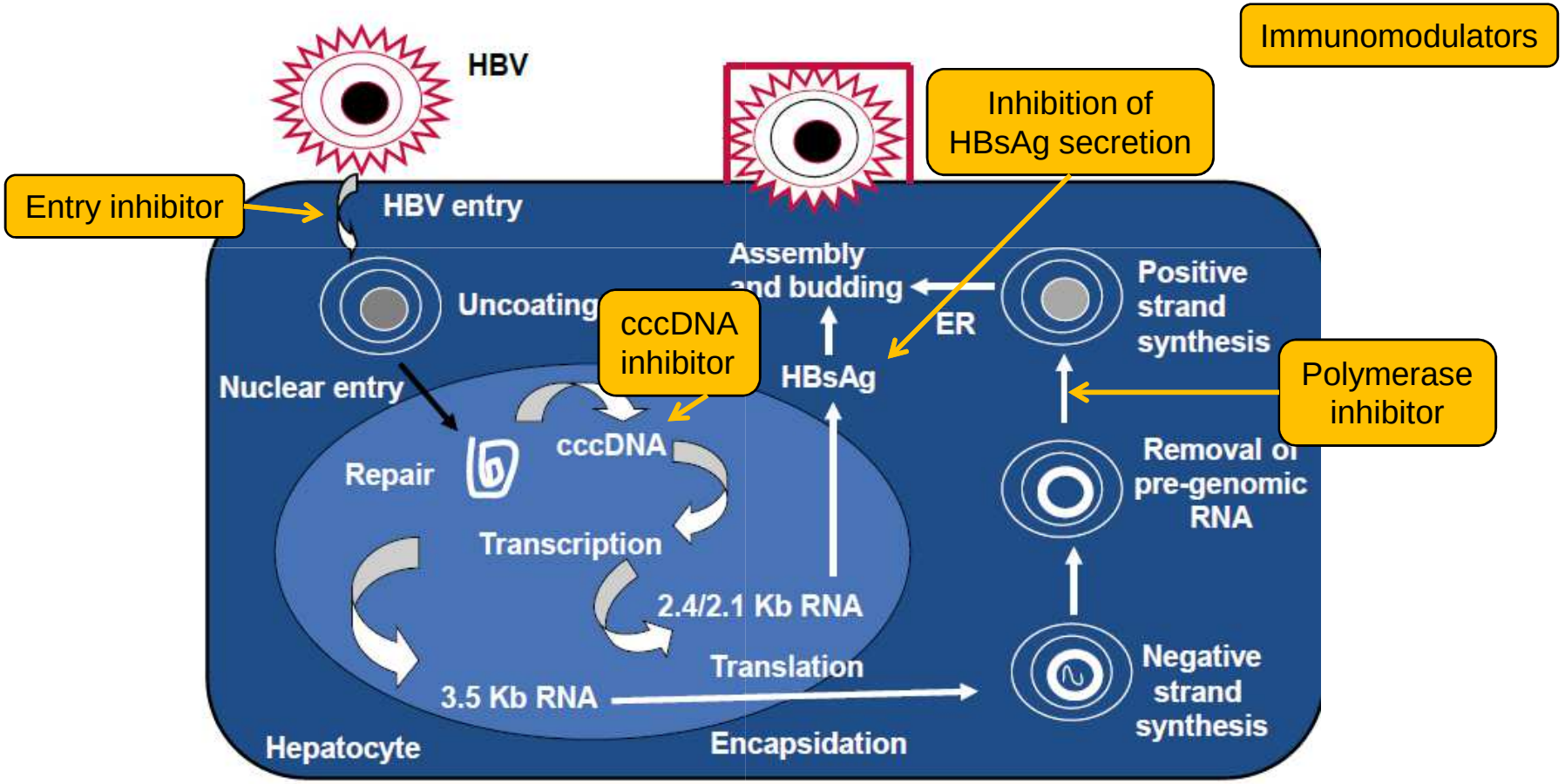
+

- Loss of cccDNA

Not achievable… YET

What pathways or approaches might we take?

- The virus replication cycle offers many targets

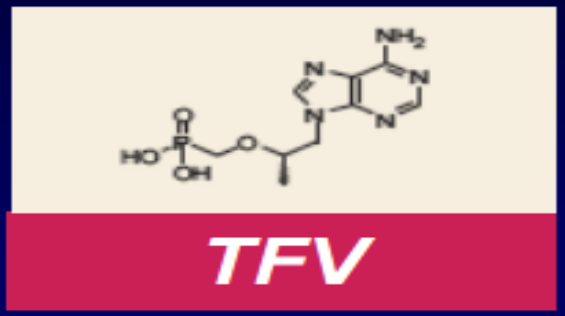


Adapted from Stein LL, Loomba R. Infect Disord Drug Targets 2009;9:105–16

ER: endoplasmic reticu

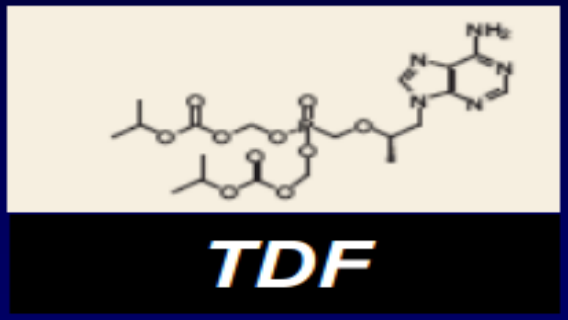
Tenofovir Alafenamide Fumarate (TAF

Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI s)



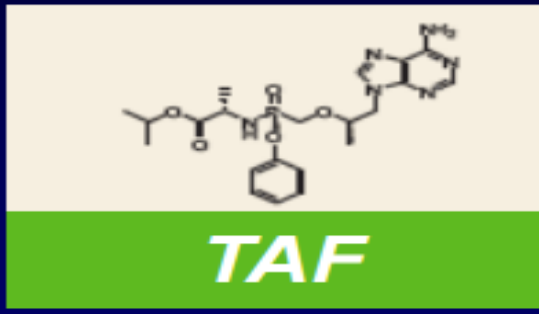
TFV

Tenofovir



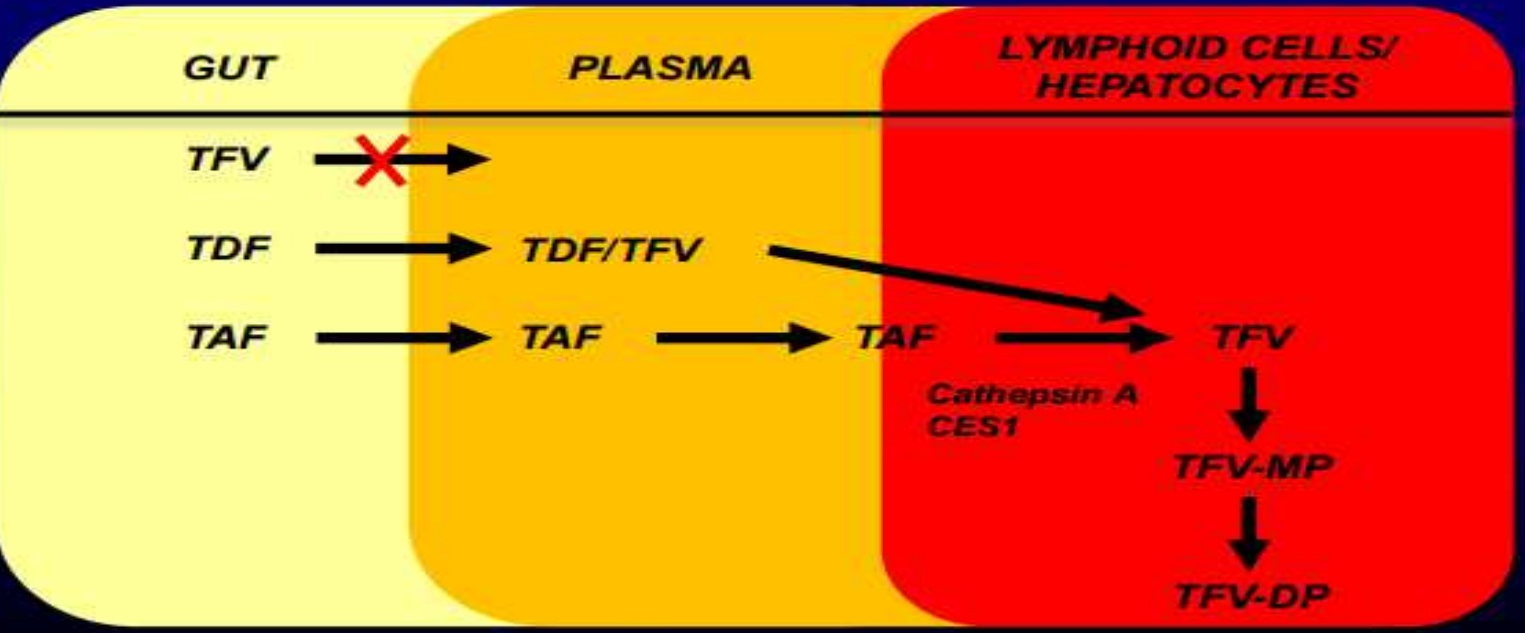
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide

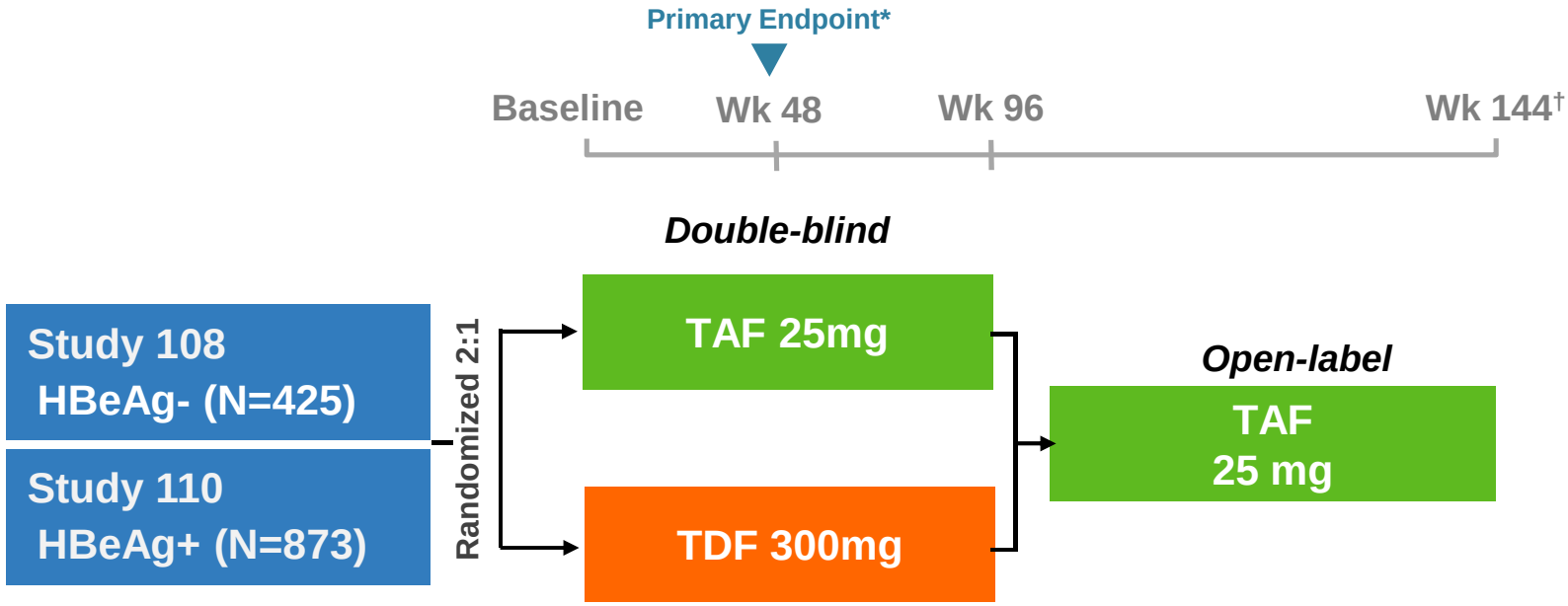


- *Improved stability in plasma:*
  - *Enhanced delivery active form (TFV-D hepatocytes*
  - *Lower doses are us systemic exposures TFV reduced*

Agarwal K et al. AASLD 2
Murakami E et al. HepDAR

CES1 = carboxylesterase 1; DP= di-phosphate; MP= mono-phosphate.

TAF HBV Phase 3 Program



- Two phase 3, randomised, double-blind studies
- Inclusion criteria
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females)
- Primary endpoint (non inferiority margin of 10%):
  - HBV DNA <29 IU/mL at Week 48
- Key secondary safety endpoints
  - Bone mineral density and renal parameters at Week 48

†Amendment to extend double-blind to Week 144 and open-label phase to Week 384 (Year 8) is currently underway
*Non-inferiority margin of 10%

Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

‡

Demographics

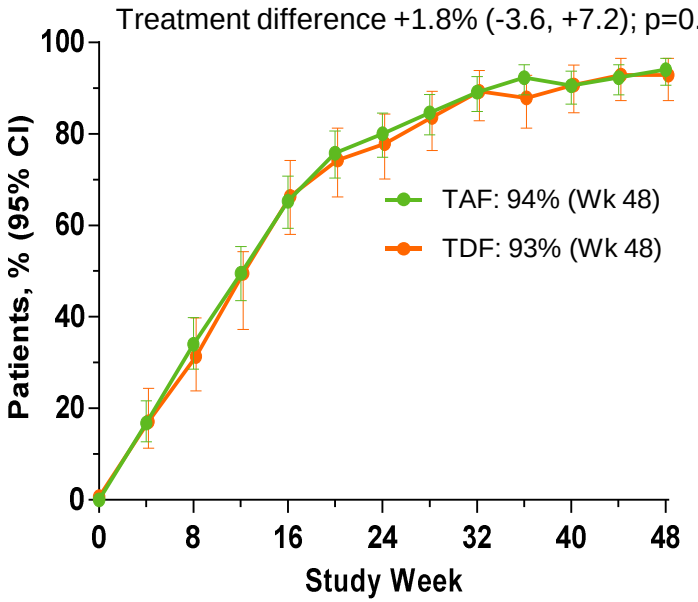
	Study 108 (HBeAg-) (N=425)		Study 110 (HBeAg+) (N=873)	
	TAF n=285	TDF n=140	TAF n=581	TDF n=292
Mean age, y (range)	45 (19–80)	48 (25–72)*	38 (18–69)	38 (18–68)
Male, n (%)	173 (61)	86 (61)	371 (64)	189 (65)
Asian, n (%)	205 (72)	101 (72)	482 (83)	232 (79)
Mean BMI, kg/m^2 (SD)	25 (4)	25 (4)	24 (4)	24 (4)
Treatment experienced, n (%)	60 (21)	31 (22)	151 (26)	77 (26)
East Asia region†, n (%)	114 (40)	64 (46)	287 (49)	145 (50)
Mean HBV DNA, log_{10} IU/mL (SD)	5.7 (1.34)	5.8 (1.32)	7.6 (1.3)	7.6 (1.4)
Elevated HBV DNA, n (%) HBeAg- (≥7 log_{10} IU/mL) HBeAg+ (≥8 log_{10} IU/mL)	55 (19)	24 (17)	272 (47)	142 (49)
Median ALT, U/L (Q1, Q3)	67 (44, 102)	67 (47, 102)	85 (61, 139)	86 (57, 137)
FibroTest score ≥0.75, n/n (%)	31/280 (11)	20/139 (14)	45/566 (8)	22/282 (8)

**P*=0.011
†East Asia region denotes Hong Kong, Japan, Singapore (Study 110 only), South Korea, and Taiwan
Q, quartile; SD, standard deviation
Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12

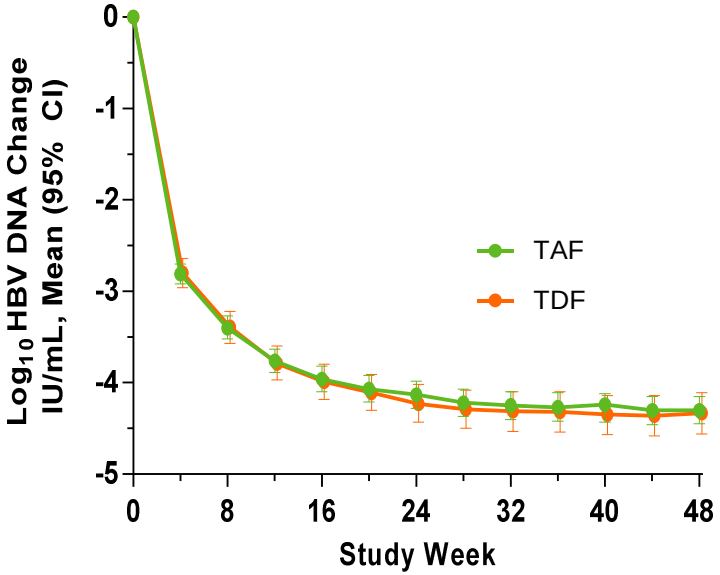
HBV DNA Response at 48 Weeks

Study 108 (HBeAg-subjects)

HBV DNA <29 IU/mL (%)



Log_{10} HBV DNA Change



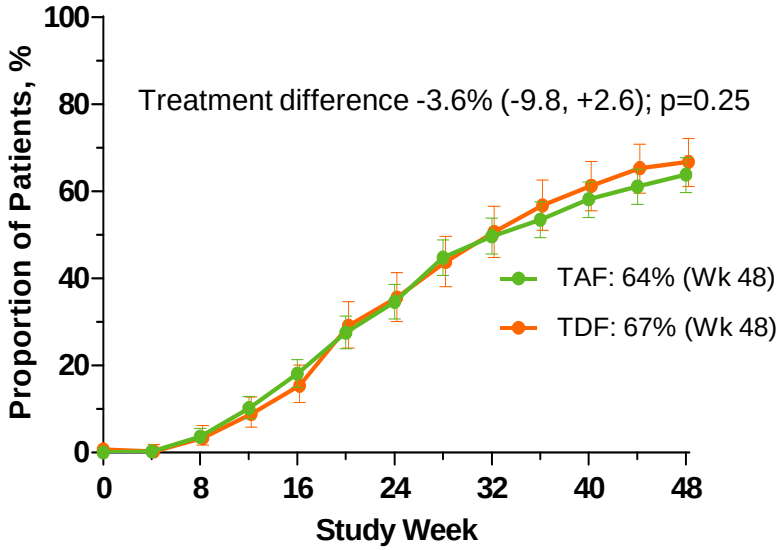
- Similar and non-inferior rates of virologic suppression with TAF and TDF at Week 48
- No resistance detected in either treatment group

Buti, EASL 2016, Oral GS06

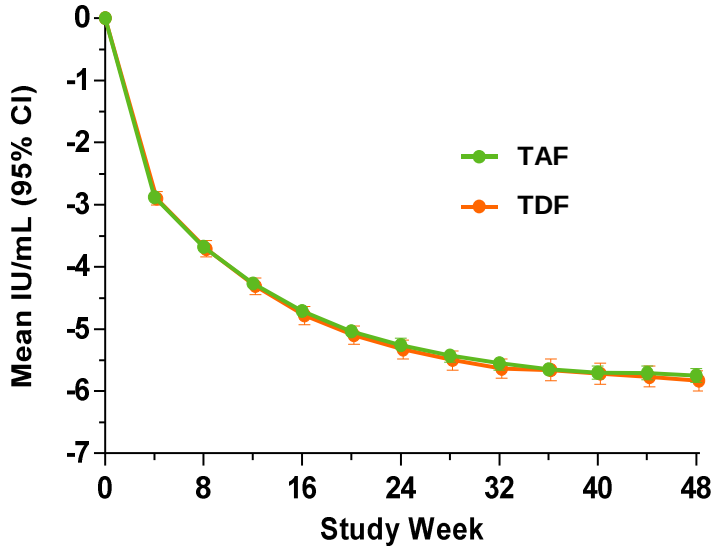
HBV DNA Response at 48 Weeks

Study 110
(HBeAg+ subjects)

HBV DNA <29 IU/mL (%)



Log_{10} HBV DNA Change



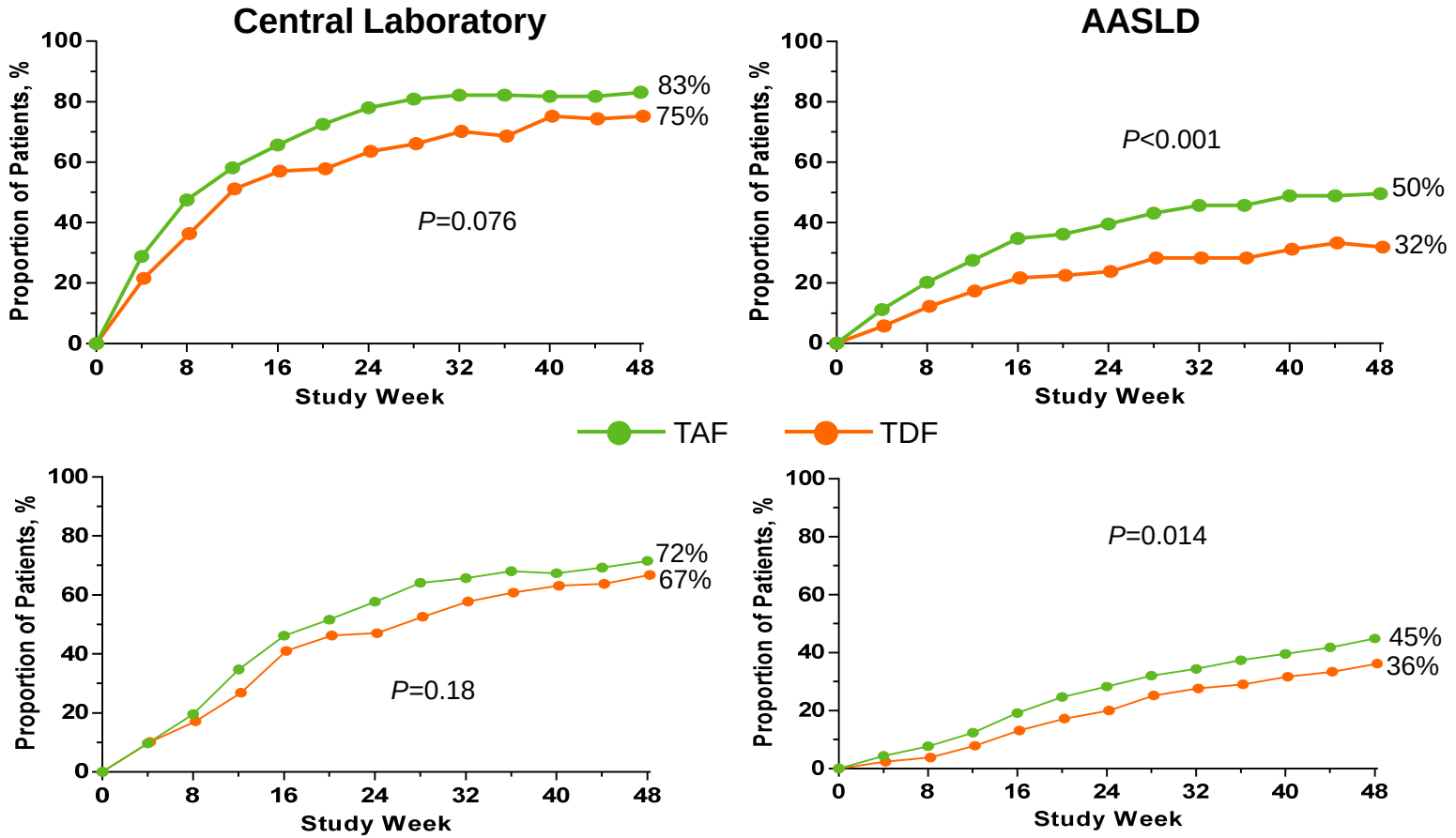
- Similar and non-inferior rates of virologic suppression with TAF and TDF at Week 48
- No resistance detected in either treatment group

Chan, EASL 2016, Oral GS12

ALT Normalization at 48 Weeks

Study 108

Study 110



TAF showed statistically significant increased ALT normalization rates utilizing AASLD ALT criteria

Central lab upper limit of normal (ULN): males ≤43 U/L, females ≤34 U/L (≥69 y, males ≤35 U/L, females ≤32 U/L); AASLD ULN: males ≤30 U/L, females ≤19 U/L.
Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12

‡

Serologic Results

n/N (%)	HBeAg+ (N=873)		
	TAF n=581	TDF n=292	*P*-value
HBeAg loss	78/565 (14)	34/285 (12)	0.47
HBeAg seroconversion	58/565 (10)	23/285 (8)	0.32
HBsAg loss	4/576 (<1)	1/288 (<1)	0.52
HBsAg seroconversion	3/576 (<1)	0	0.22

Similar serologic response between TAF and TDF arms in HBeAg-positive subjects

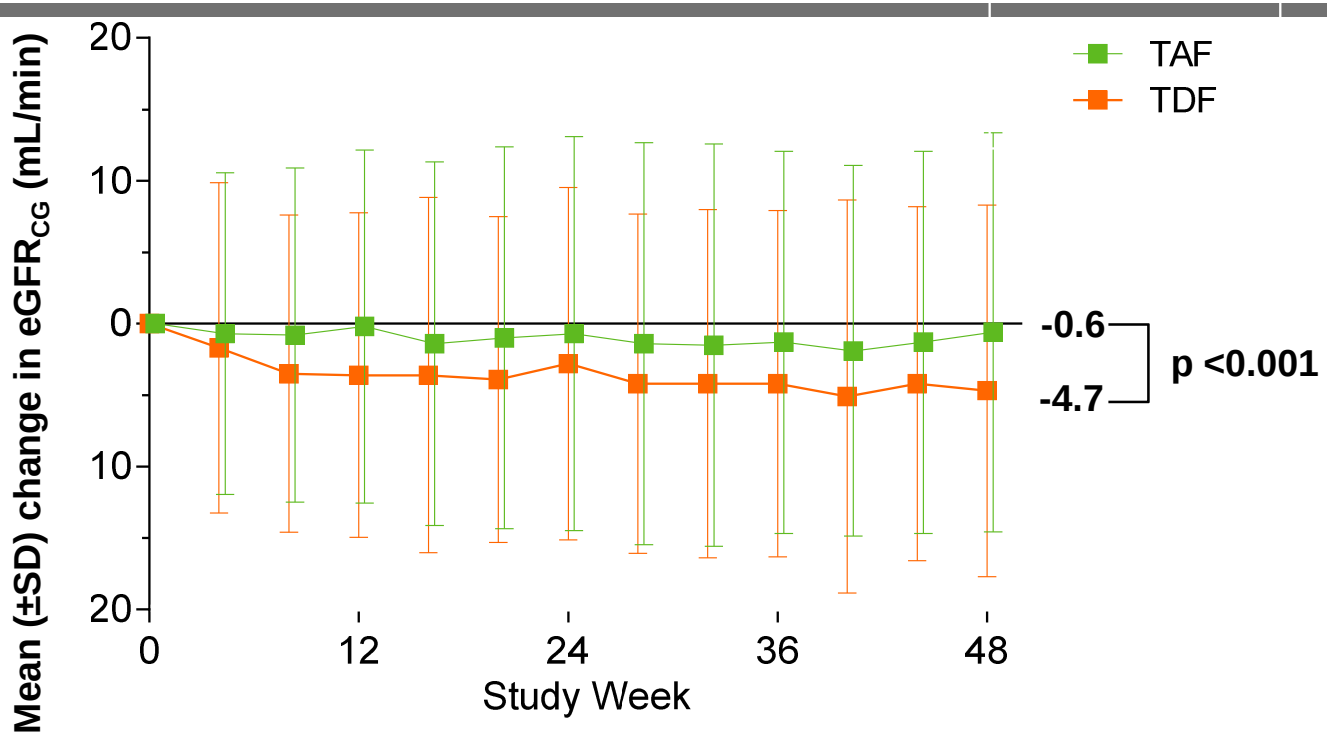
[a]ULN 30 U/L males, 19 U/L females
Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12

Overall Safety

	Patients, n (%)	TAF n=866	TDF n=432
Adverse Events	AE	608 (70)	291 (67)
	Grade 3–4 AE	39 (5)	17 (4)
	Serious AE	36 (4)	21 (5)
	D/C due to AE	9 (1)	5 (1)
	Death	1*	1†
	HCC	1 (<1)	5 (1)
Laboratory Abnormalities, ≥1%	Grade 3–4	269 (31)	126 (29)
	ALT	70 (8)	40 (9)
	AST	28 (3)	23 (5)
	Amylase	23 (3)	10 (2)
	Fasting LDL cholesterol	37 (4)	1 (<1)
	Fasting glucose (hyperglycemia)	9 (1)	0
	GGT	3 (<1)	6 (1)

*54-year old Asian woman died due to H1N1 influenza at \week 14 (non-treatment-emergent)
†51-year old Asian man with cirrhosis died due to HCC at Week 56 (non-treatment-emergent)
Buti, EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12
Gilead Sciences, Data on File

Results: Renal Safety

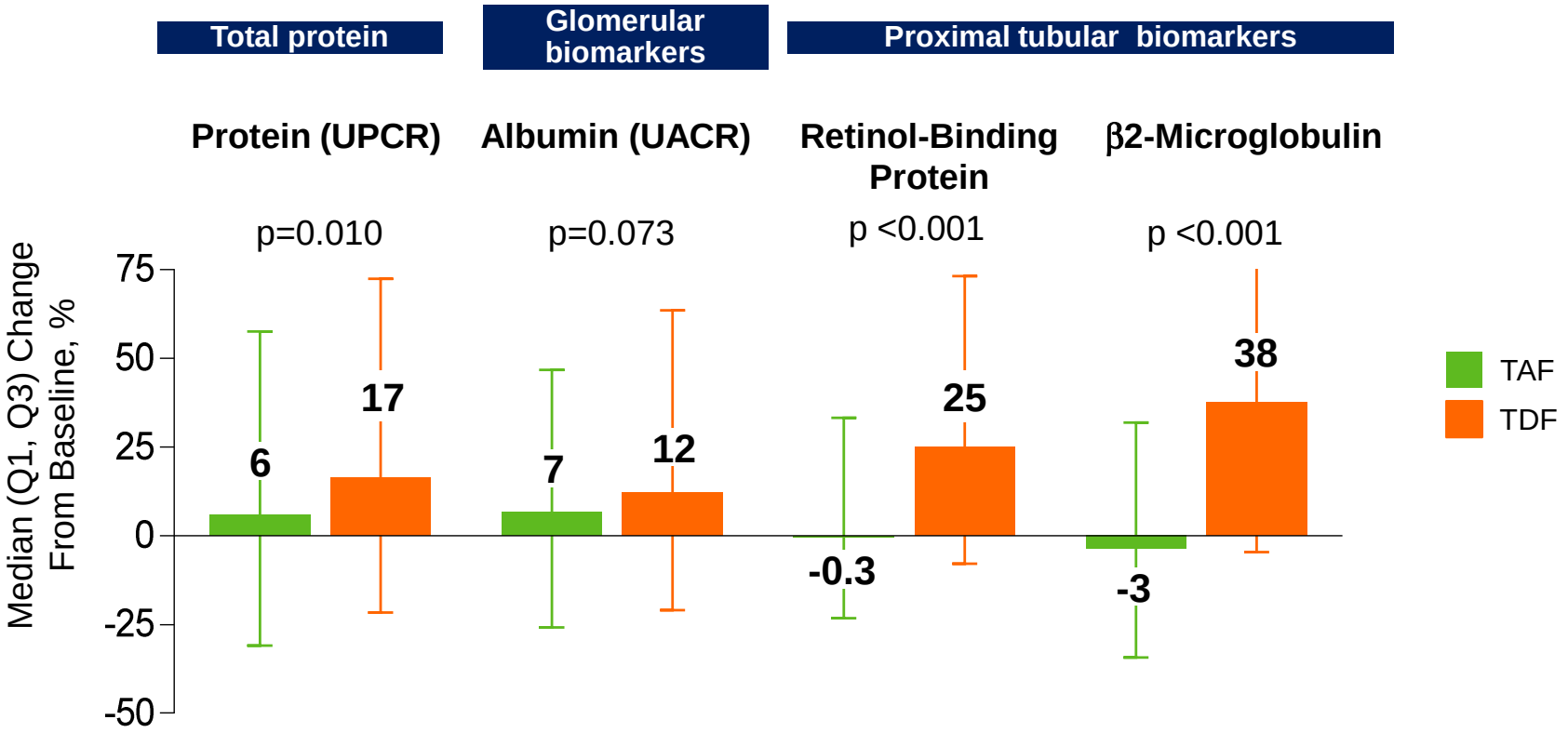


	TAF n=866	TDF n=432	P-value
Change in sCr, mg/dL	0.010 (0.11)	0.024 (0.10)	0.012

Subjects receiving TAF experienced significantly less change in eGFR$_{CG}$ and sCr at Week 48 compared to TDF

Continuous data are expressed as mean (SD)
sCr, serum creatinine; eGFR$_{CG}$, creatinine clearance by Cockcroft-Gault
Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12
Gilead Sciences, Data on File

Results: Quantitative Proteinuria at Week 48

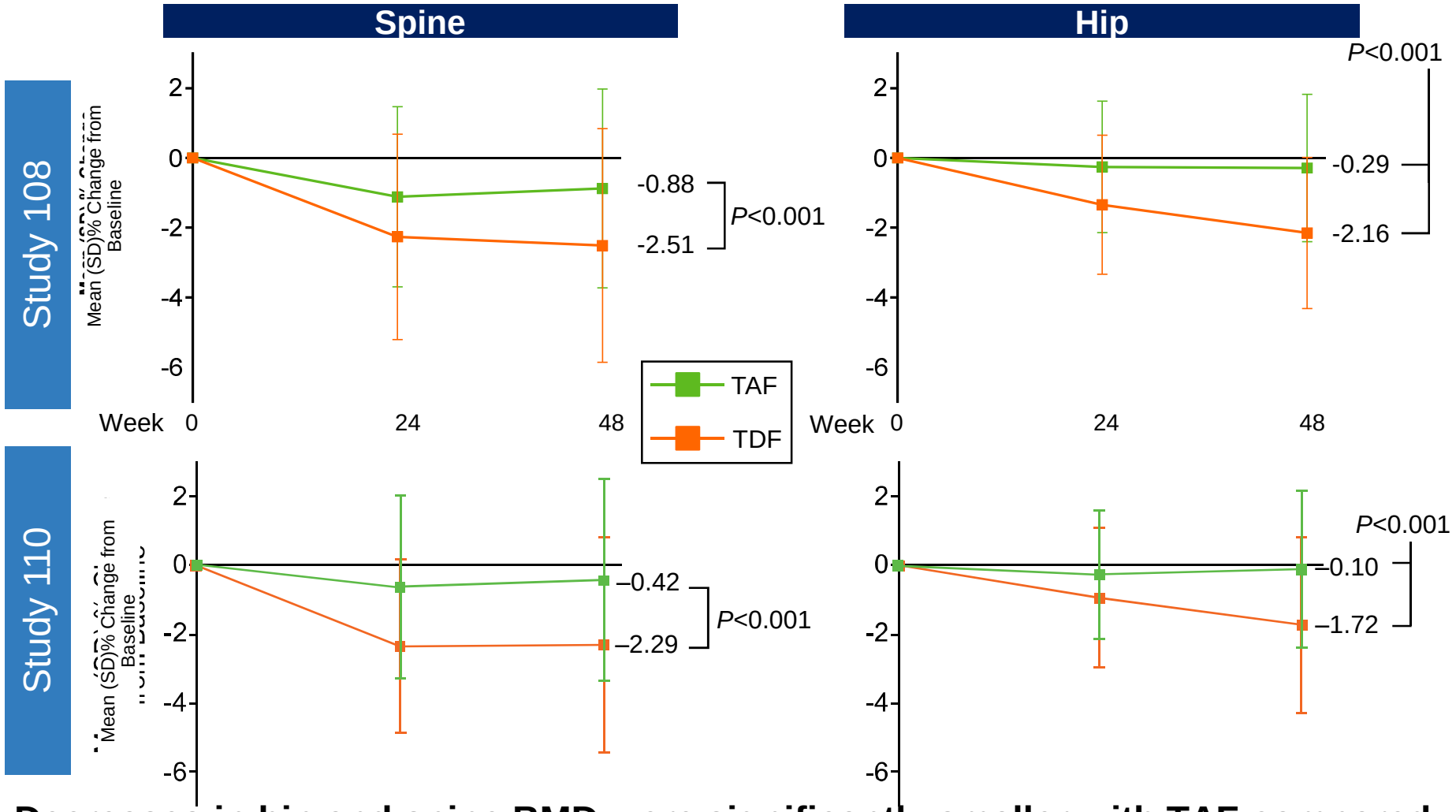


Changes in tubular proteinuria were significantly lower with TAF compared to TDF

UPCR: Urine Protein Creatinine Ratio
UACR: Urine Albumin Creatinine Ratio

Buti EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12
Gilead Sciences, Data on File

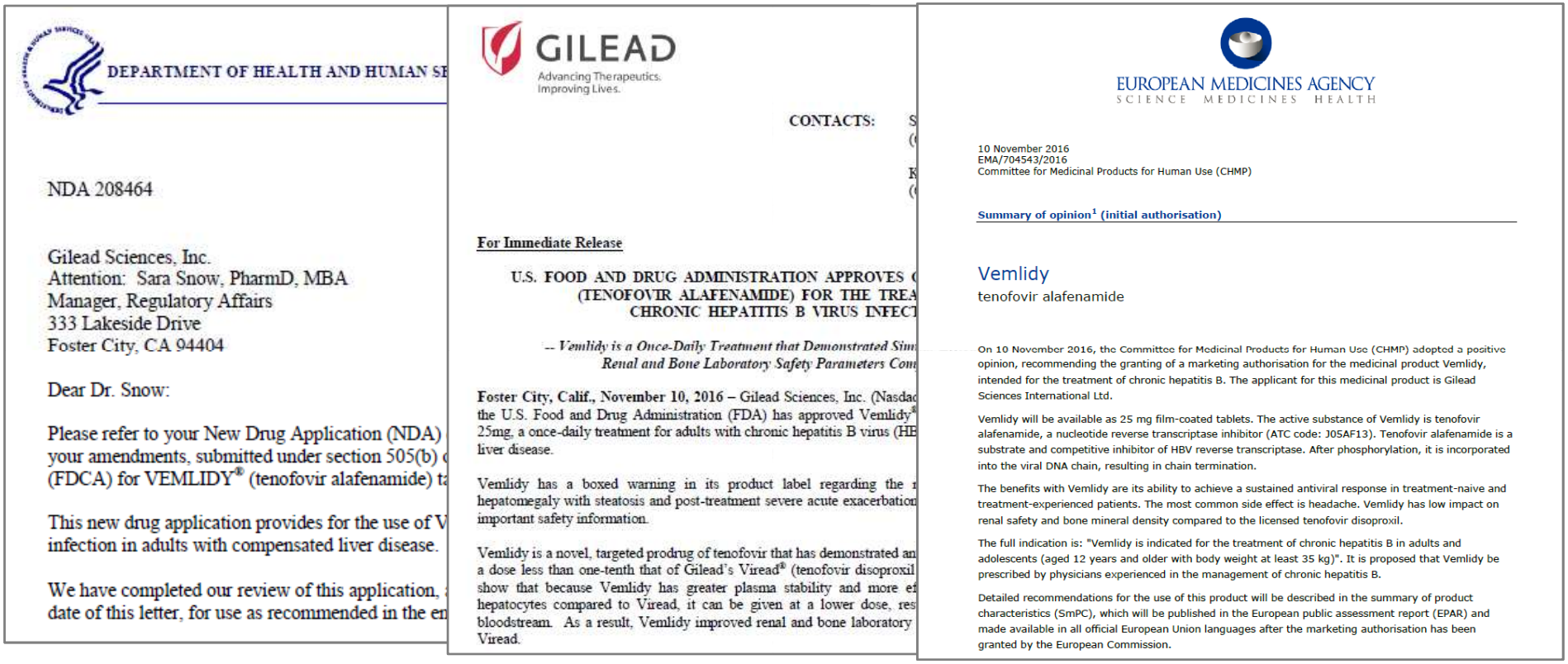
Changes in Spine and Hip BMD Through Week 48



Decreases in hip and spine BMD were significantly smaller with TAF compared to TDF

Buti, EASL 2016, Oral GS06
Chan, EASL 2016, Oral GS12

FDA Approval of VEMLIDY (Tenofovir Alafenamide: TAF) and EMA Approval



DEPARTMENT OF HEALTH AND HUMAN SE

NDA 208464

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

Please refer to your New Drug Application (NDA)
your amendments, submitted under section 505(b)
(FDCA) for VEMLIDY® (tenofovir alafenamide) t

This new drug application provides for the use of V
infection in adults with compensated liver disease.

We have completed our review of this application,
date of this letter, for use as recommended in the en

GILEAD
Advancing Therapeutics. Improving Lives.

CONTACTS:

For Immediate Release

U.S. FOOD AND DRUG ADMINISTRATION APPROVES
(TENOFOVIR ALAFENAMIDE) FOR THE TREA
CHRONIC HEPATITIS B VIRUS INFECT

-- *Vemlidy is a Once-Daily Treatment that Demonstrated Sim*
Renal and Bone Laboratory Safety Parameters Com

Foster City, Calif., November 10, 2016 – Gilead Sciences, Inc. (Nasdac
the U.S. Food and Drug Administration (FDA) has approved Vemlidy®
25mg, a once-daily treatment for adults with chronic hepatitis B virus (HE
liver disease.

Vemlidy has a boxed warning in its product label regarding the r
hepatomegaly with steatosis and post-treatment severe acute exacerbation
important safety information.

Vemlidy is a novel, targeted prodrug of tenofovir that has demonstrated an
a dose less than one-tenth that of Gilead's Viread® (tenofovir disoproxil
show that because Vemlidy has greater plasma stability and more ef
hepatocytes compared to Viread, it can be given at a lower dose, res
bloodstream. As a result, Vemlidy improved renal and bone laboratory
Viread.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMA/704543/2016
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Vemlidy
tenofovir alafenamide

On 10 November 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Vemlidy, intended for the treatment of chronic hepatitis B. The applicant for this medicinal product is Gilead Sciences International Ltd.

Vemlidy will be available as 25 mg film-coated tablets. The active substance of Vemlidy is tenofovir alafenamide, a nucleotide reverse transcriptase inhibitor (ATC code: J05AF13). Tenofovir alafenamide is a substrate and competitive inhibitor of HBV reverse transcriptase. After phosphorylation, it is incorporated into the viral DNA chain, resulting in chain termination.

The benefits with Vemlidy are its ability to achieve a sustained antiviral response in treatment-naive and treatment-experienced patients. The most common side effect is headache. Vemlidy has low impact on renal safety and bone mineral density compared to the licensed tenofovir disoproxil.

The full indication is: "Vemlidy is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg)". It is proposed that Vemlidy be prescribed by physicians experienced in the management of chronic hepatitis B.

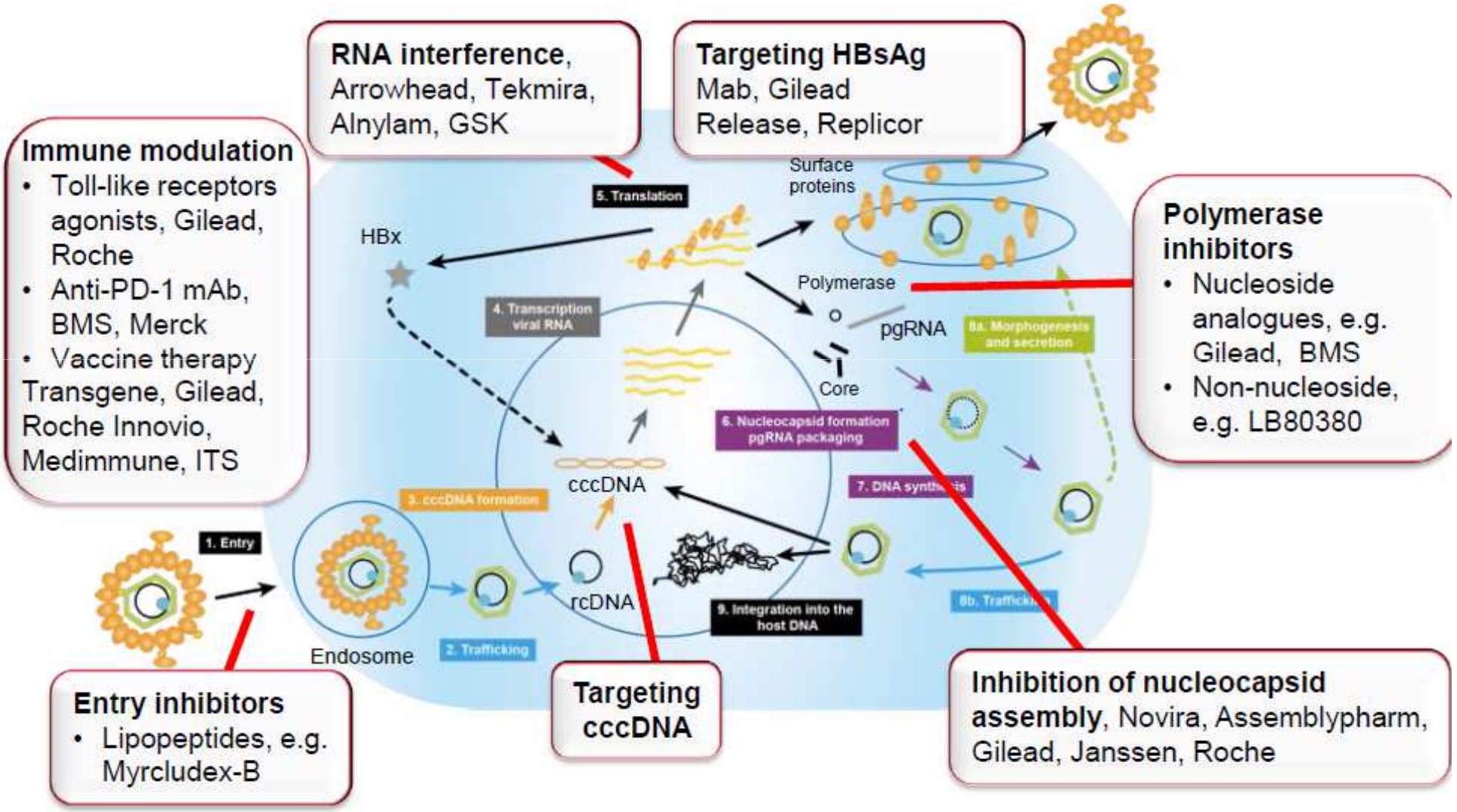
Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

"Clinical trials demonstrated Vemlidy is efficacious with improved renal and bone safety parameters compared to Viread, representing an important development for people living with this chronic disease."

- Calvin Pan, MD, Clinical Professor of Medicine, NYU Langone Medical Center, and investigator in the Vemlidy clinical trials.

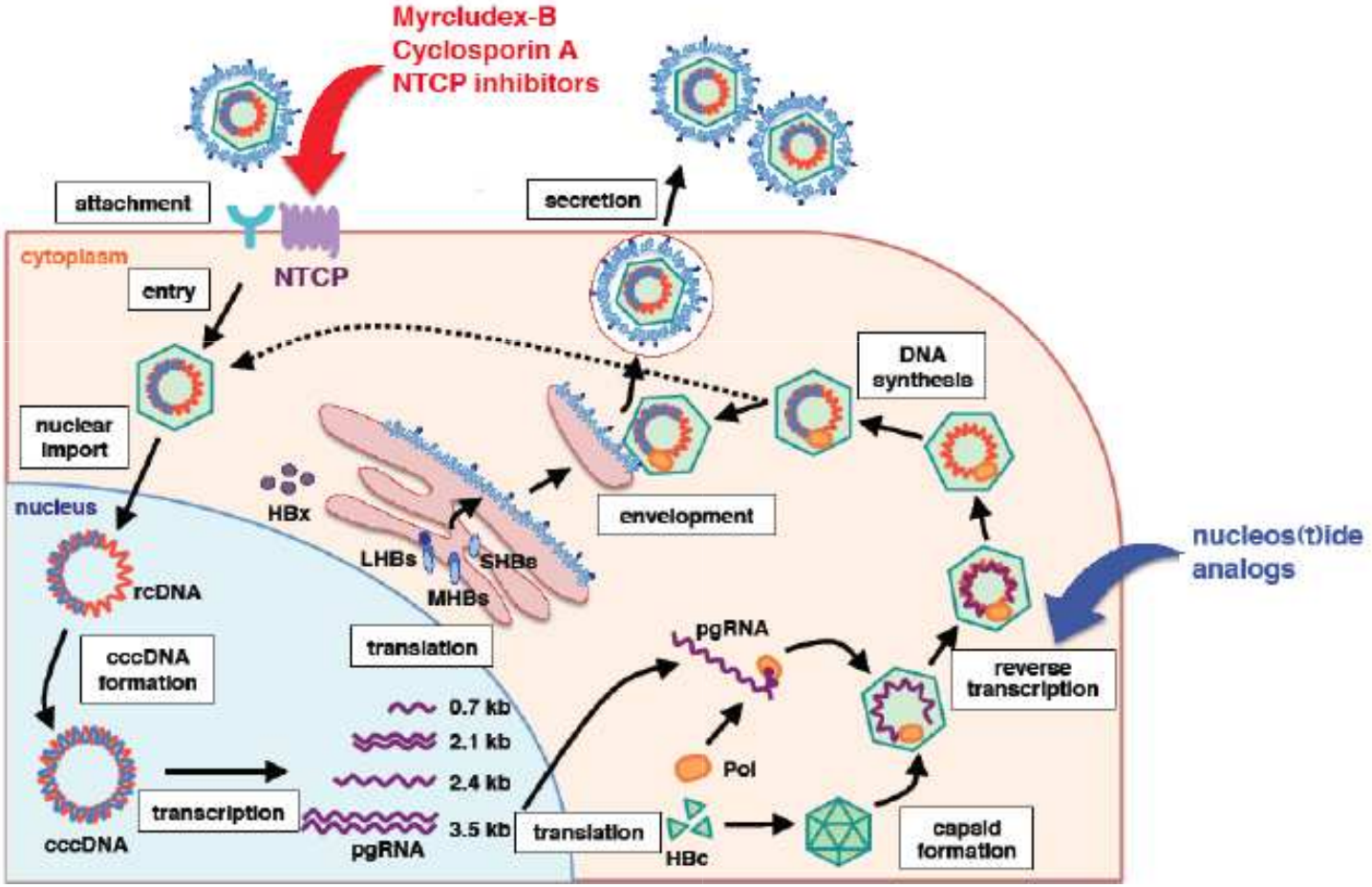
Press Release. US FDA Approves VEMLIDY for the Treatment of Chronic Hepatitis B virus Infection. November 10, 2016:

Future directions: target & drug discovery to cure HBV infection



Zoulim F, et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch. Available at:

Identification of NTCP as an HBV receptor

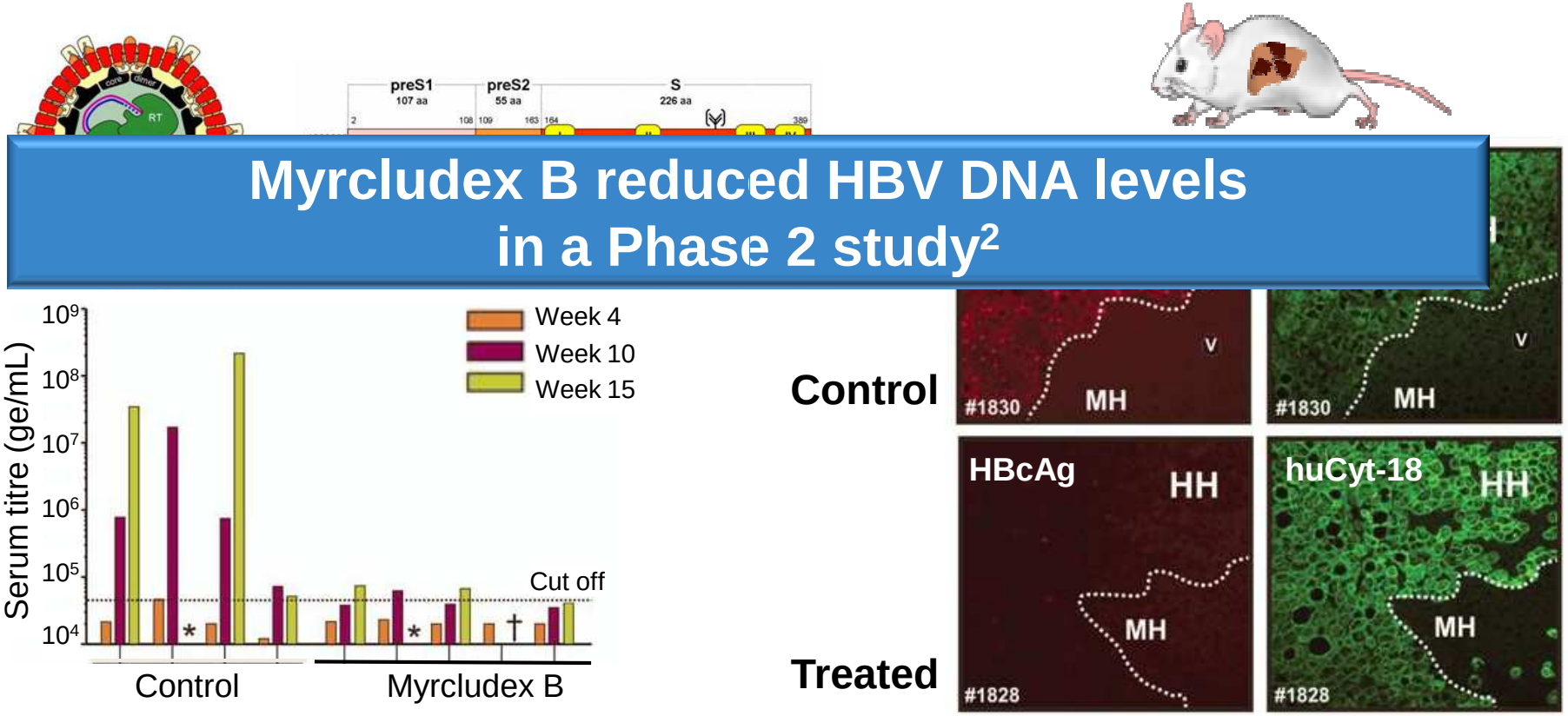


ed from Watashi K, et al. Int J Mol Sci 2014;15:2892–5

NTCP: sodium taurocholate cotransporting polype

The entry inhibitor, Myrcludex B, blocks HBV infection in PHH-transplanted mice

- Myrcludex B is a chemically synthesised lipopeptide derived from the preS1 domain of HBV. It blocks de novo HBV and HDV infection in vitro and in vivo[1]



apted from Petersen J, et al. Nat Biotech 2008;26:335–41;
ban S, et al. AASLD 2014; Poster #LB-20

HBcAg: hepatitis B core antigen; HH: human hepatocyte; MH: mouse hepatocyte; PHH: primary human hepatocyte

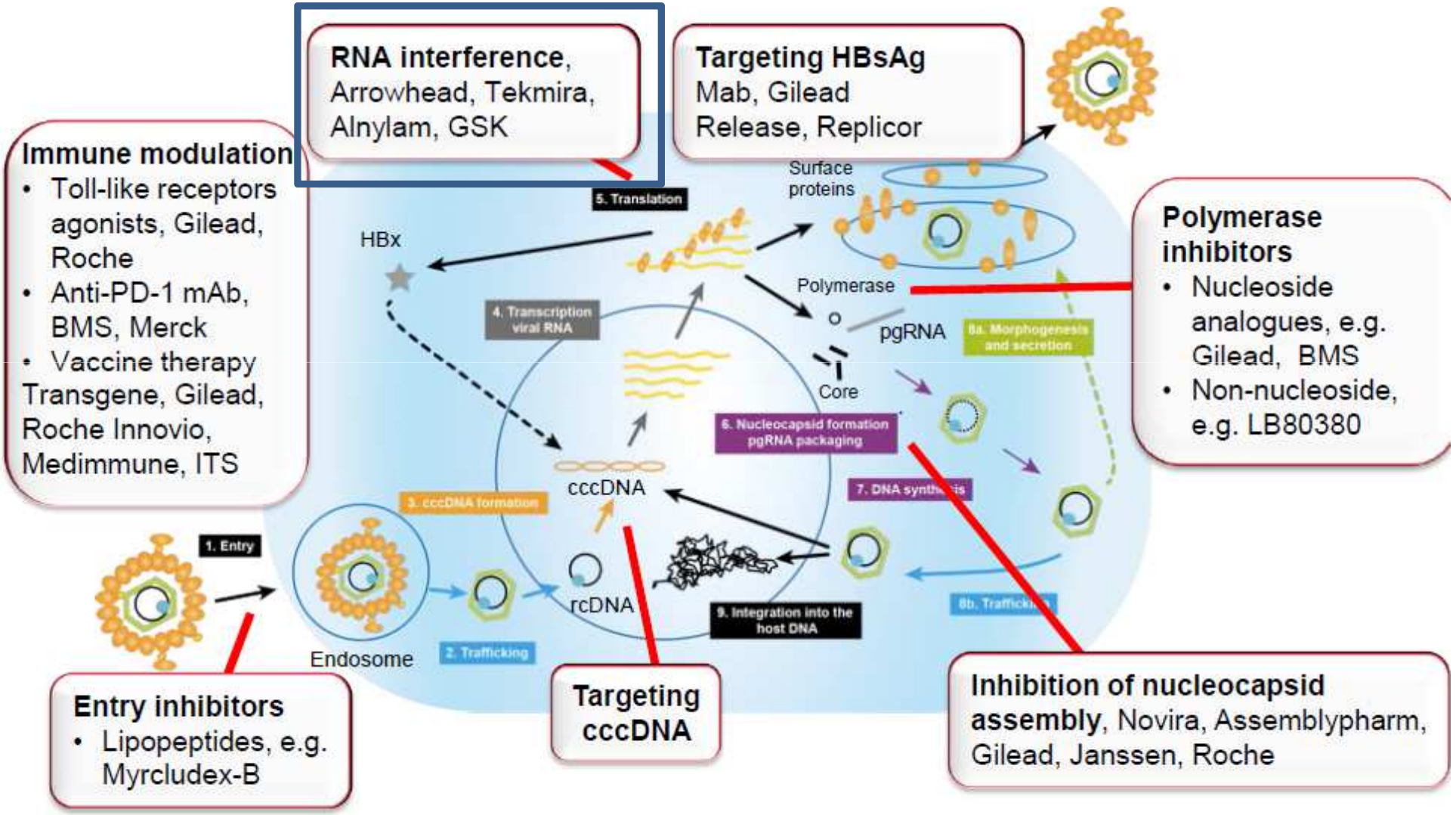
A proof-of-concept Phase IIa clinical trial to treat chronic HBV/HDV with the entry inhibitor myrcludex B for 24 wks

udex B eatment	**HDV RNA** →	HDV RNA decline in 6/7 patients (Week 24) but rebounded on IFN
	HBV DNA →	Moderate HBV DNA decline in 4/8 patients (Week 24), which continued on IFN
	HBsAg →	No significant HBsAg changes (Week 24), but declined on IFN
udex B gIFNα	**HDV RNA** →	RNA negativation in 5/7 patients (Week 24), but relapsed on IFN
	HBV DNA →	HBV DNA levels decline in 5/8 patients (synergism), but relapsed on IFN
	HBsAg →	**No effects on HBsAg levels in 5/6 patients until EOF**
IFNα	**HDV RNA** →	HDV RNA negativation in 2/6 patients
	HBV DNA →	No HBV DNA decline at EOT at Week 48, but relapsed off IFN
	HBsAg →	Only 1/7 patients showed HBsAg negativation at EOT

- 2 mg MyrB is safe
- Decline and negativation of HD RNA and ALT normalization und MyrB monotherap
- Strong synergistic effect on HBV DN and HDV RNA in combination with PEG-IFNα
- Rebound of HBV and HDV RNA aft cessation of MyrB under IFNα treatm

holov P, et al. AASLD 2016, Boston. #229

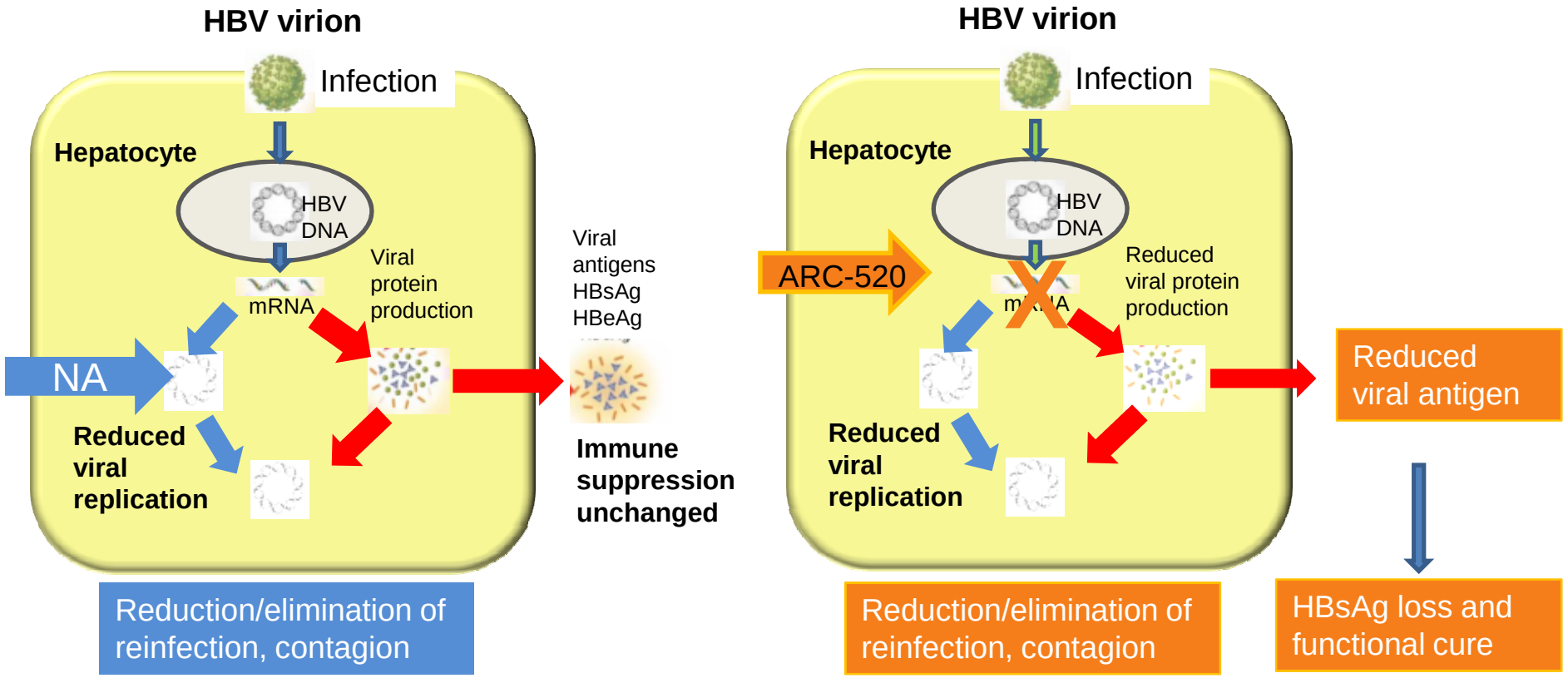
Future directions: target & drug discovery to cure HBV infection



Zoulim F, et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch. Available at:

The RNA therapeutic ARC-520 aims to reverse immune suppression

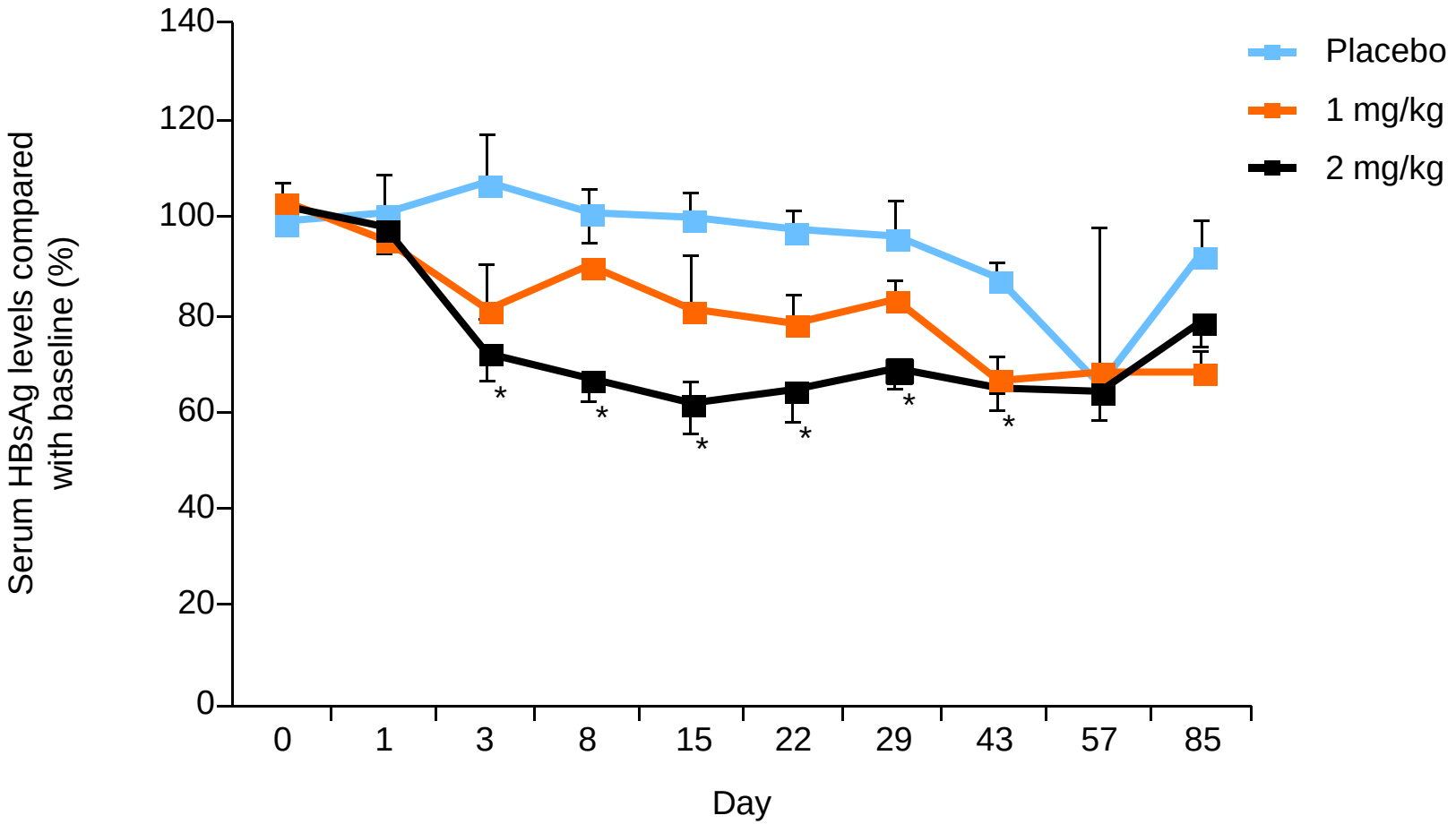
- ARC-520 is comprised of two siRNA sequences targeted against two regions of the HBV genome and is actively targeted to the liver



ted from Yuen M, et al. AASLD 2014; Poster #LB-21

mRNA: messenger I

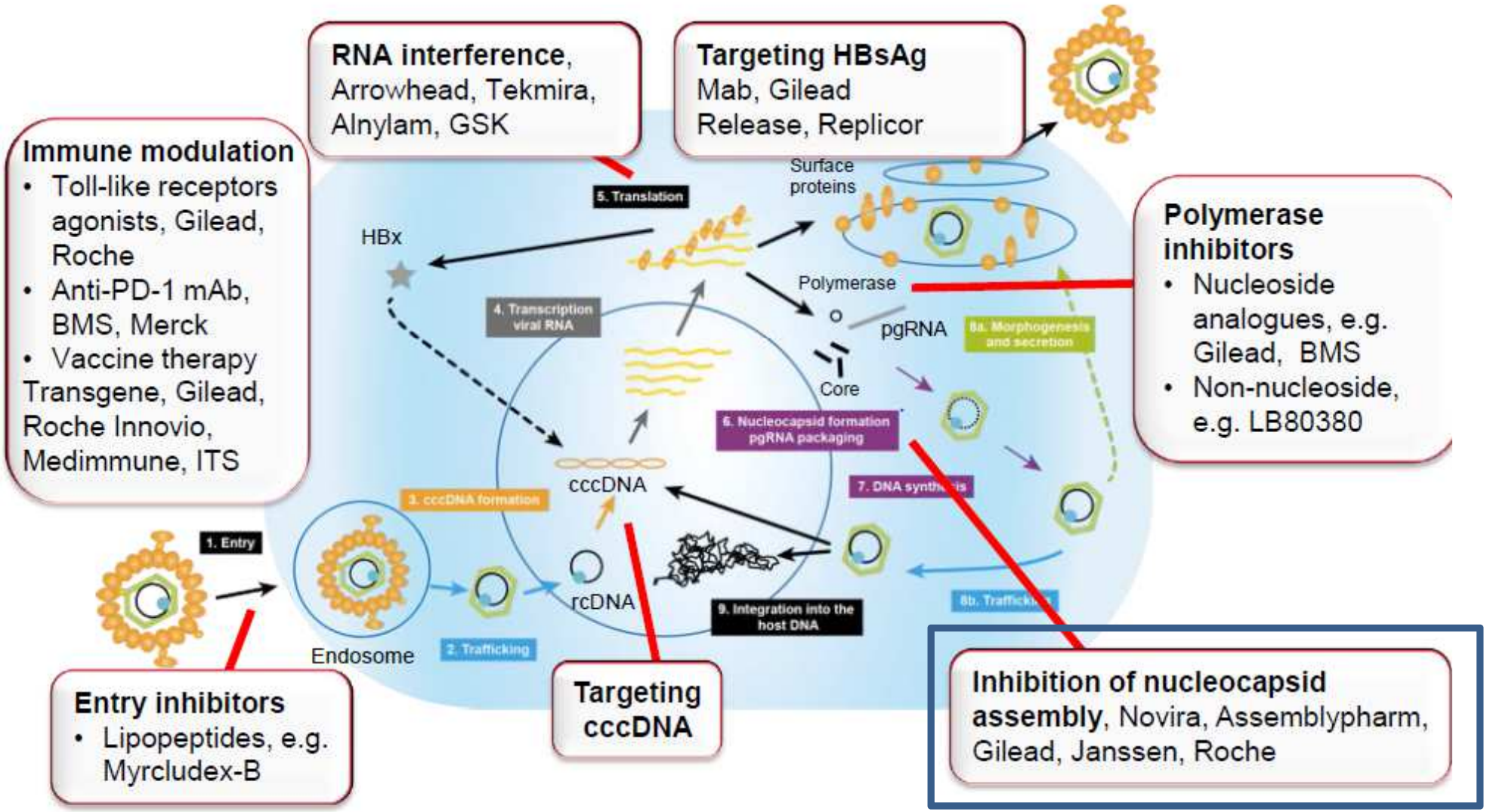
Reduction in quantitative HBsAg levels in patients with CHB treated with ARC-520



ed from Yuen M, et al. AASLD 2014; Poster #LB-21

*P>0.05; Error bars: standard error of the m

Future directions: target & drug discovery to cure HBV infection



Zoulim F. et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch. Available at:

Capsid assembly modulator JNJ-379 prevents de novo infection of primary human hepatocytes with hepatitis B virus

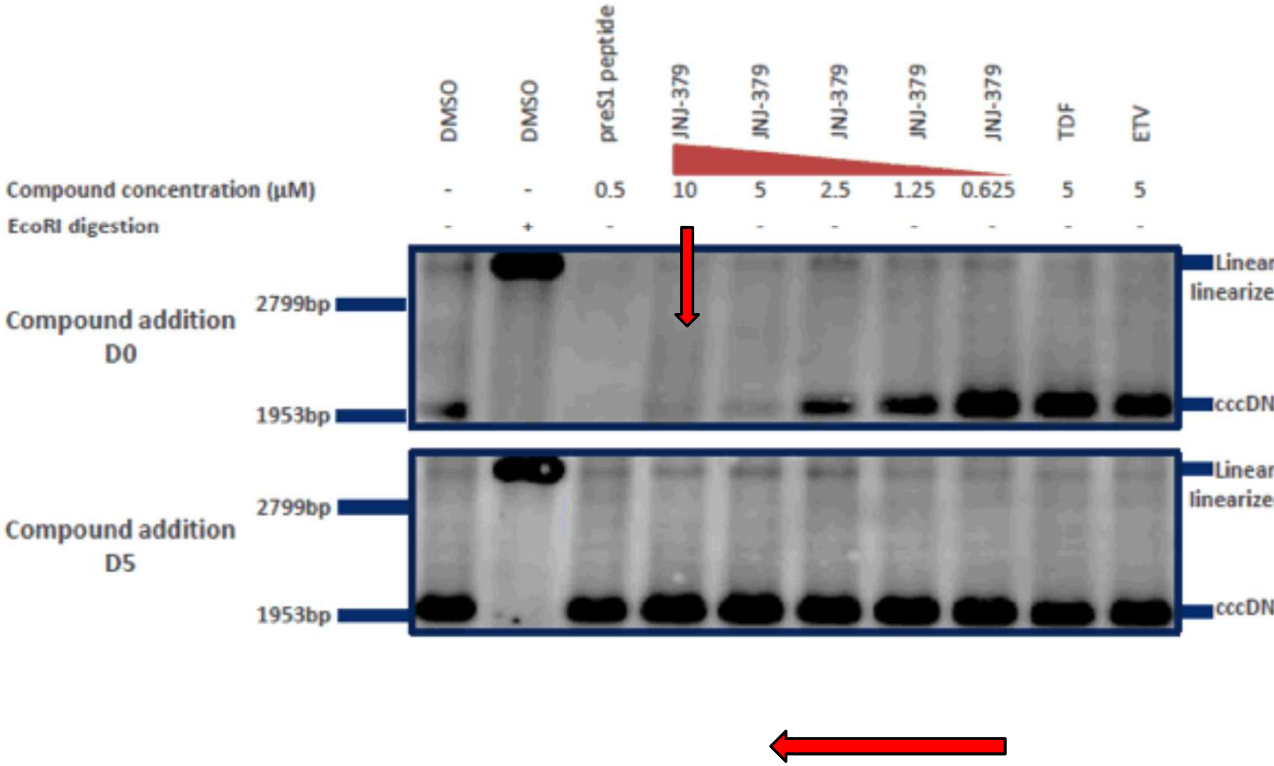
Dose dependent inhibition of HBV cccDNA

sid assembly modulators: Induction of distinct capsid phenotypes

nduce the formation of two types of capsids *in vitro:*

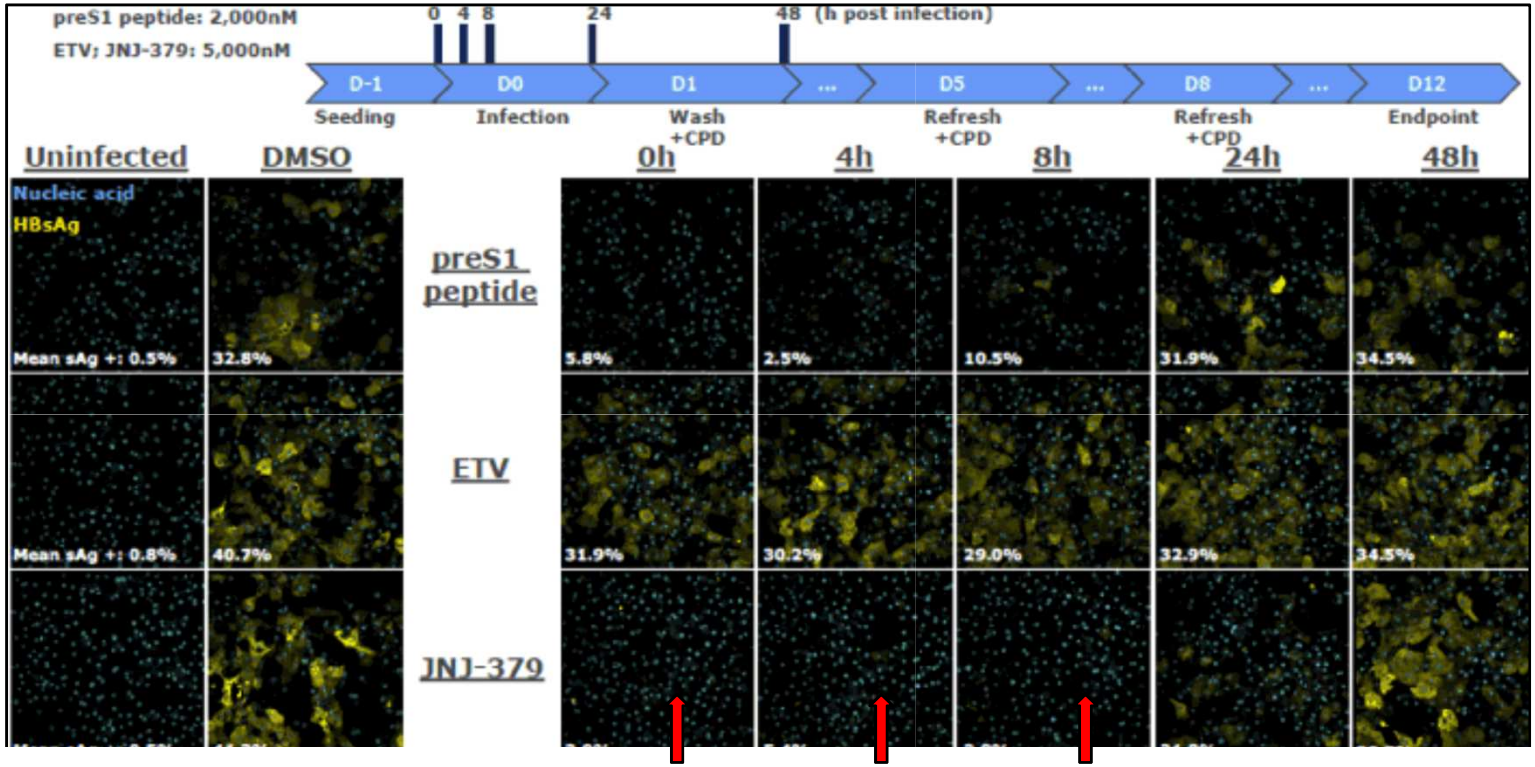
ty capsids with normal geometry and size (class I MOA).
enylpropenamides (e.g. AT130) and sulfamoylbenzamide derivatives.

ty capsids with abnormal geometry and size (class II MOA).
teroaryldihydropyrimidines (e.g. BAY41-4109).



Berke JM, et al. AASLD 2016, Boston. #234

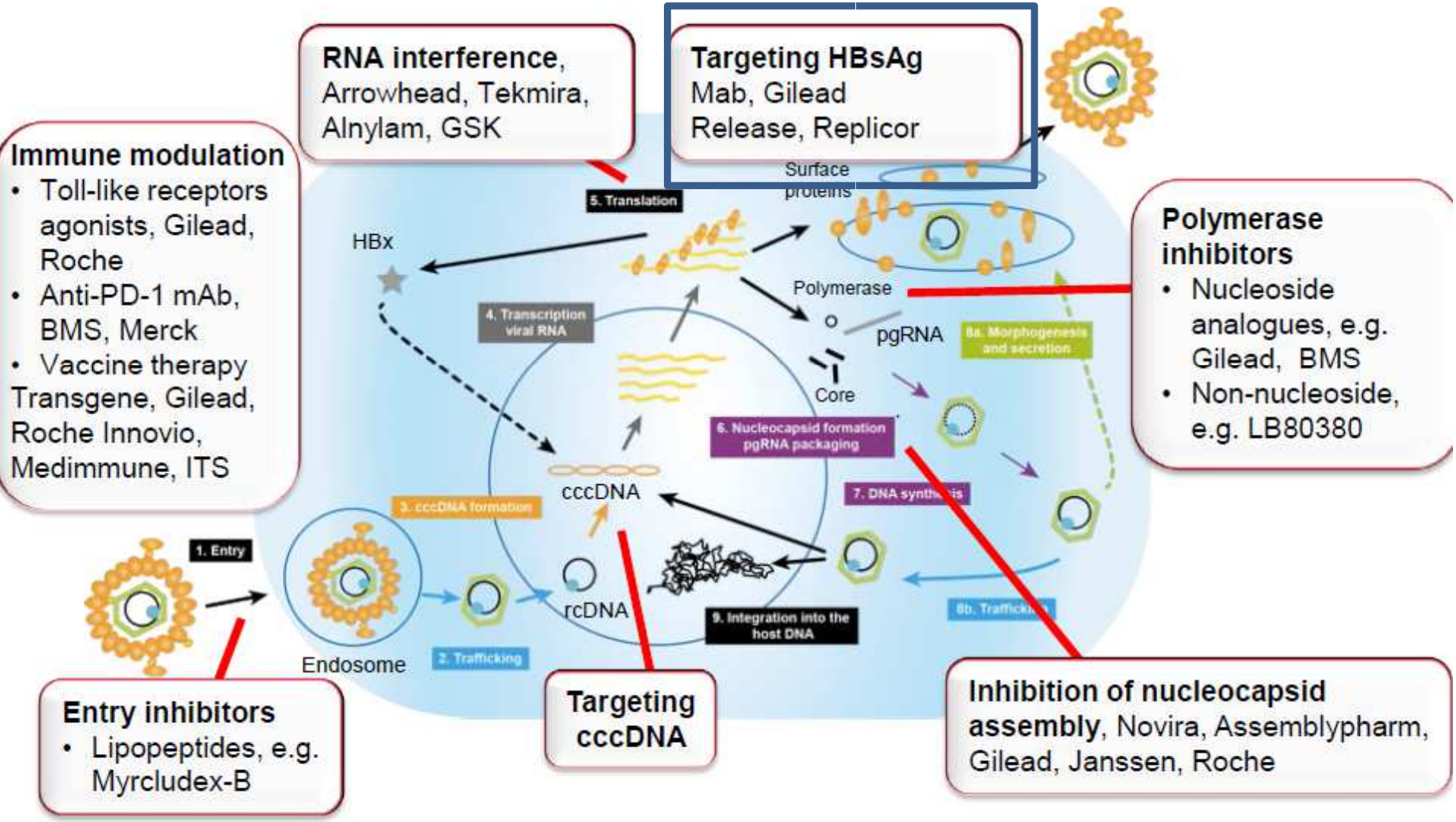
Capsid assembly modulator JNJ-379 prevents de novo infection of primary human hepatocytes with hepatitis B virus



JNJ-379 bloquea la infección del VHB cuando se administra en las primeras 8 horas tras la infección. Entecavir no la previene

- **JNJ-379 es un modulador del ensamblaje de la cápsula (MOA-1)**
- **Inhibe la replicación del VHB (Inhibidor de la cápsula y de formación cccDNA VHB)**
- **Previene la infección de hepatocitos primarios**

Future directions: target & drug discovery to cure HBV infection

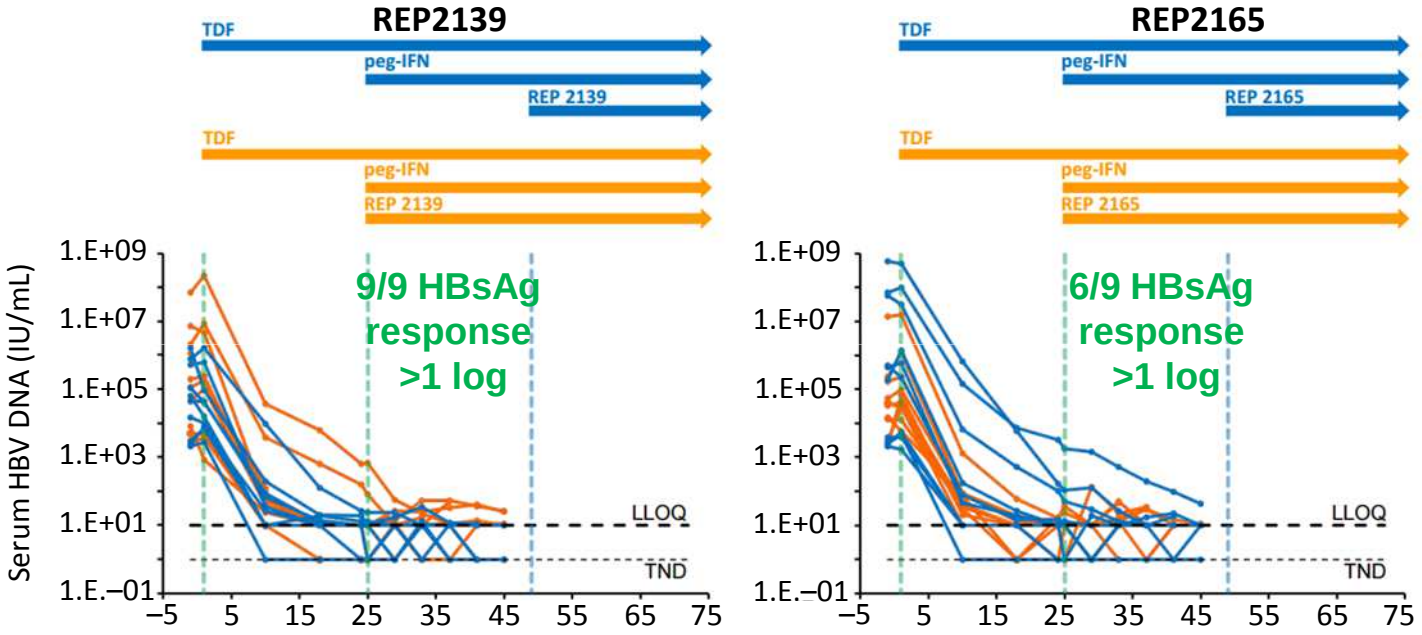


Zoulim F. et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch. Available at:

Preliminary safety and efficacy of REP 2139-Mg or REP 2165-Mg in combination with TD Fand PegIFNα-2a in treatment-naive Caucasian patients with chronic HBeAg-negative HBV infection

HBsAg release inhibitor

Interim efficacy data



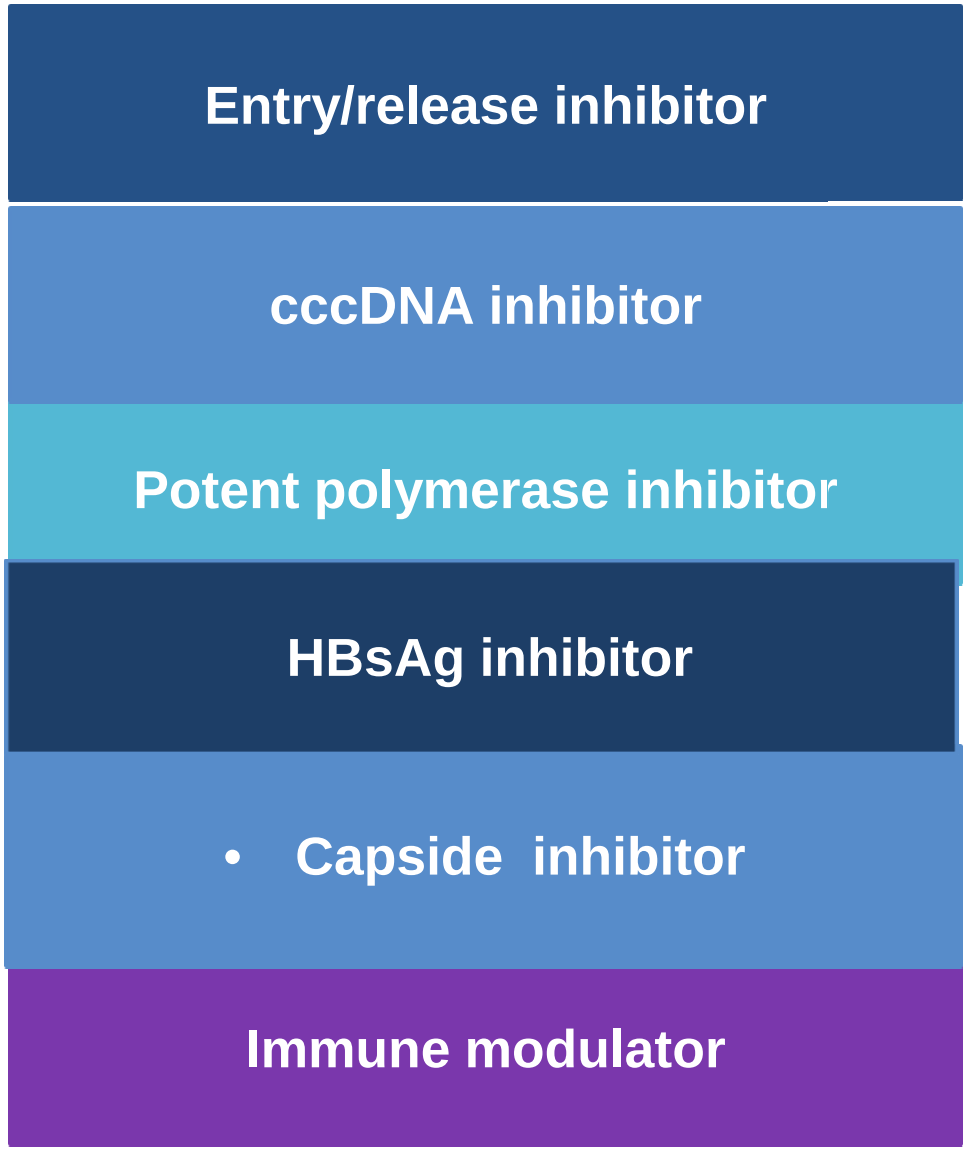
Reductions in multi-log in HBsAg and development of HBsAb

HBsAg reductions accompanied by ALT/AST/GGT flares greater compared to control group

HBsAg reduction improves PegIFN efficacy

t A, et al. AASLD 2016, Boston. #LB-7

Future of Hepatitis B Therapy



Combination of at least 3 or more drugs

with different mechanisms of action

But studies are still in phase 2