Nuevos tratamientos, nuevas dianas y posible cura

Maria Buti
Hospital Universitario Valle Hebron
Barcelona

Disclosures

- Advisor: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis
- Lecturer: Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis
- Clinical trials: Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Roche

HBV can not be cured unlike HCV

VIRUS	HIV	Hepatitis C	Hepatitis B
Genetic archive	Yes	NO	Yes
Ability to cure most patients	No (Integrated viral DNA)	YES (No DNA integration)	No (cccDNA)
Current therapeutic goal	Lifelong suppression	Cure: Clearance from plasma and liver	Lifelong suppression

Pitfalls of Current Treatment

- Nucleoside Analogues are highly potent suppressing HBV DNA but
  - has little effect on HBsAg levels and depletion of cccDNA
  - Long-term therapy is the rule. Concerns on safety?

- IFN finite therapy duration but
  - Limited response
  - Low applicability
  - Side effects

Goal “Cure” of Hepatitis B

- Ultimate aim would be to ‘cure’ CHB
  - Functional cure
    - Off-therapy persistent HBV suppression
  - HBsAg loss and seroconversion
  - cccDNA eradication
  - Prevention of negative outcomes (HCC)

Grimm D, et al. Hepatol Int 2011;5:644–53

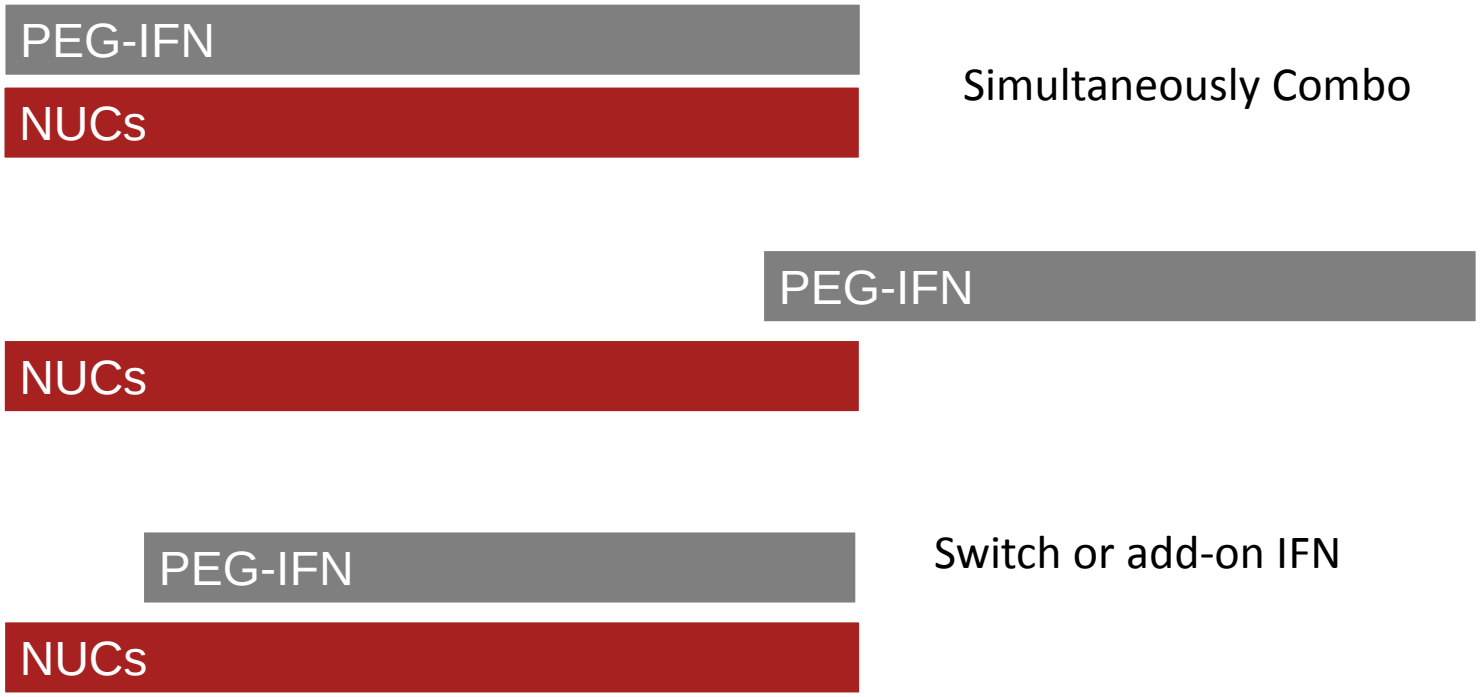
cccDNA: covalently closed circular DNA

New Strategies for Finite HBV therapy

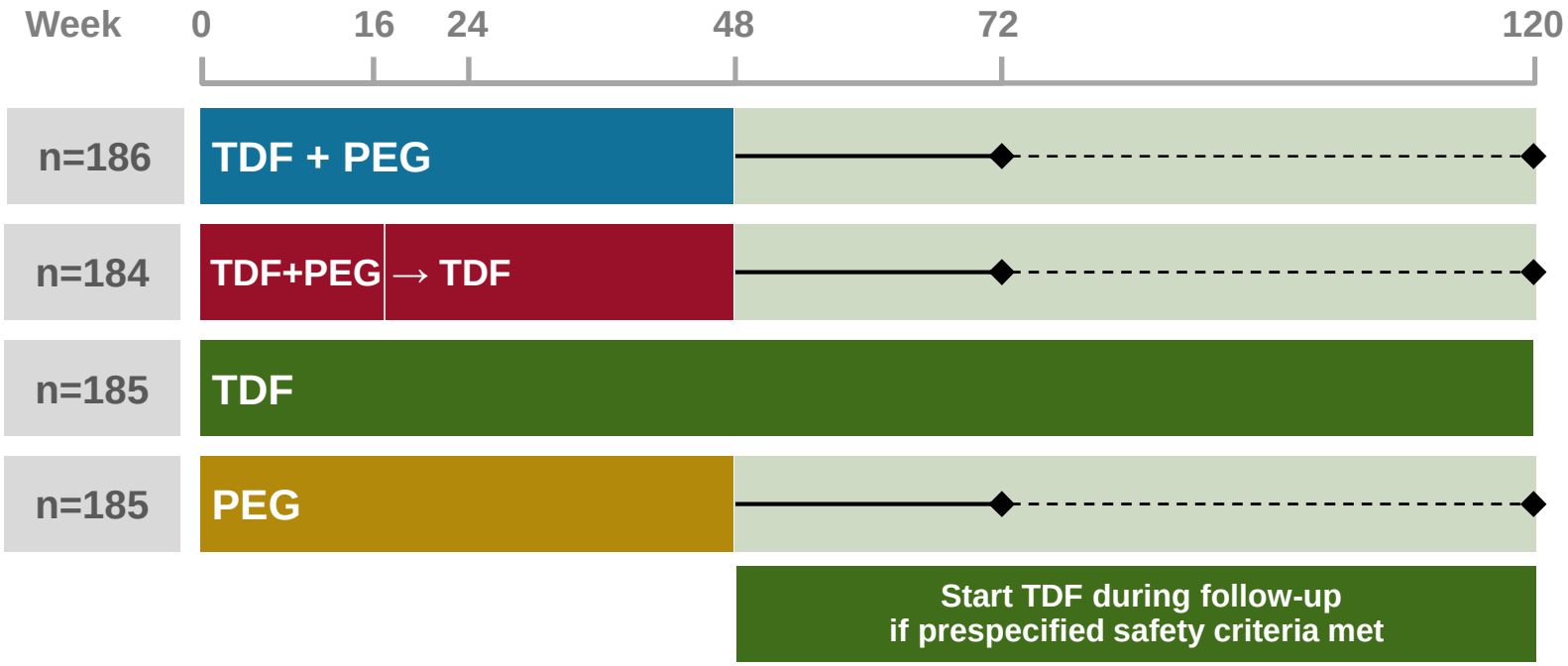
- With the Current available drugs

- With New Drugs

Which strategy to enhance HBsAg loss rates?



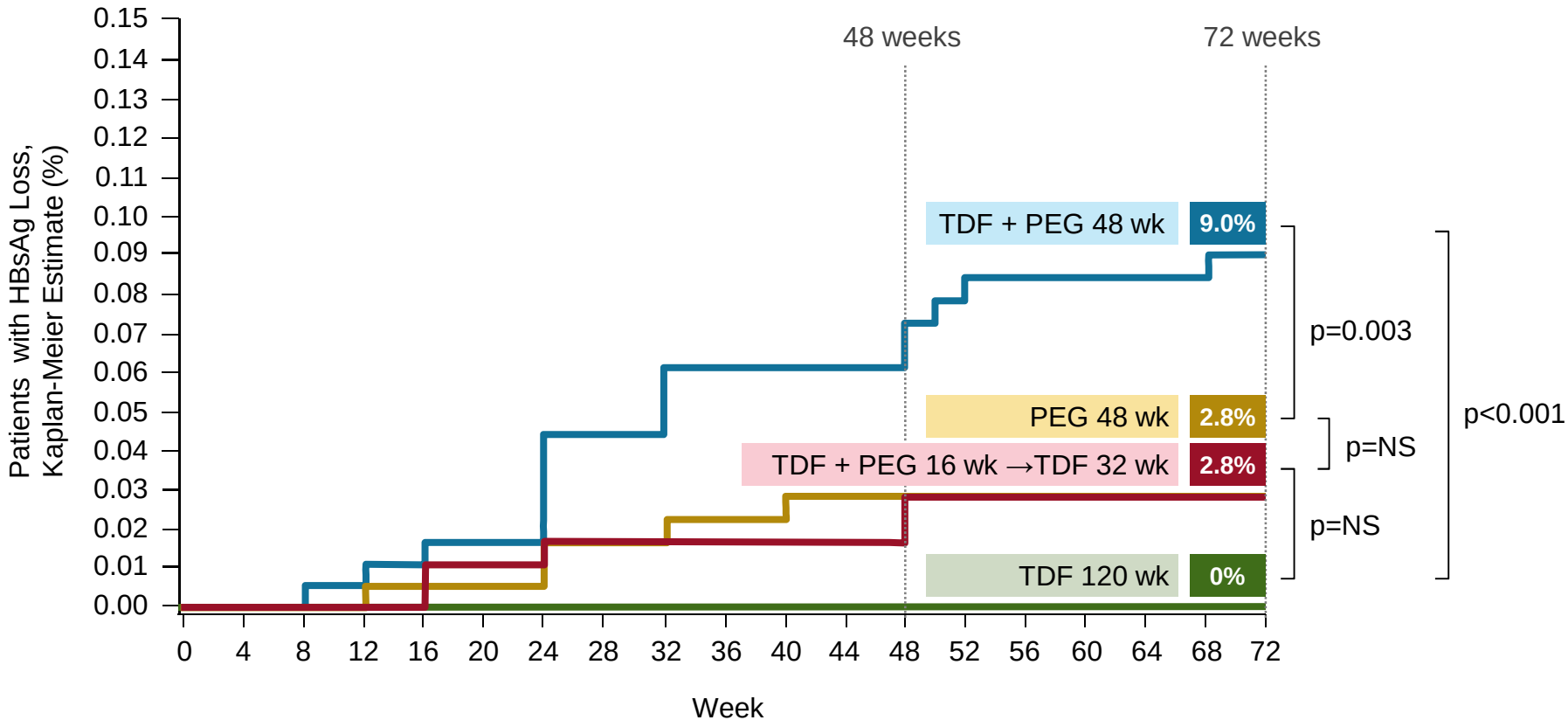
Tenofovir Disoproxil Fumarate plus Peginterferon Alfa-2a Combination Therapy for Chronic Hepatitis B Study Design



- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Chan et al. AASLD 2104

Results: HBsAg Loss Over Time (Week 72)



- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])
  - 5/7 had ≤1 week of therapy after HBsAg loss

Chan et al AASLD 2104

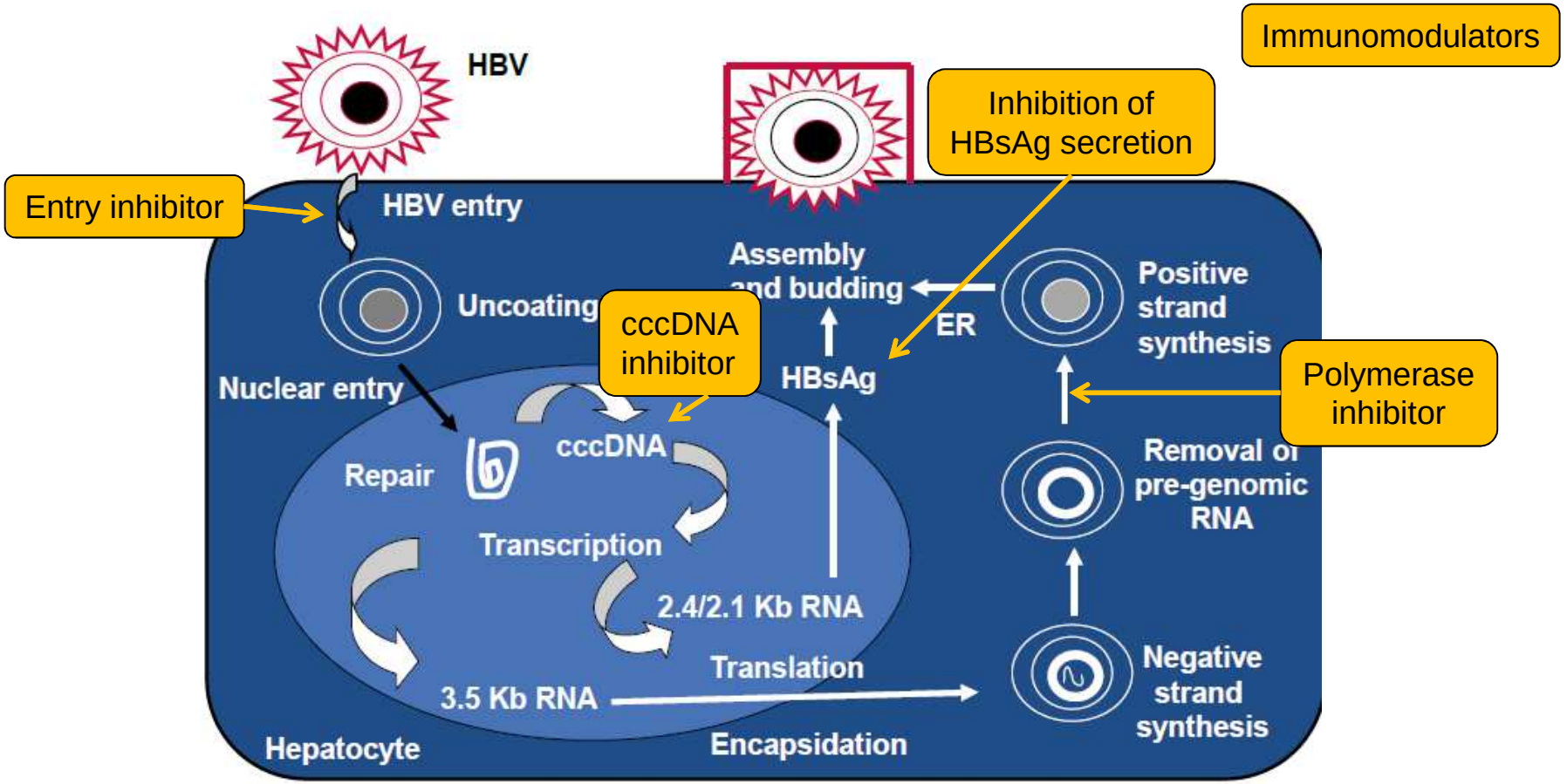
New Strategies for Finite HBV therapy

- With the current available drugs

- With New Drugs

What pathways or approaches might we take?

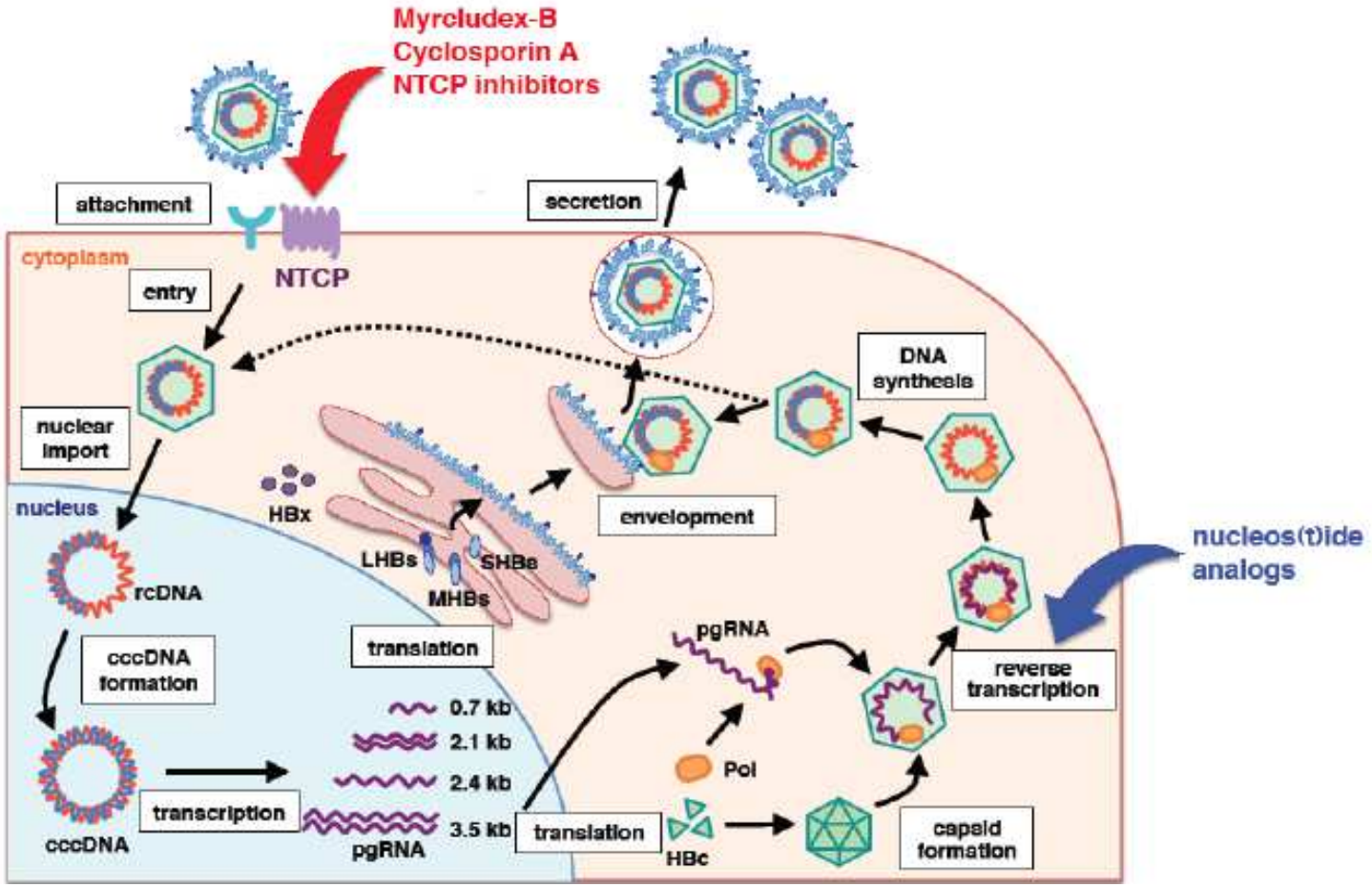
- The virus replication cycle offers many targets



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

ER: endoplasmic reticulum

Identification of NTCP as an HBV receptor



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

NTCP: sodium taurocholate cotransporting polypeptide

A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

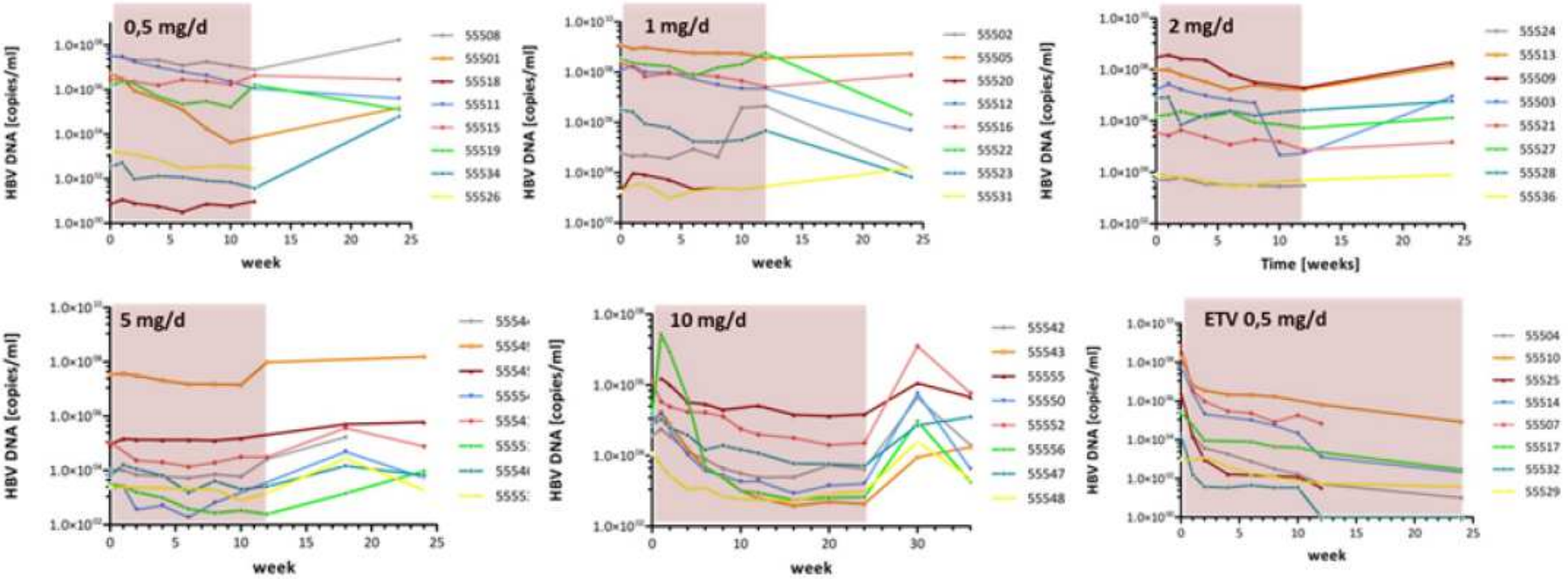
Myrcludex-B is a synthetic lipopeptide consisting of a myristoylated pre-S1 domain of the large HBsAg with binding to the HBV entry receptor

Patient Population	Treatment Arms	Endpoints
Cohort A Chronic HBV HBeAg negative HBV DNA > 2000 IU/mL No Cirrhosis • N=40	• Myr B, daily SC at 0.5, 1, 2, 5&10 mg • 12 wk treatment, with 12 wk follow-up (10 mg received 24 wk of treatment)	• Safety and tolerability • Efficacy (ALT, HBV DNA, HBsAg) • PK • Immunogenicity • Bile salt elevations
Cohort B Chronic HDV 12.5% cirrhosis • N=24	• 24 wk of Myr B, daily SC at 2 mg, followed by 48 wk Peg-IFN • 24 wk of Myr B added to 48 wk Peg-IFN • 48 wk Peg-IFN alone	• Safety and tolerability • Efficacy (ALT, HDV DNA) • PK • Immunogenicity • Bile salt elevations

Urban S et al. AASLD 2014;LB20

A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B

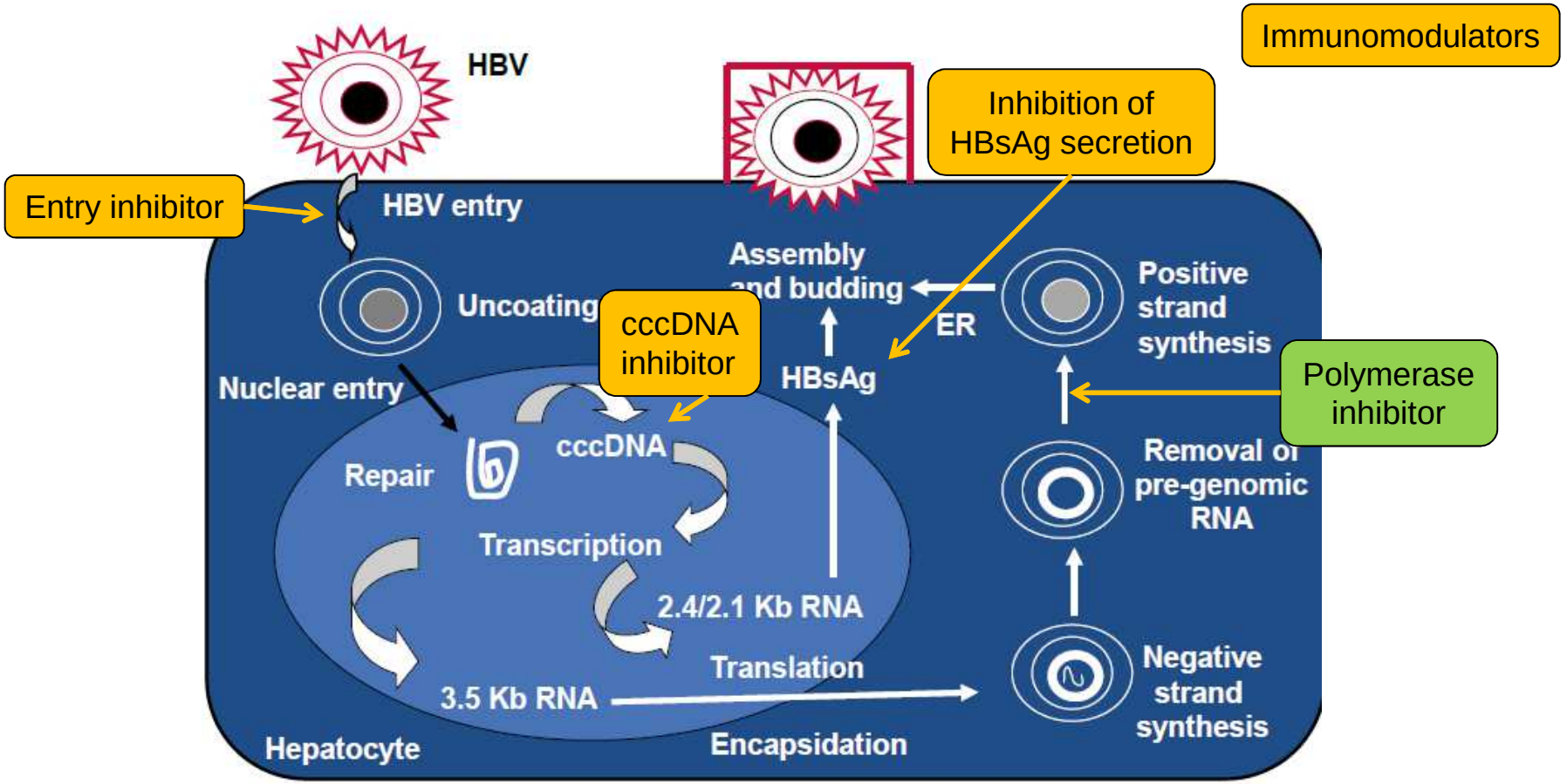
- At week 24, HBV DNA levels declined in all treatment groups
- >1 log reduction was observed in 6/8 (75%) patients in the 10 mg cohort
- 7/40 patients showed >1 log HBV DNA reduction in lower dosing groups
- No significant effect on HBsAg was observed after 24 weeks of treatment



Urban S et al. AASLD 2014;LB20

What pathways or approaches might we take?

- The virus replication cycle offers many targets

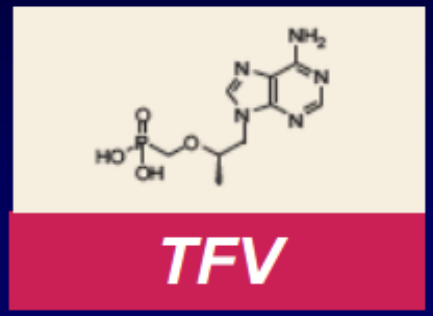


Adapted from Stein LL, Loomba R. Infect Disord Drug Targets 2009;9:105–16

ER: endoplasmic reticulum

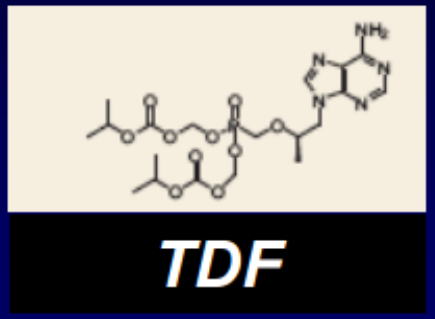
Tenofovir Alafenamide Fumarate (TAF)

Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI s)



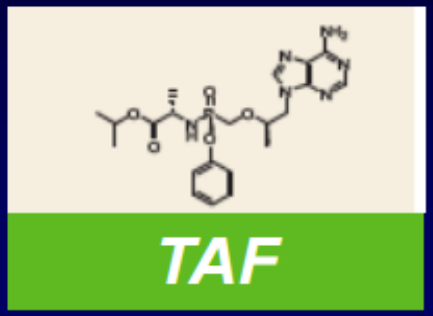
TFV

Tenofovir



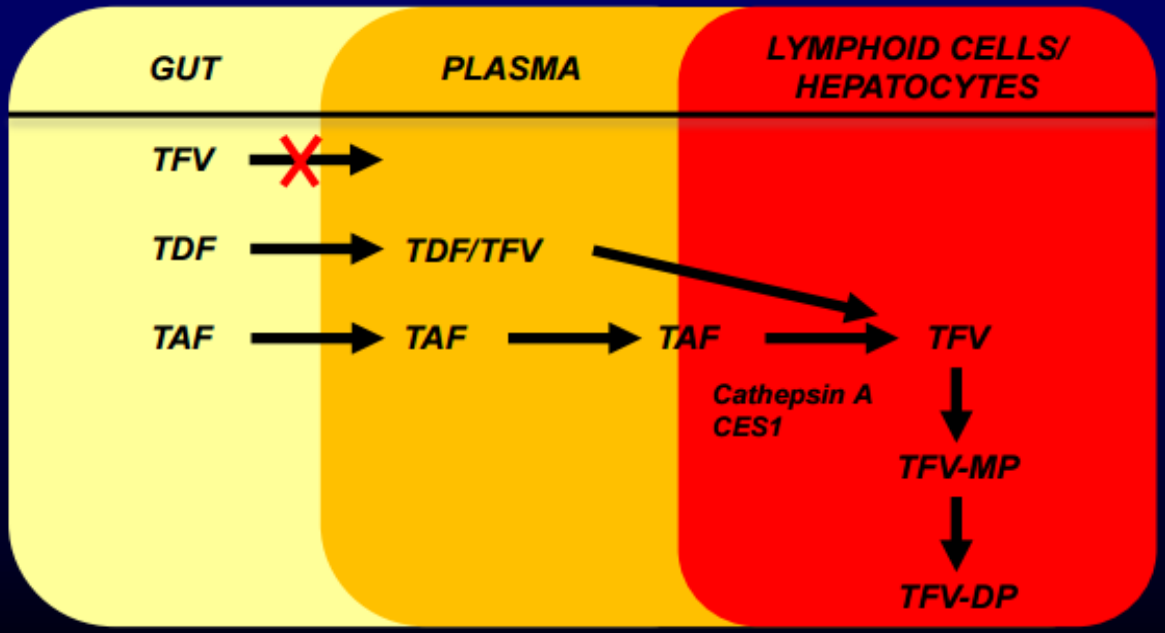
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide

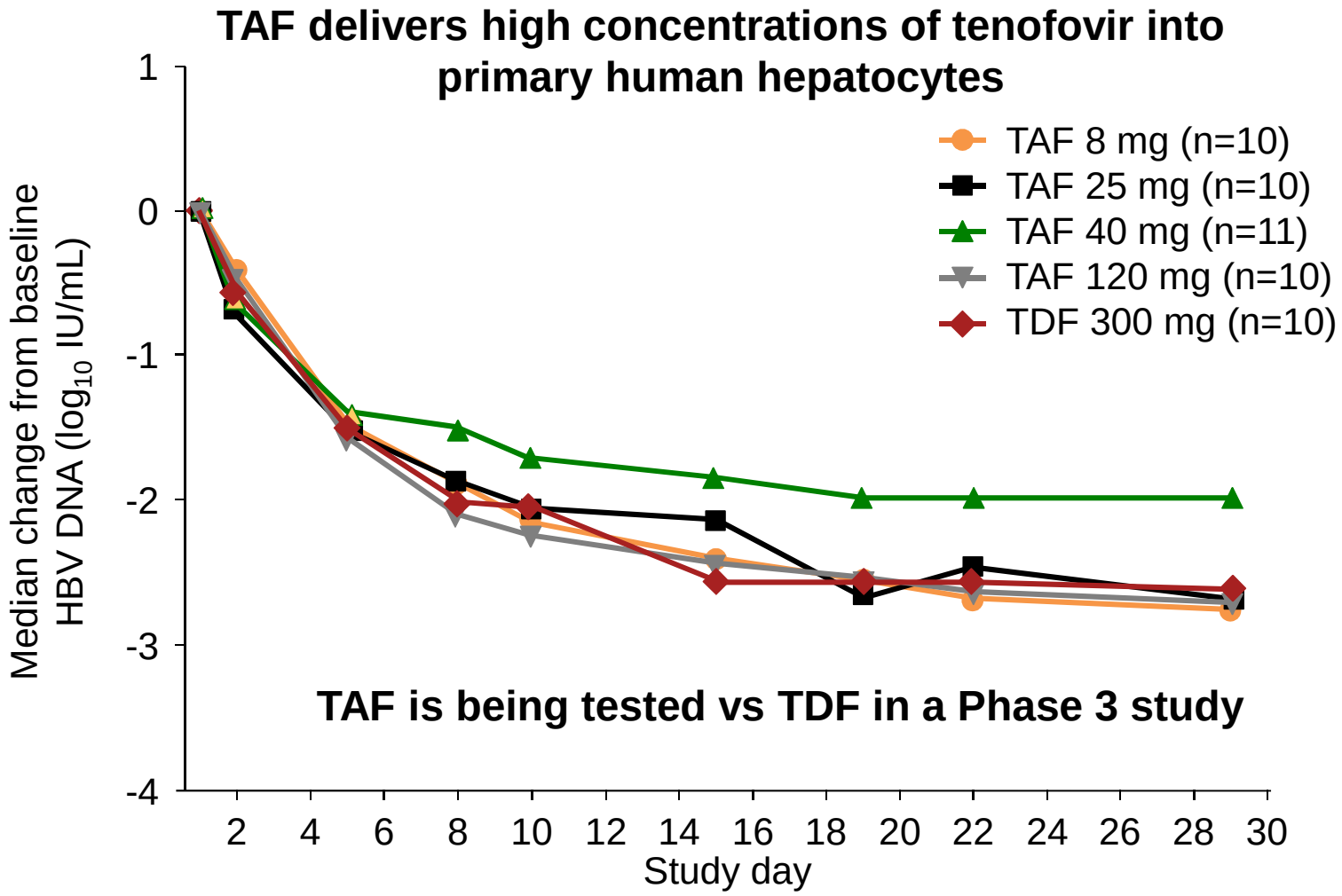


- *Improved stability in plasma:*
  - *Enhanced delivery of active form (TFV-DP) to hepatocytes*
  - *Lower doses are used; systemic exposures of TFV reduced*

Agarwal K et al. AASLD 2013
Murakami E et al. HepDART 2013

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

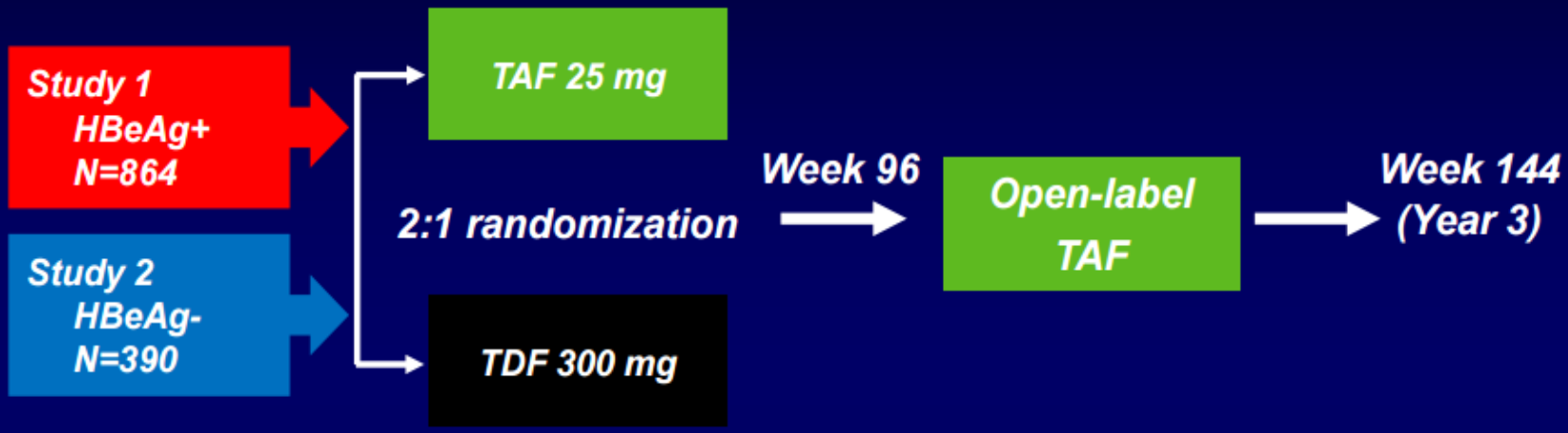
28 day safety, and antiviral activity of tenofovir alafenamide for treatment of chronic hepatitis B



Agarwal K, et al. J Hepatol 2015

TAF is an investigational agent and not licensed for use in CHB

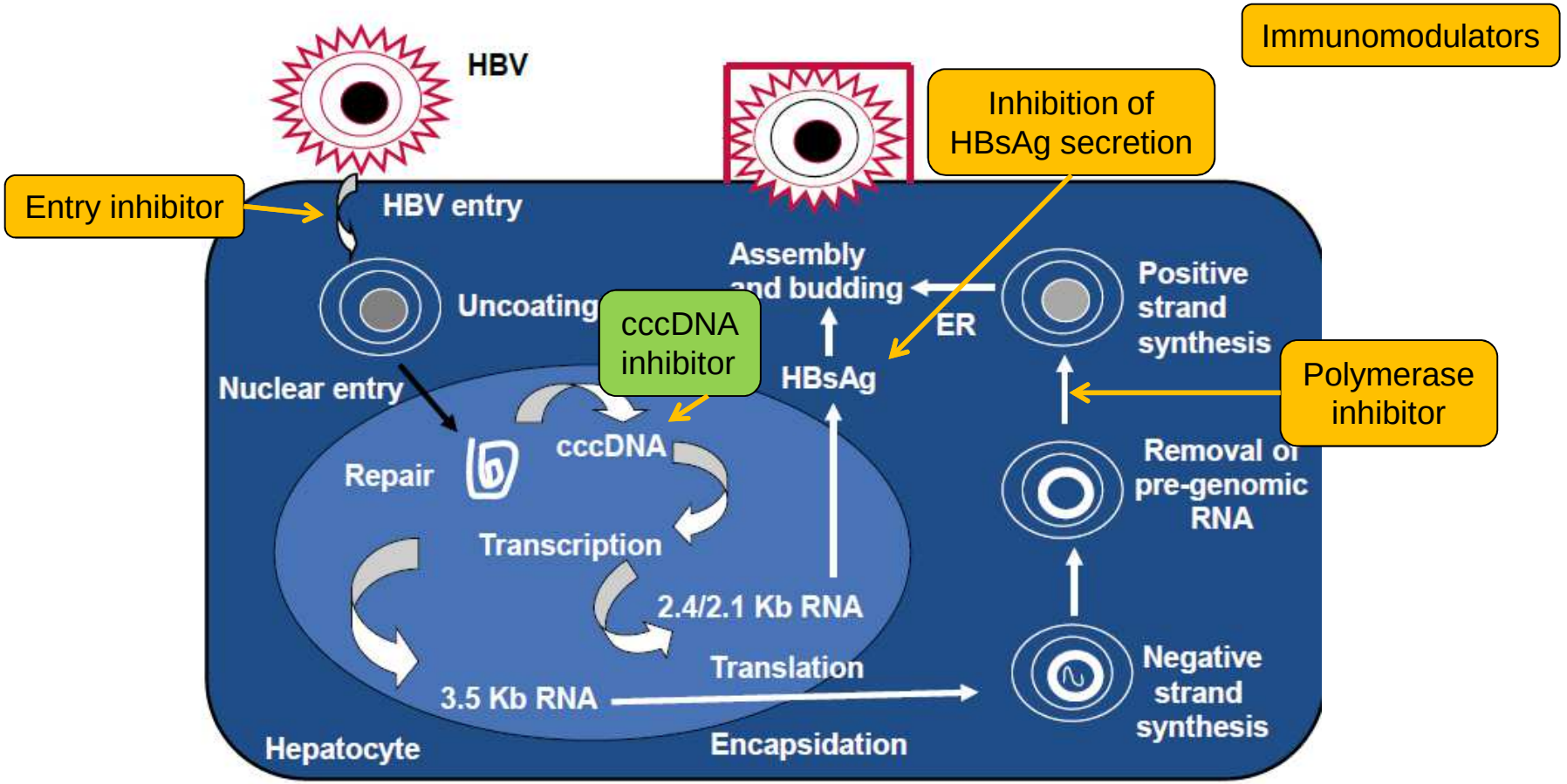
TAF Phase III Studies



- 2 phase 3, randomized, double-blind studies
- Primary endpoint (non inferiority margin of 10%)
  - HBV DNA <29 IU/mL at Week 48
- Secondary endpoints
  - Bone mineral density
  - Renal parameters

What pathways or approaches might we take?

- The virus replication cycle offers many targets

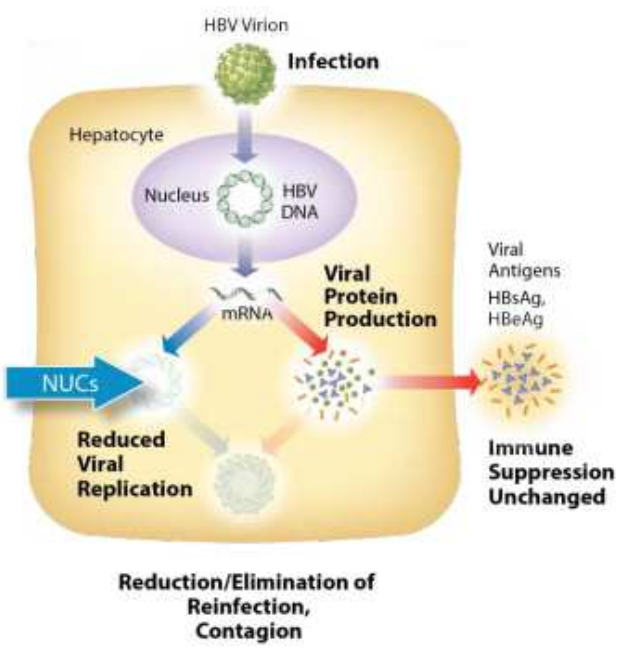


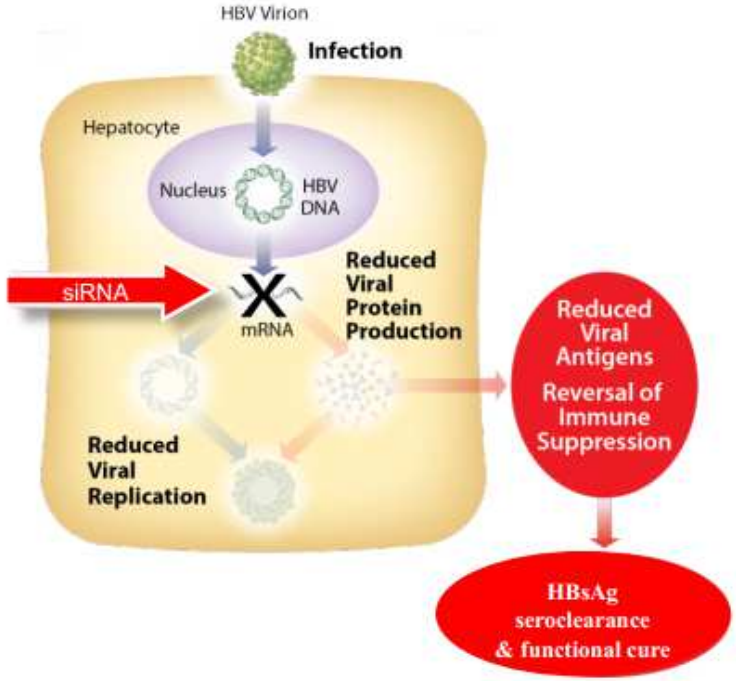
Adapted from Stein LL, Loomba R. Infect Disord Drug Targets 2009;9:105–16

ER: endoplasmic reticulum

Phase II, study of ACR-520 a short interfering RNA containing (*siRNA)*

- ARC-520, an RNAi therapeutic, liver targeted aimed to reduce all HBV transcripts via RNA interference
- In HBV infected chimpanzee a reduction of viral particles and decreased expression of viral proteins was observed.
- Viral proteins (HBsAg and HBeAg) have been implicated in immune tolerance, sustained infection and disease progression

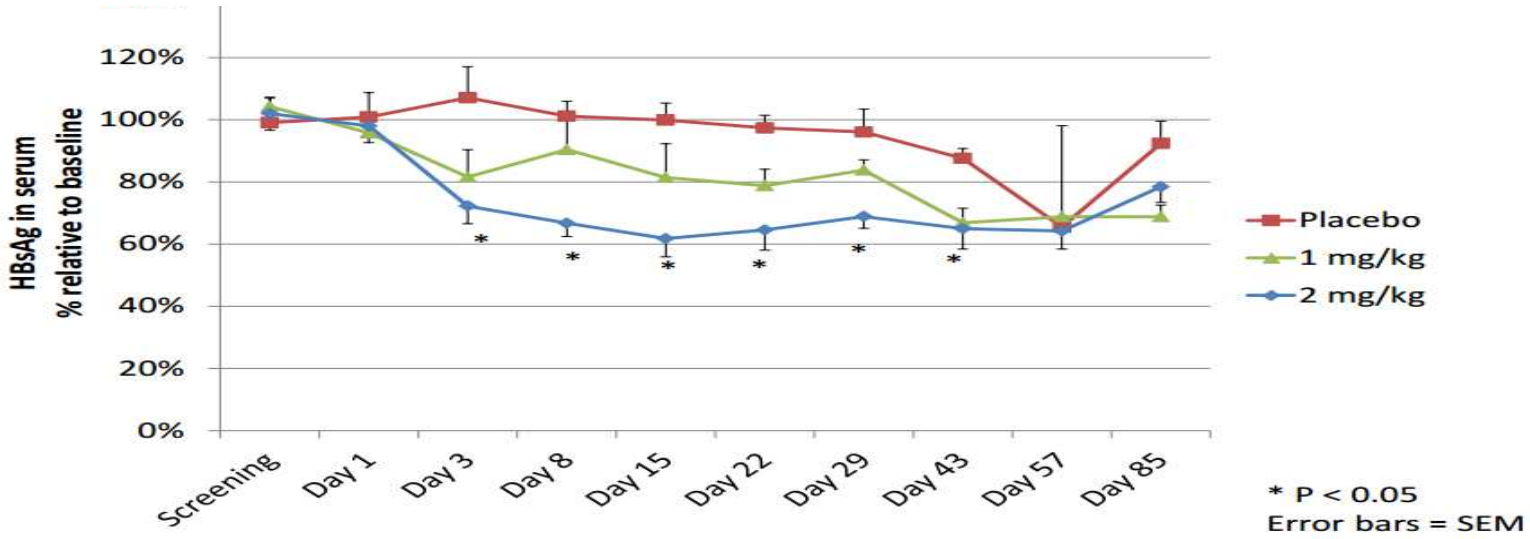




Phase II, Dose-Ranging Study of ACR-520, a siRNA-Based Therapeutic, in Patients with Chronic HBV Infection

16 Chinese patients with Chronic hepatitis B

ARC-520 activity is measured by % of qHBsAg decline from baseline after a single iv dose



- In Cohort 1, mean nadir HBsAg was -39% (range -22 to -57) with a mean change on day 85 of -31% (range -14 to -39)
- In cohort 2, mean nadir HBsAg was -51% (range -46 to -59) with a mean change on day 85 of -22% (range -7 to -40)

Yuen M et al. AASLD 2014 LB-21

Phase 1a Safety and Pharmacokinetics of NVR 3-778 HBV Core Inhibitor

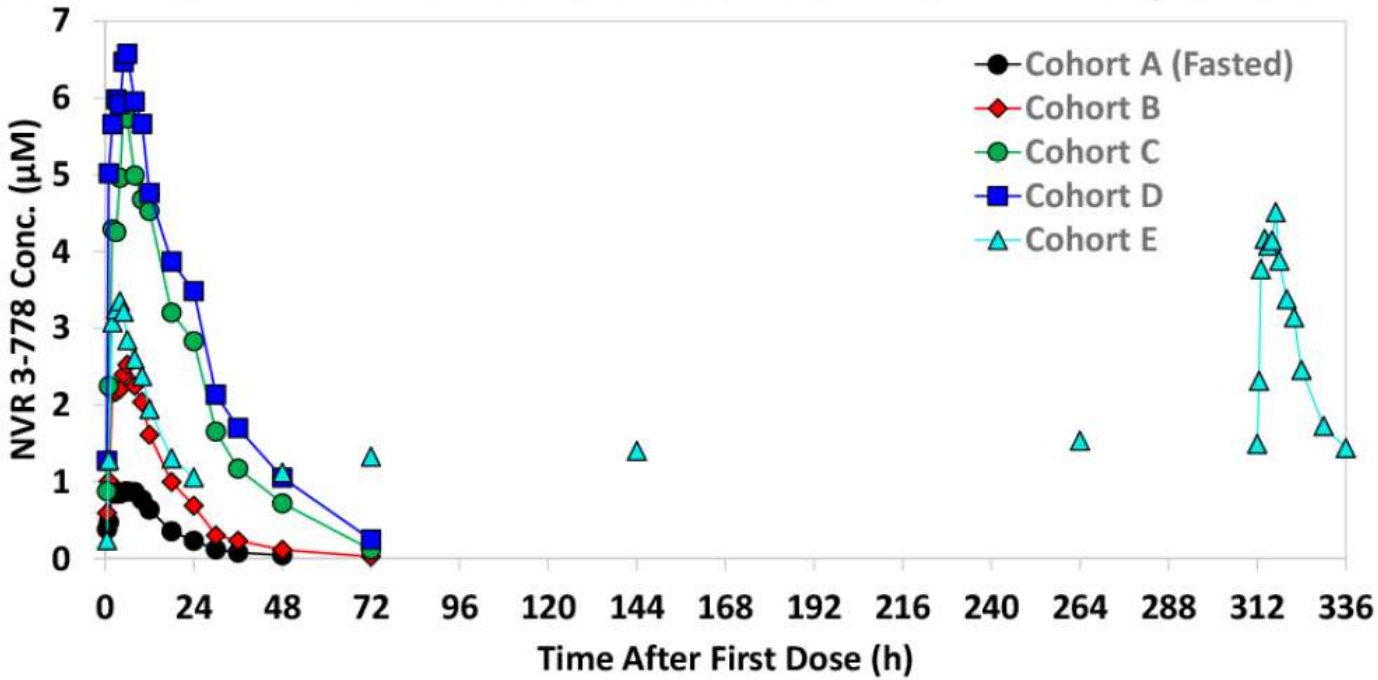
- NVR 3-778 is a potent and selective oral HBV core inhibitor that inhibits HBV nucleocapsid assembly and potentially other core-mediated functions in the HBV lifecycle
- HBV Core inhibitors potential to boost durable responses by inhibiting HBV DNA replication, viral assembly, cccDNA replenishment and hepatic reinfection
- In vitro antiviral HBV activity similar to potent NAs

Patient Population	Treatment Arms	Endpoints
Part I: Healthy volunteers **Part II**: Chronic HBV Treatment-naïve HBeAg positive N=112	**Part I**: 28 days of NVR 3-778 (50-200 mg QD oral) vs. placebo **Part II**: 28 days of NVR 3-778 (QD oral) + Pegasys (subQ) vs. Pegasys	**Part I**: Safety and PK **Part II**: Safety, PK, and antiviral activity

Gane E et al. AASLD 2014 LB19

Phase 1a Safety and Pharmacokinetics of NVR 3-778 HBV Core Inhibitor

- Cohort E (200 mg QD): peak levels (C_{max}) = ~3.5 µM, 24 hr trough levels > 1 µM
- Exposures exceed HBV inhibitory concentration in HepG2 cells (EC_{50} = 0.24 µM; EC_{90} = 0.62 µM)
- Doses > 200 mg may afford continuous HBV inhibition with QD dosing schedule
- **Phase 1a: Mean NVR 3-778 Plasma Concentrations Over Time by Cohort**



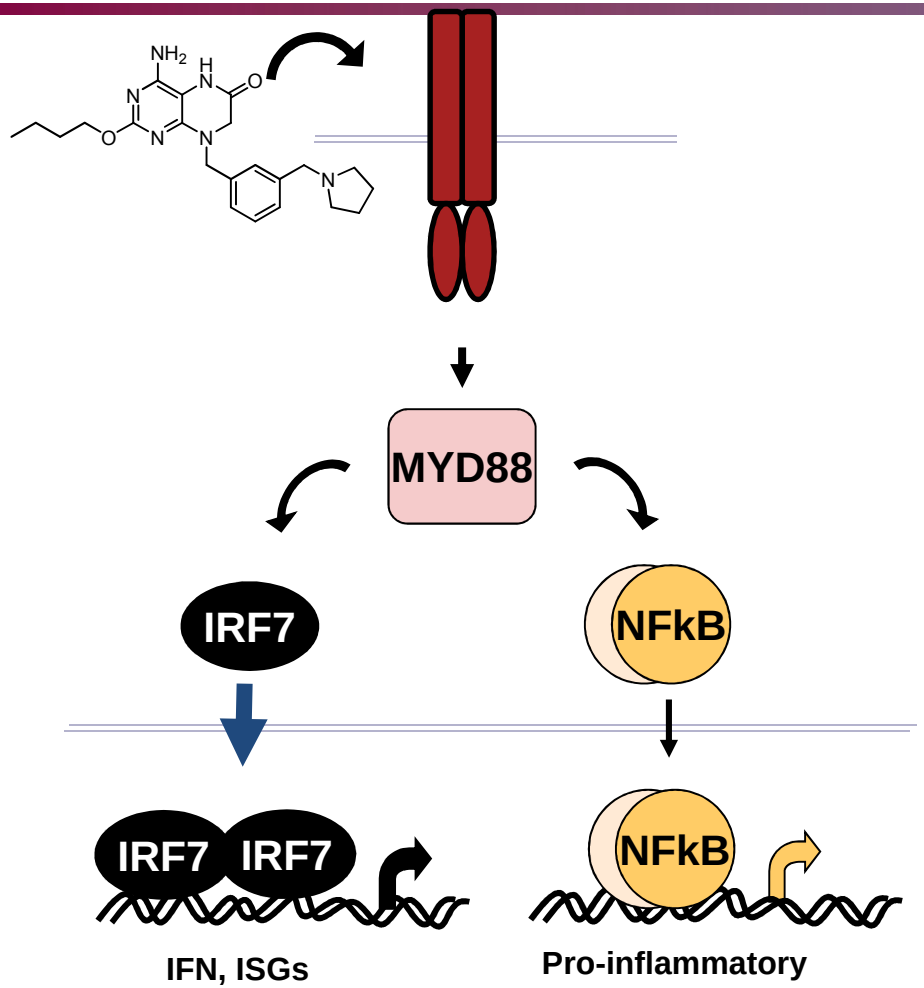
Gane E et al. AASLD 2014 LB19

Immunomodulators

- **Immune dysfunction is the basis for chronic HBV infection**
  - Immune modulation aims to induce immune control with a view to finite therapy
  - Potential for therapeutic immune modulation in CHB shown by durable responses in a low proportion of patients treated with a finite course of PEG-IFN
- **Toll-like receptors (TLRs)**
  - Recognise a variety of broadly conserved pathogen-associated molecular patterns
  - TLR agonists trigger innate and adaptive immune responses
  - Currently in Phase 1/2
- **Therapeutic vaccines**
  - Vaccination with recombinant HBV proteins overcomes diminished T-cell response in CHB

Marcellin P, et al. Gastroenterology 2009;136:2169–79;
Moucari R, et al. J Hepatol 2009;50:1084–92;
Lanford RE, et al. Gastroenterology 2013;144:1508–17

TLR-7 agonists



- TLR-7 activation leads to secretion of type I IFN, T-cell co-stimulation and B-cell differentiation
- GS-9620 is an oral TLR-7 agonist with nanomolar potency
- Preclinical studies show GS-9620 reduces HBsAg and HBV DNA in woodchucks and chimpanzees
- Phase 1a single ascending dose study complete: favourable safety profile shown in healthy volunteers (N=75)

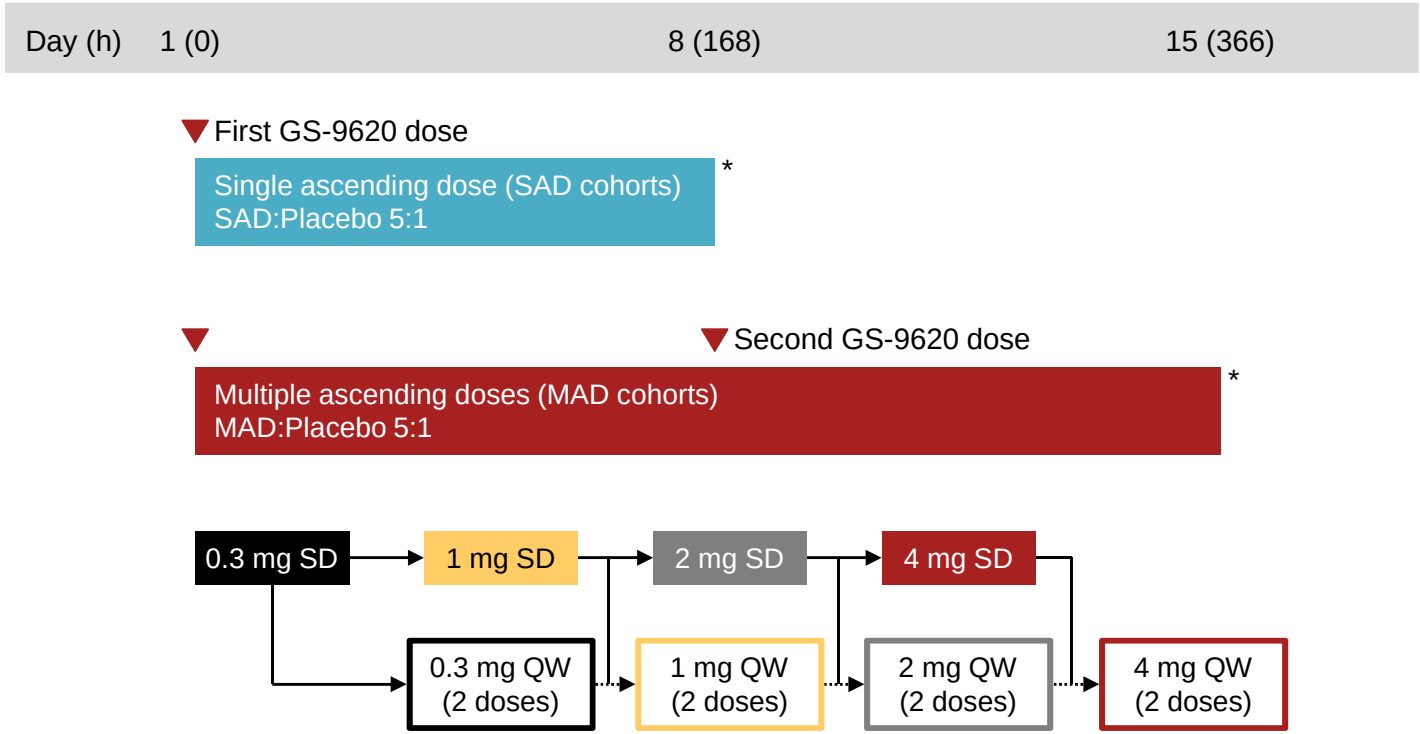
Gane E, et al. AASLD 2013; Abstract 9896

GS-9620 is an investigational agent and not licensed for use in CHB;
IRF: interferon regulatory transcription factor;
NFκB: nuclear factor kappa B; ISG: interferon stimulating genes

TLR-7 agonist (GS-9620) in patients with CHB

TLR-7 activation leads to secretion of type I IFN,
T-cell co-stimulation and B-cell differentiation

Patients with CHB: treatment naïve (N=49) or virologically suppressed (N=50)

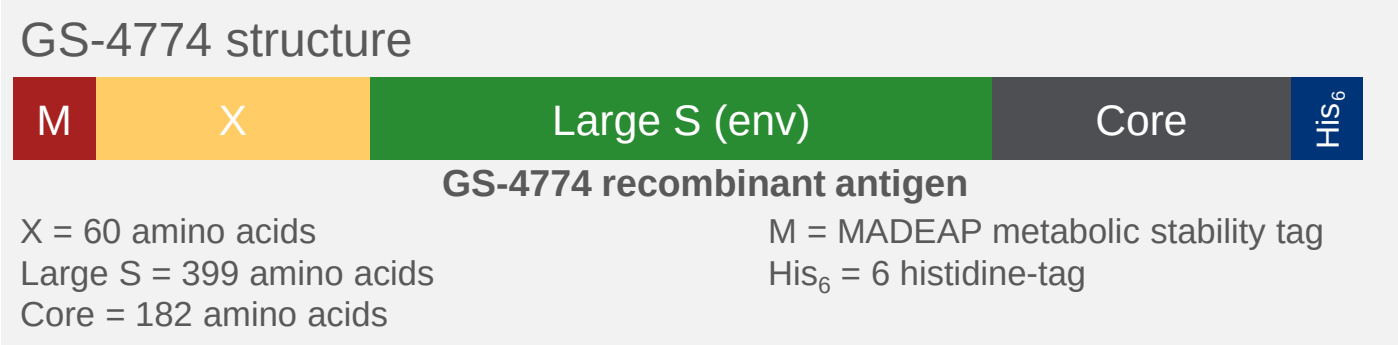


Gane E, et al. EASL 2014; Poster 1052;
Clinicaltrials.gov NCT01590654 and NCT01590641

*Follow-up visits at 2 and 4 weeks from last dose;.
GS-9620 is an investigational agent and not licensed for use in CHB;
QW: once weekly; SD: single dose

Therapeutic vaccination with GS-4774

- GS-4774 is a yeast-based vaccine expressing recombinant X, large S and core HBV antigens



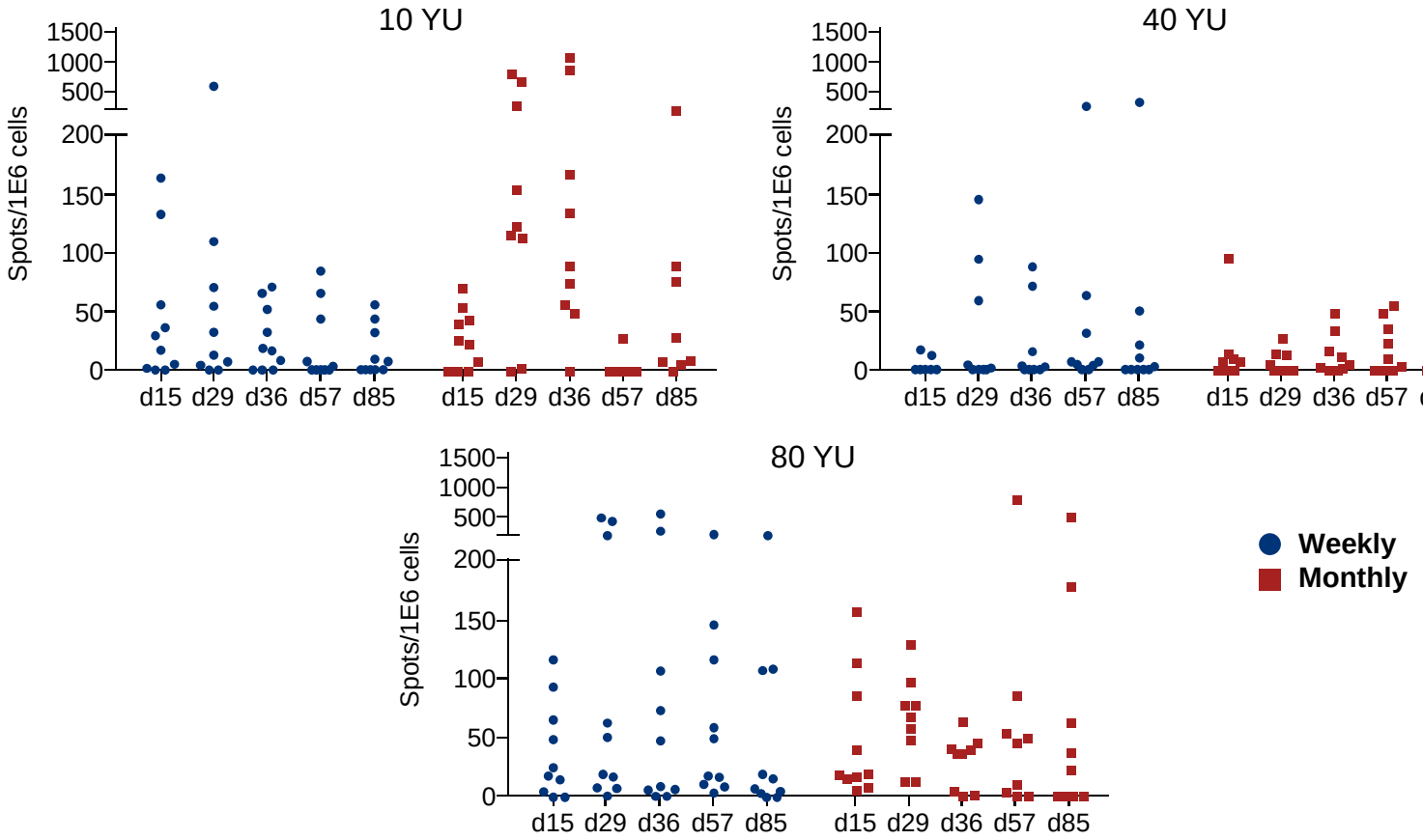
- Weekly versus monthly doses for 3 consecutive months studied in healthy volunteers (n=60)
- Immune response was assessed

Gaggar A, et al. AASLD 2013; Abstract 9952;
Clinicaltrials.gov NCT01779505

GS-4774 is an investigational agent and not licensed for use in CHB;
env: envelope

Detectable HBV-specific immune responses in the majority of patients

Combined response to HBsAg, HBcAg and HBx



Gaggar A, et al. AASLD 2013; Abstract 9952;
Clinicaltrials.gov NCT01779505

GS-4774 is an investigational agent and not licensed for use in CHB;
HBcAg: hepatitis B core antigen; HBx: hepatitis B x-gene

How may a HBV curative regimen look in the future – a combination approach?

Approach	Potential benefit
Entry/release inhibitor	Prevent entry/spread
cccDNA inhibitor	Deplete cccDNA reservoir
Potent polymerase inhibitor	Suppress replication
Immune modulator	Activate or restore antiviral immunity