Managing HBV Infection

HBsAg Seroclearance in Untreated Patients With CHB

- Retrospective cohort study of untreated patients with CHB in North America (n = 1635) and Asia (n = 8979)
- Male sex, higher age or ALT level, HBeAg negativity predicted spontaneous HBsAg seroclearance in multivariable analysis
- Annual HBsAg seroclearance rate: 1.33% (95% CI: 1.26% to 1.40%)
  - CIR: 4.92% at 5 yrs, 11.27% at 10 yrs, 19.36% at 15 yrs, 25.42% at 20 yrs

BL Characteristic		aHR* (95% CI)	*P* Value
Sex	▪ Female	1	
	▪ Male	1.17 (1.04-1.33)	.012
Age, yrs	▪ < 35	1	
	▪ 35-44	1.25 (1.06-1.48)	.009
	▪ 45-54	1.52 (1.28-1.80)	< .001
	▪ > 55	1.79 (1.49-2.15)	< .001
HBeAg status	▪ Negative	1	
	▪ Positive	0.25 (0.19-0.32)	< .001
ALT	▪ Every 10 U/L increase	1.01 (1.00-1.01)	< .001

*Adjusted for age, sex, race, study setting, BL cirrhosis, ALT level, and HBeAg status.

Yeo. AASLD 2018. Abstr 212.

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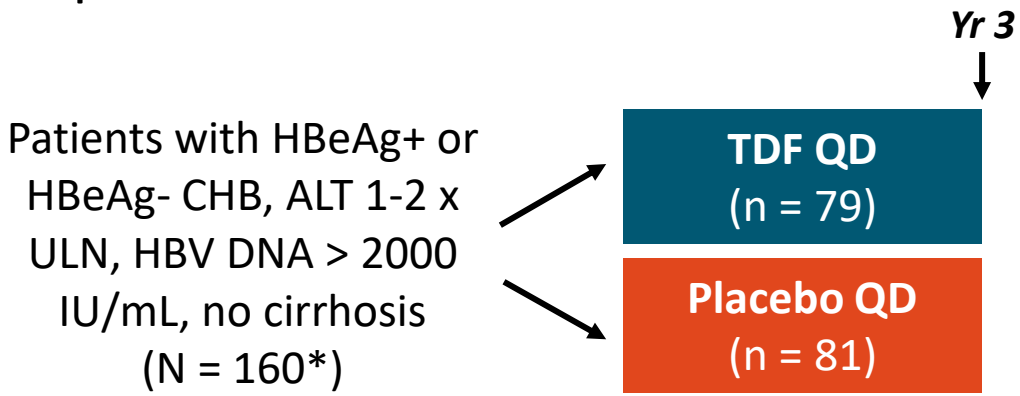
TDF vs Placebo for Patients With HBsAg-Positive CHB and Mild ALT Elevation

- Multicenter, randomized, triple-blind phase IV trial



*Results for 132 patients completing treatment with paired biopsy; last patient to finish in December 2018.

- Primary endpoint: histological progression of liver fibrosis, resolution of necroinflammation

Baseline Characteristic	TDF (n = 65)	Placebo (n = 67)
Fibrosis stage, %		
▪ 0	9.2	10.5
▪ 1	43.1	34.3
▪ 2	35.4	28.4
▪ 3	9.2	13.4
▪ 4	3.1	13.4
HBeAg positive, %	20.0	26.9
Median HBsAg, log IU/mL (IQR)	3.03 (2.39-3.61)	3.15 (2.61-3.84)

Hsu. AASLD 2018. Abstr 264. NCT01522625.

Slide credit: clinicaloptions.com

TDF vs Placebo for Patients With HBsAg-Positive CHB and Mild ALT Elevation: Key Findings

Outcome at Yr 3	TDF (n = 65)	Placebo (n = 67)	*P* Value
Progression, n (%)			
▪ In fibrosis stage*	15 (23.1)	30 (44.8)	.01
▪ To cirrhosis†	2 (3.1)	9 (13.4)	.05
Inflammation score, n (%)			
▪ Median (IQR)	2 (1-2)	3 (2-4)	.0004
▪ Decrease	34 (52.3)	29 (43.3)	.38
Undetectable HBV DNA,‡ %	81.5	13.4	< .0001
ALT normalization, %	75.4	52.2	.007
Entecavir given for clinical flare, n	2	10	NR
HCC, n	2	1	1.0
HBsAg loss, n	0	1	1.0
HBeAg loss in HBeAg-positive patients, n/N (%)	2/13 (15.4)	5/18 (27.8)	.67

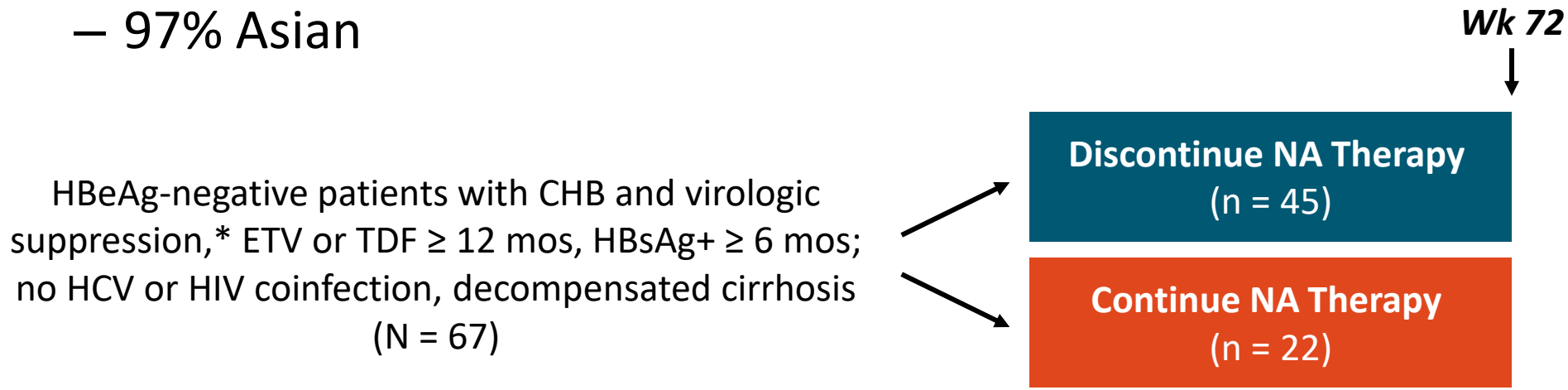
*RR: 0.52 (95% CI: 0.31-0.85). †RR: 0.23 (95% CI: 0.06-0.88). ‡< 6 IU/mL.

Hsu. AASLD 2018. Abstr 264.

Slide credit: clinicaloptions.com

STOP: Nucleos(t)ide Analogue Cessation in HBeAg-Negative Patients With CHB

- Prospective, randomized, controlled, open-label phase IV trial
  - 97% Asian



*If HBeAg+ at NA start, HBeAg seroconversion + undetectable HBV DNA ≥ 12 mos; if HBeAg-, undetectable HBV DNA ≥ 36 mos.

- Primary endpoint: HBV DNA < 2000 IU/mL at Wk 48

Patients retreated for HBeAg seroreversion, HBV DNA > 2000 IU/mL + (ALT > 5 x ULN at 2 consecutive visits or > 15 x ULN at any visit), or HBV DNA > 20,000 IU/mL at 2 consecutive visits; ALT ULN: 40 IU/mL.

Liem. AASLD 2018. Abstr 268.

STOP: Virologic and Safety Outcomes

Outcome, n (%)	Stop (n = 45)	Continue (n = 22)
HBV DNA < 2000 IU/mL		
▪ Wk 48*	11 (24)	21 (95)
▪ Wk 72	12 (27)	NR
ALT		
▪ Grade 3 (> 5 x ULN)	22 (49)	0
▪ Grade 4 (> 20 x ULN)	7 (16)	0

*Primary endpoint.

- Limited HBsAg decline across arms

Outcome, %	Stop (n = 45)			
	Wk 0	Wk 24	Wk 48	Wk 72
Retreatment	0	27	29	38
Clinical relapse†	0	7	4	13
Virologic relapse‡	0	33	40	20
Sustained response§	100	31	24	27
HBsAg loss	0	2	2	2

†HBV DNA > 2000 IU/mL + ALT > 1.5 x ULN.
‡Lone HBV DNA > 2000 IU/mL.
§HBeAg negative + HBV DNA < 2000 IU/mL + ALT < 1.5 x ULN.

Liem. AASLD 2018. Abstr 268.

Slide credit: clinicaloptions.com

Predictors of Relapse After NA Cessation in CHB

- Unmet need for biomarkers to assess risk of treatment withdrawal
  - Data from multiple small prospective studies support use of HBcrAg and/or HBsAg to predict risk of relapse

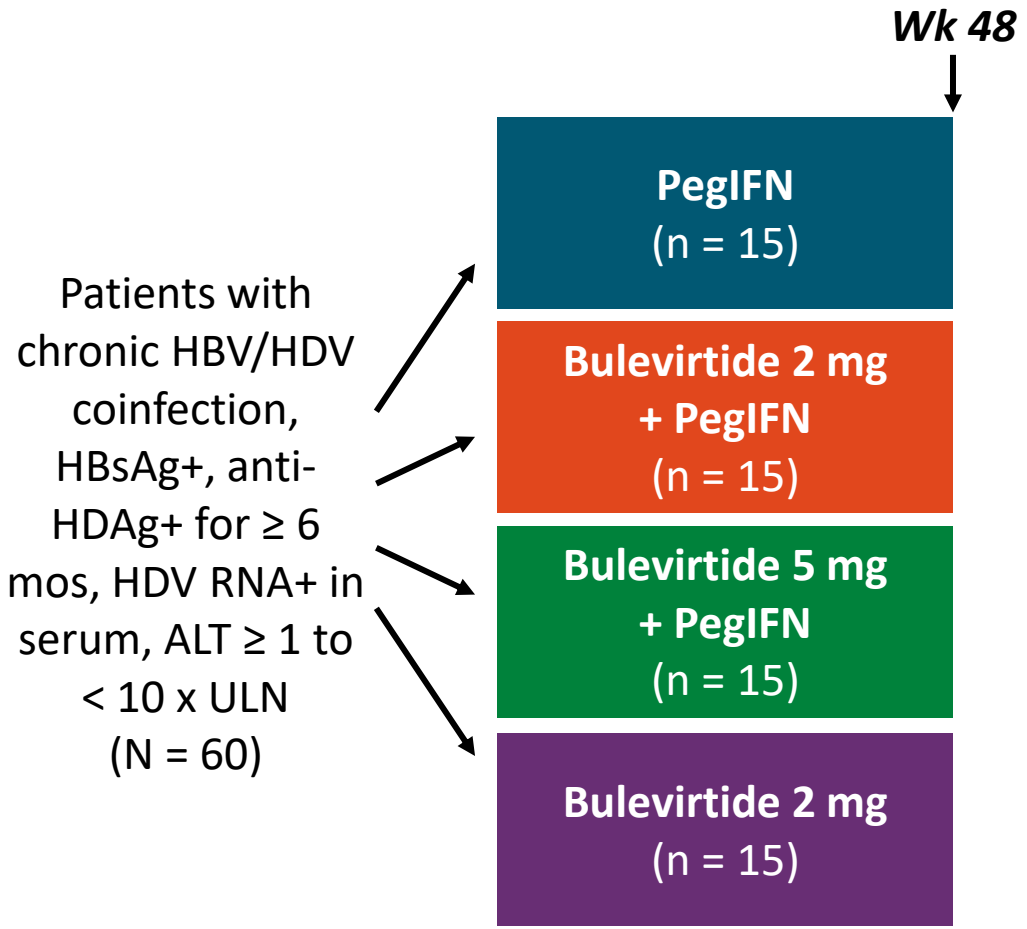
Prospective Study	Findings
(N = 135)[1]	▪ HBcrAg, HBsAg independently predict off-treatment clinical relapse, can be combined with age, ALT, and TDF use in novel risk score
DARING-B (N = 60)[2]	▪ HBsAg loss associated with lower levels of HBsAg at ETV/TDF d/c ▪ HBcrAg levels at d/c, 1 mo before retreatment predict probability of retreatment
(N = 103)[3]	▪ Significantly lower HBV reactivation rate in patients with BL HBsAg ≤ vs > 10 IU/mL ▪ Lower BL HBcrAg level associated with reduced HBV reactivation rate in patients with BL HBsAg > 20 IU/mL
(N = 15)[4]	▪ HBcrAg or pregenomic HBV RNA at TDF d/c may predict significant ALT flares necessitating retreatment

1. Hsu. AASLD 2018. Abstr 397. 2. Papatheodoridi. AASLD 2018. Abstr 408. 3. Seto. AASLD 2018. Abstr 417. 4. Carey. AASLD 2018. Abstr 530.

Slide credit: clinicaloptions.com

MYR203: Bulevirtide ± PegIFN in Patients With Chronic HBV/HDV Coinfection

- Interim analysis of randomized, multicenter, open-label phase II study
  - **Bulevirtide**: first-in-class, investigational HBV/HDV entry inhibitor
    - Synthetic peptide that blocks bile salt transporter NTCP
    - Self-administered SC QD
- Primary endpoint: undetectable HDV RNA at Wk 72



Wedemeyer. AASLD 2018. Abstr 16.

Slide credit: clinicaloptions.com

MYR203: Efficacy and Safety

Wk 48 Outcome	PegIFN (n = 15)	Bulevirtide 2 mg + PegIFN (n = 15)	Bulevirtide 5 mg + PegIFN (n = 15)	Bulevirtide 2 mg (n = 15)
Median Δ from BL in HDV RNA, $\log_{10}$	-1.14	-3.62	-4.48	-2.84
Undetectable HDV RNA, n	2	9	6	2
ALT normalization, n	4	4	7	10
Combined treatment response,* n	2	4	6	8
HBsAg response,† n	0	7	2	0
Asymptomatic rise in bile salts, %	67	60	87	53

*Undetectable or ≥ 2 $\log_{10}$ IU/mL decline in HDV RNA + normal ALT. †Undetectable or ≥ 1 $\log_{10}$ decline.

- 95% (57/60) completed 48 wks of treatment; 13.6% (6/44) missed bulevirtide doses
- Most bulevirtide-related AEs were mild to moderate (none serious, none causing d/c), not dose dependent, resolved without intervention or sequelae

Wedemeyer. AASLD 2018. Abstr 16.

Slide credit: clinicaloptions.com

JNJ-6379 in Treatment-Naive Patients With CHB

- Phase I dose-escalating study in the European Union and Asia/Pacific
  - **JNJ-6379**: investigational capsid assembly modulator

- Main endpoints including: safety, PK, antiviral activity

Zoulim. AASLD 2018. Abstr 74. NCT02662712.

Slide credit: clinicaloptions.com

JNJ-6379 in CHB: Safety and Efficacy

- No drug-related serious AEs; 1 d/c for AEs (grade 4 ALT, grade 3 AST elevation at Day 8 in 150-mg group)
- Mean HBV DNA and RNA levels declined with JNJ-6379, regardless of dose
  - No relevant changes observed in HBsAg or HBeAg
- Dose-proportional pharmacokinetics, with similar clearance between doses

Outcome	JNJ-6379				Placebo (n = 14)
	25 mg (n = 8)	75 mg (n = 8)	150 mg (n = 9)	250 mg (n = 9)	
≥ 1 AE, n (%)	5 (63)	4 (50)	6 (67)	4 (44)	9 (64)
Mean Δ from BL at Day 28					
▪ HBV DNA, log_{10} IU/mL (SD)	-2.16 (0.49)	-2.89 (0.48)	-2.70 (0.53)	-2.70 (0.33)	-0.11 (0.36)
▪ HBV RNA, log_{10} c/mL (SD)	-2.30 (0.59)	-1.85 (1.42)	-1.83 (0.93)*	-1.43 (1.13)	0.02 (1.10)

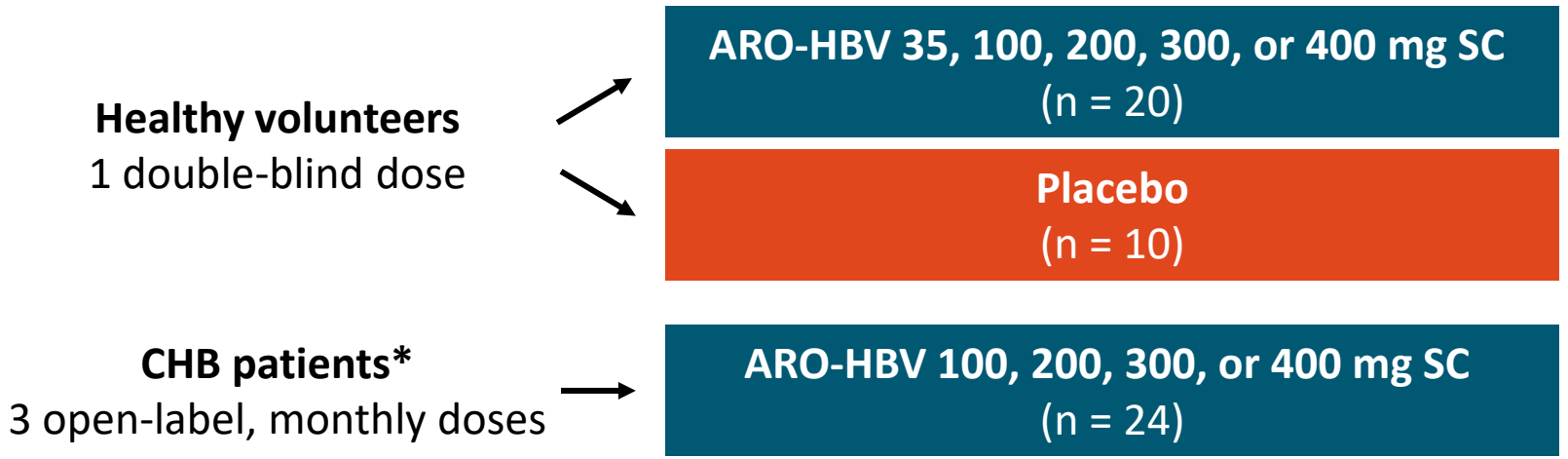
*n = 8 evaluable.

Zoulim. AASLD 2018. Abstr 74.

Slide credit: clinicaloptions.com

AROHBV1001: RNAi in Healthy Volunteers, Patients With CHB

- Interim analysis of phase I/IIa dose-escalating study
  - **ARO-HBV**: 2 siRNAs directly conjugated to N-acetyl galactosamine



*HBeAg positive or negative, treatment naive or experienced at BL; untreated patients began daily nucleos(t)ide therapy on Day 1.

- Main endpoints including: safety/tolerability, HBsAg reduction

Gane. AASLD 2018. Abstr LB-25. NCT03365947.

Slide credit: clinicaloptions.com

AROHBV1001: Safety and Efficacy

Safety Outcome, n	Healthy Volunteers		CHB Patients
	ARO-HBV (n = 20)	Placebo (n = 10)	ARO-HBV (n = 24)
Any AE in > 1 individual	39	17	22
Injection-site reactions	2*	0	7†

*Bruising, tenderness. †Erythema, bruising/hematoma, rash, tenderness.

- No serious AEs
- 12% of subcutaneous injections in CHB patients accompanied by an AE
  - All were mild in severity
- Mean nadir HBsAg reduction: -1.9 $\log_{10}$ (range: -1.3 to -3.8)
  - Similar responses across CHB dose cohorts, regardless of previous treatment experience or HBeAg status

Gane. AASLD 2018. Abstr LB-25.

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