End of Study Results from LIMT HDV Study: 36% Durable Virologic Response at 24 Weeks Post-Treatment with Pegylated Interferon Lambda Monotherapy in Patients with Chronic HDV Infection

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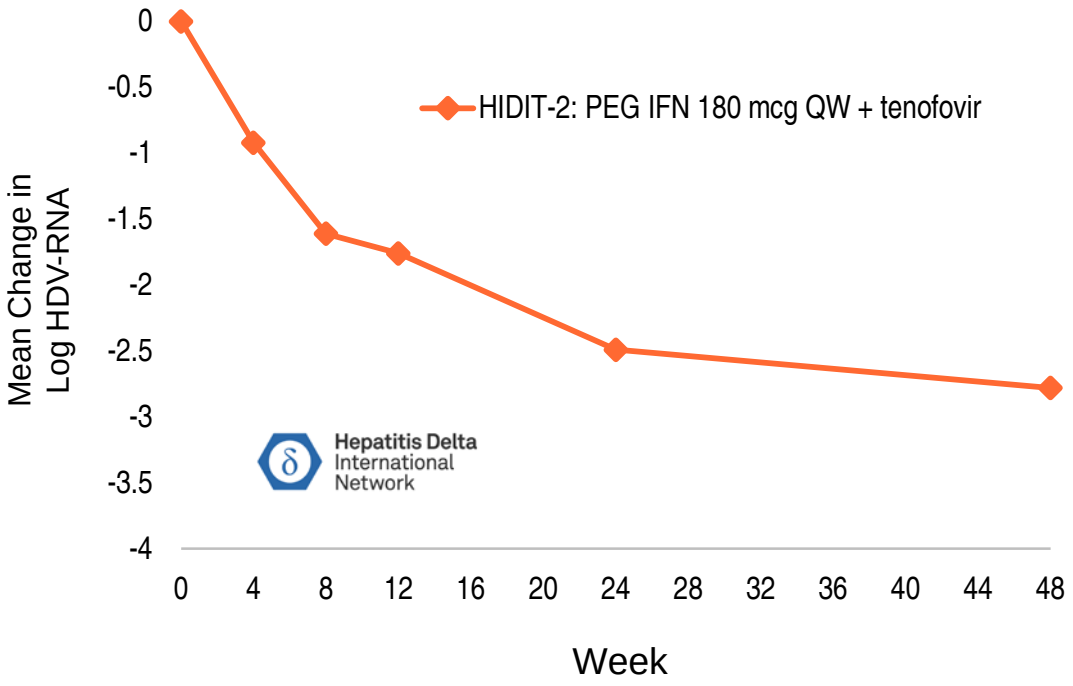
HEPATITIS DELTA VIRUS (HDV)

OVERVIEW

- Most severe form of human viral hepatitis
- Most rapid progression to liver cirrhosis & cancer
- Always a co-infection with HBV
- 4-6% of HBV patients co-infected with HDV
- 15-20 M HDV infected patients worldwide
- No FDA approved Rx

Severe Side-Effects with PEG IFN-alfa

Better Tolerated Interferon Needed



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PEGINTERFERON LAMBDA

A Better Tolerated Interferon

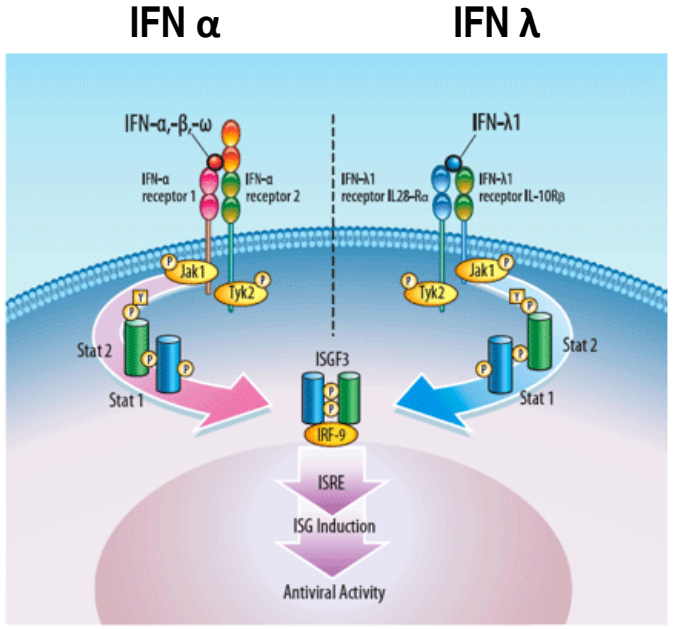
- A novel first-in-class Type III IFN

- Binds to a unique receptor versus Type I IFN
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells

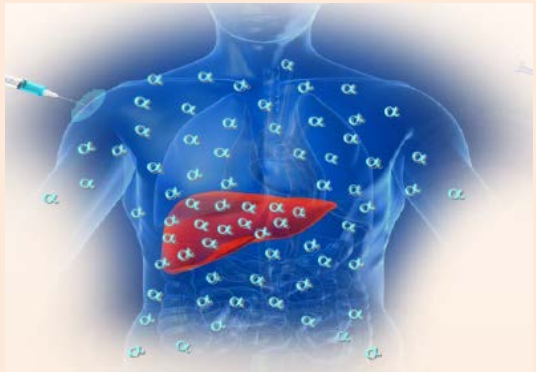
Similar downstream signaling pathway as Type I IFN

- > 3,000 patients in 17 clinical trials (HCV / HBV)

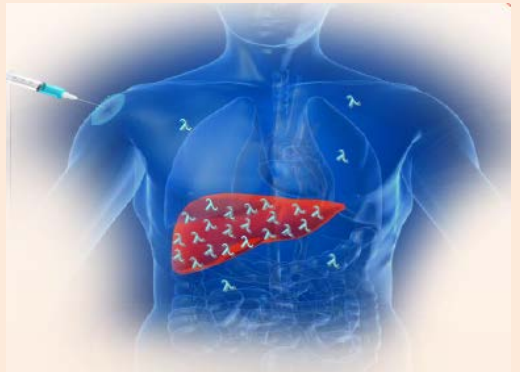
- Less of the typical IFN alfa related side effects*



Alfa Receptor Expression



Lambda Receptor Expression



*Chan, HLY et al, J Hepatology 2016

LIMT HDV "MONO": PHASE 2 STUDY

Objectives

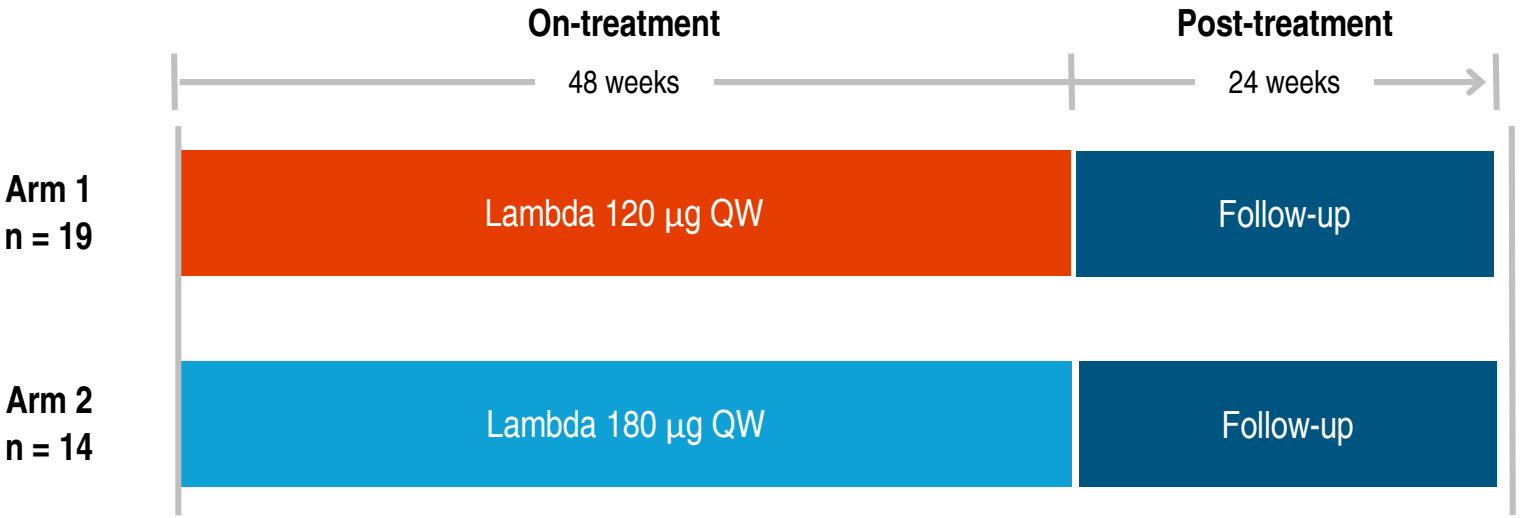
- Evaluate safety, tolerability and efficacy of Lambda monotherapy for 48 wks
  - Change in HDV RNA from BL to Week 48 and Week 72

4 Clinical Sites

- Auckland, New Zealand (N=4) 
- Karachi, Pakistan (N=15) 
- Beersheba, Israel (N=11) 
- Jerusalem, Israel (N=3) 

LIMT HDV "MONO": PHASE 2 STUDY

Lambda Interferon MonoTherapy Study in HDV



- Randomized, open-label study of Lambda 120 and 180 µg, weekly SC injections for 48 weeks in HDV patients
- Dose reductions permitted
- Major inclusion criteria: HDV RNA (+) by qPCR (BLQ 14 IU/mL)*, ULN<ALT<10×ULN, compensated liver disease
- Tenofovir or entecavir were started at baseline (BL)

*Robogene® 2.0, BLQ = below limit of quantification

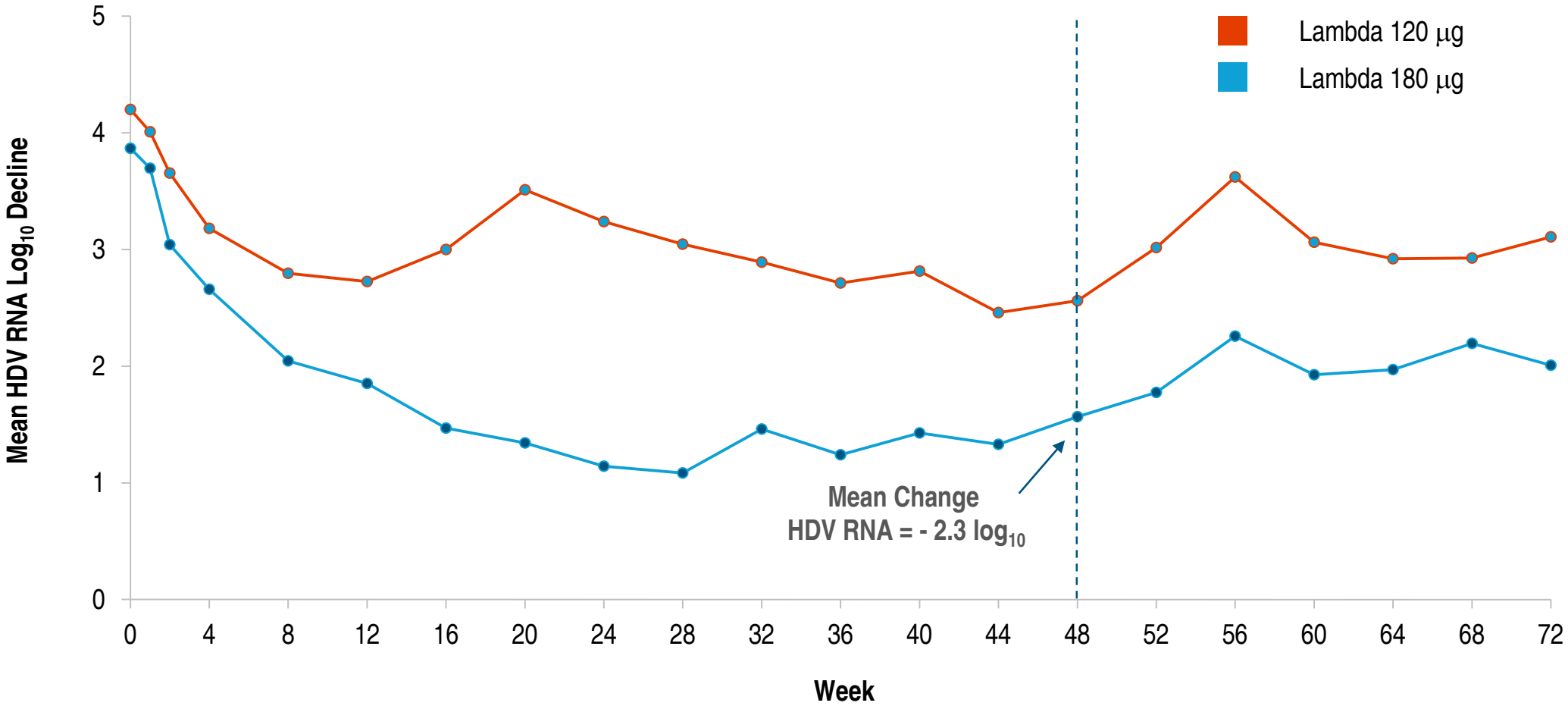
BASELINE CHARACTERISTICS

Median Characteristic Values	Values
N	33
Age, years (range)	36 (20, 63)
Male, n (%)	22 (66.7%)
Race, n (%) White Black Pacific Islander Other	 13 (39.4%) 1 (3.0%) 4 (12.1%) 15 (45.5%)
BMI, kg/m^2 (range)	24.7 (14.0, 37.1)
HDV-RNA, log_{10} IU/mL (range)	4.1 ± 1.4
ALT, U/mL (range)[1]	106 (35, 364)
Platelets, $x10^9/L$ (range)	170 (95, 281)
Albumin, g/dL (range)	4.4 (3.7, 5.2)
INR	1.2 (1.0, 1.5)
Bilirubin, mg/dL (range)[2]	0.5 (0.2, 1.2)
Cirrhotic (%)	9 (27%)
Prior Interferon Use (%)	21 (64%)

[1] Normal range for ALT = 10 – 35 U/mL (female); 10 – 50 U/mL (male); [2] Normal range for bilirubin = 0 - 1.2 mg/dL

HDV-RNA REDUCTION WITH LAMBDA

Lambda 180 μg Comparable to Historical Alfa 180 μg



DURABLE VIROLOGIC RESPONSE DEMONSTRATED

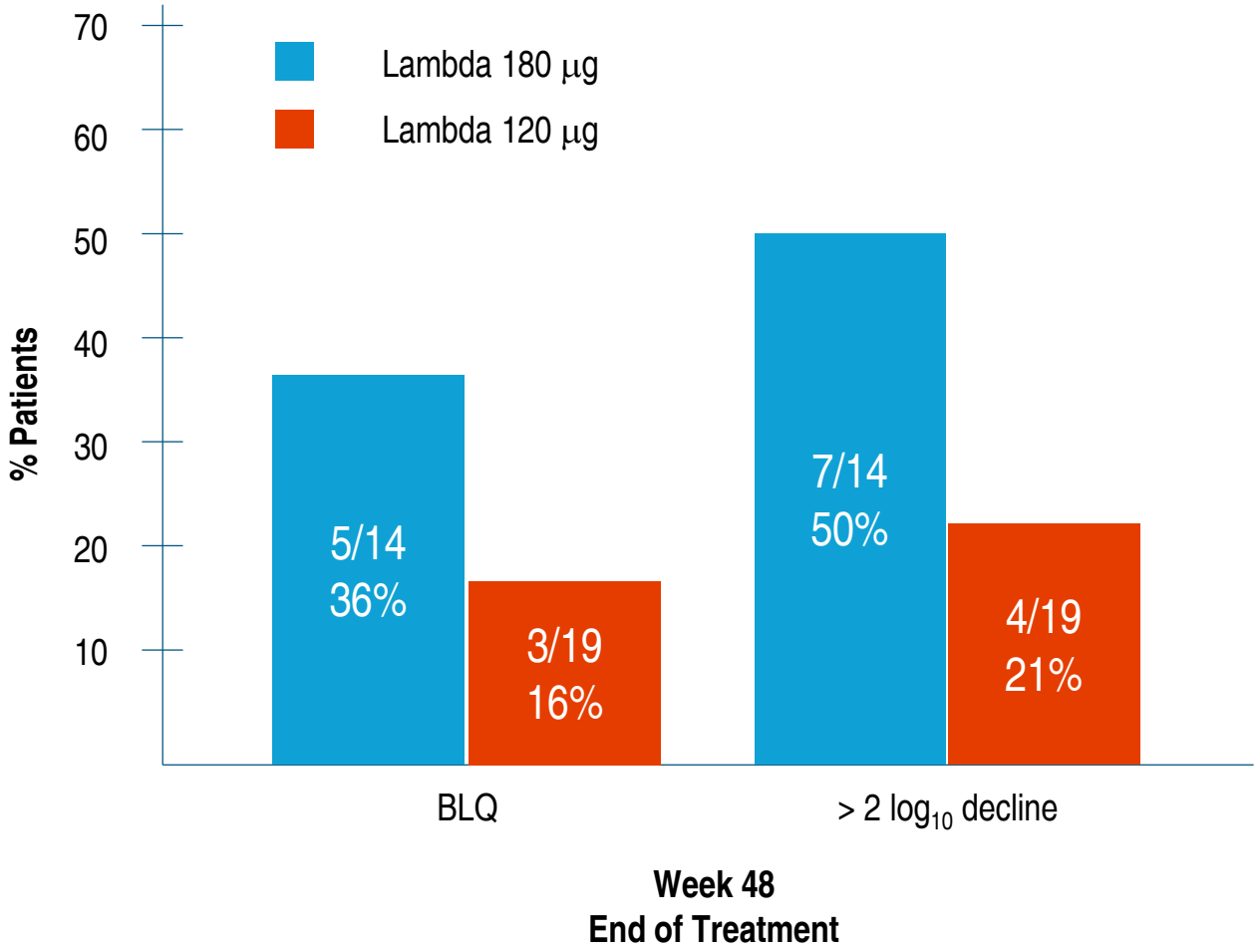
For Low and High Baseline Viral Levels

			48 Week On-Treatment		24 Week Post-Treatment
Dose		**N**	**Mean Log_{10} Decline**	**# BLQ**	**# BLQ**
180 µg	**All**	14	-2.3	5 / 14 36%	**5 / 14 36%**
	High BL VL	8		3 / 8 38%	**2 / 8 25%**
	Low BL VL	6		2 / 6 33%	**3 / 6 50%**

Low BL VL = low baseline viral loads of ≤ 4 log IU/mL

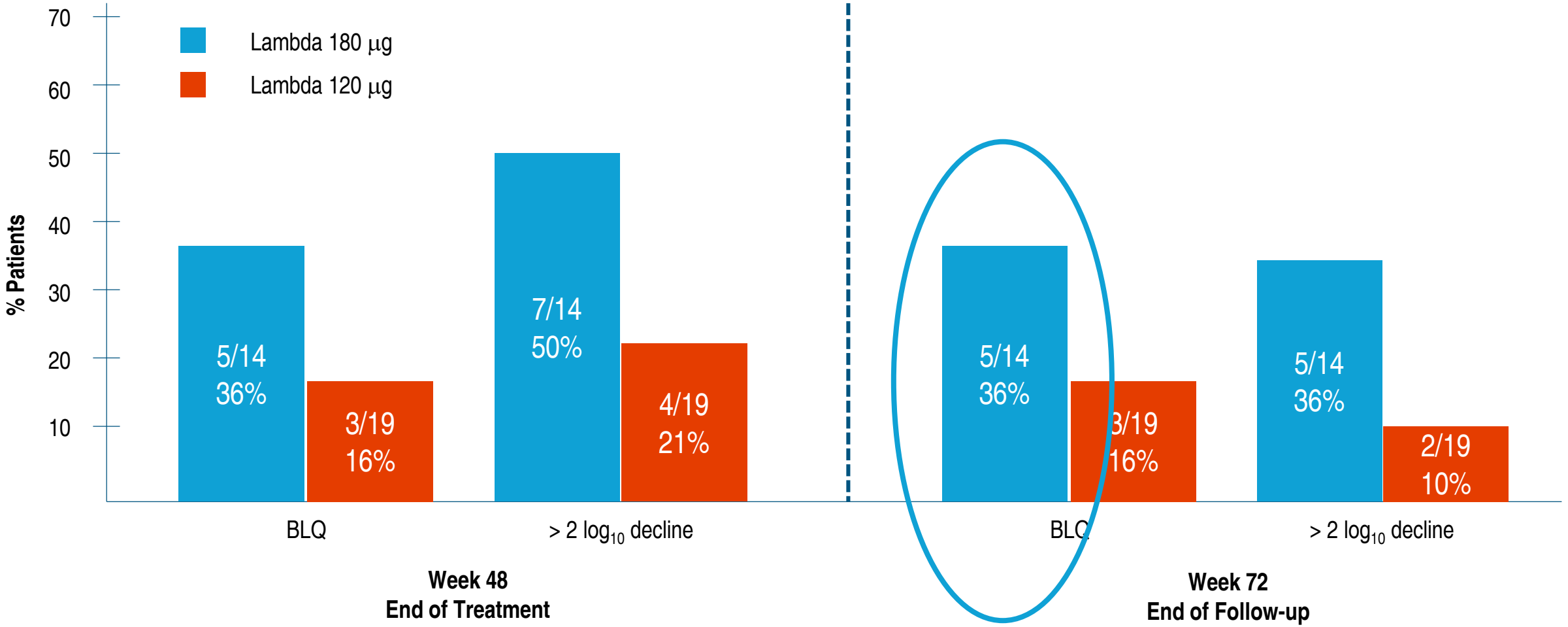
HIGH RESPONSE RATES WITH LAMBDA 180 MCG

Responder = 2 log decline or Below Limit of Quantification (BLQ) at End of Treatment



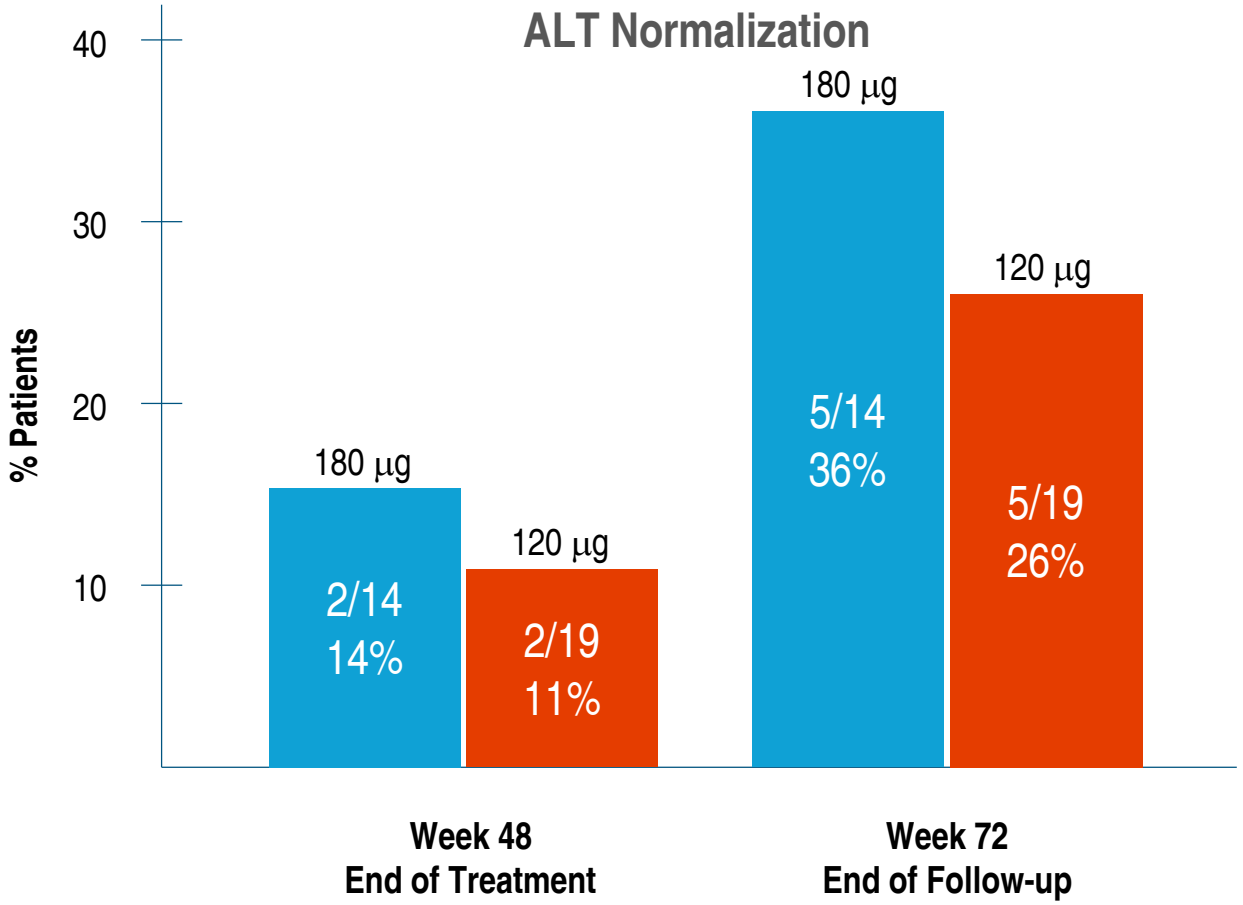
DURABLE VIROLOGIC RESPONSE (DVR) DEMONSTRATED

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



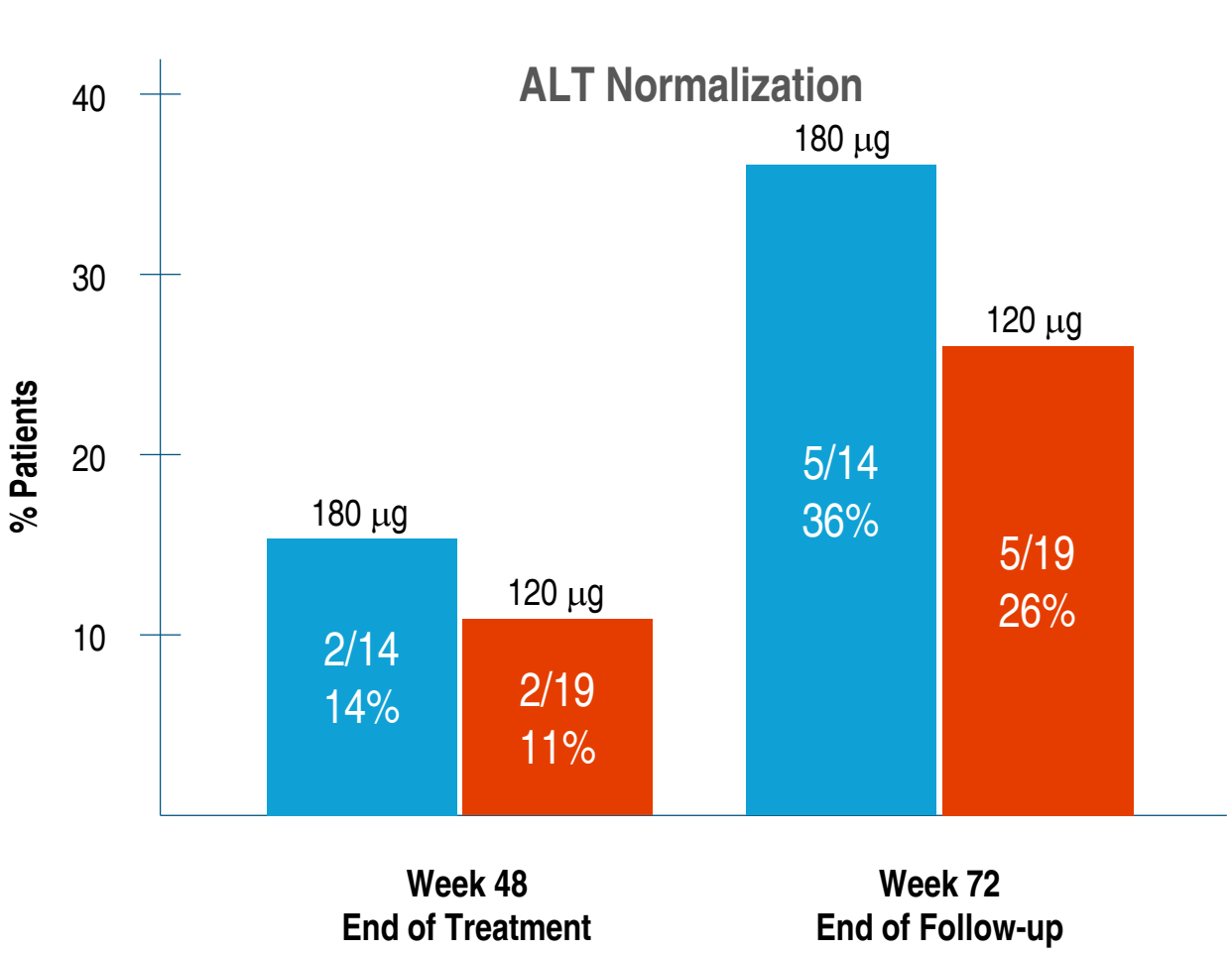
ALT NORMALIZATION

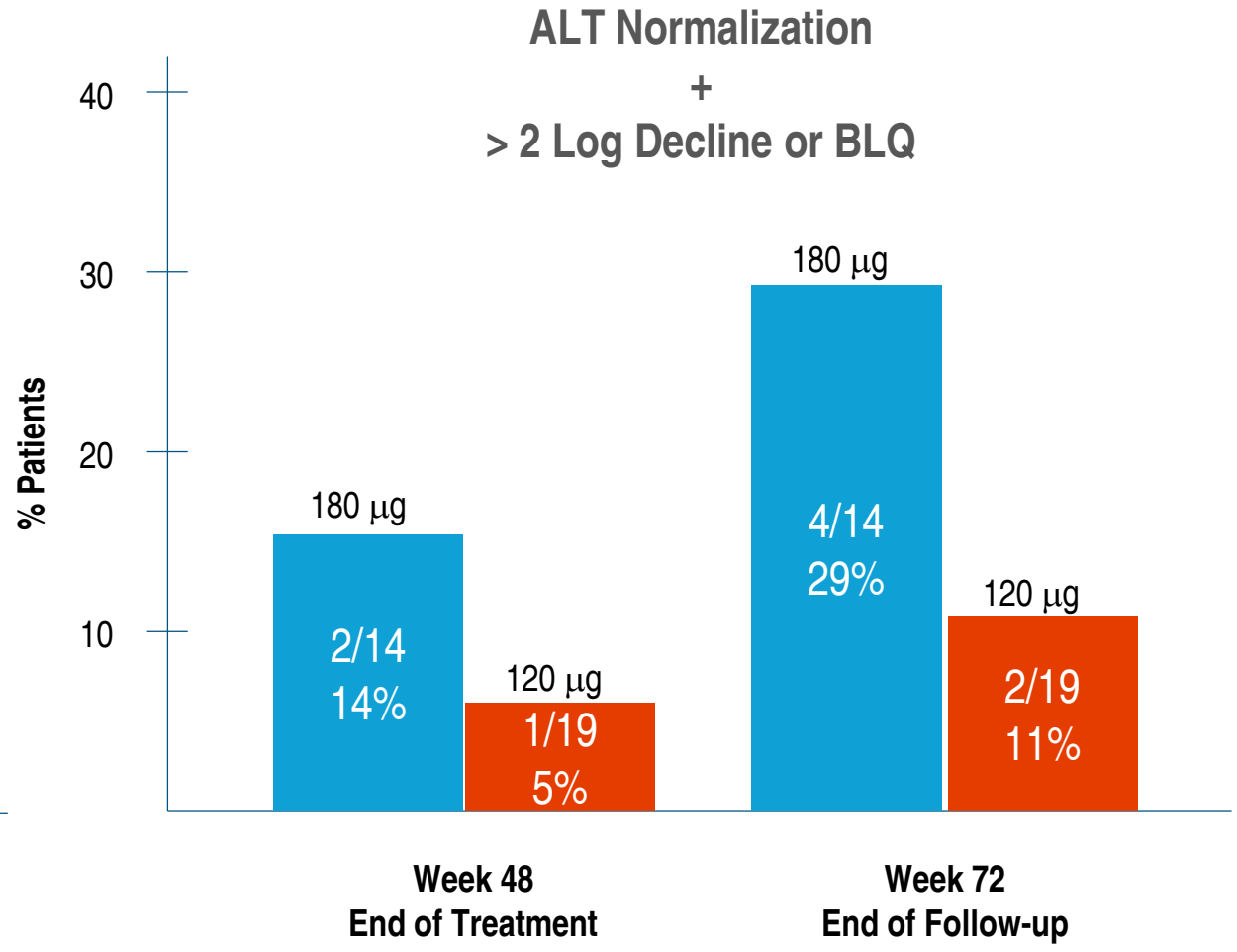
ALT Continues to Normalize Post-Treatment



ALT NORMALIZATION & HDV RNA DECLINE

Endpoints for Liver Improvement and Virologic Response





ADVERSE EVENTS: PREDOMINANTLY GRADE 1*

Classification	Adverse Event	Number of Patients Experiencing Grade of AE (N=33)			
		Gr 1	Gr 2	Gr 3	Gr 4
Constitutional	fatigue, asthenia	10	2	-	-
Flu-like	pyrexia, chills, chest pain, flu-like	21	5	-	-
Neurological	dizziness, headache	17	8	-	-
Musculoskeletal	arthralgia, myalgia, back pain, musculoskeletal pain	18	9	-	-
Psychiatric	depression, irritability, insomnia	1	-	-	-
Hematological	neutrophil count decreased	-	-	-	1**
Lab Abnormalities	bilirubin / ALT / AST / GGT increase	2	1	9	1**

- Milder flu-like and psychiatric symptoms with Lambda
- No thrombocytopenia events, no use of hematopoetic growth factors
- Elevated bilirubin and ALT levels normalized upon dose reduction or treatment discontinuation

* >1300 Weeks of Treatment
** non-serious

PAKISTAN COHORT

Higher Instances of Hyperbilirubinemia

- 15 of 33 (45%) patients randomized to Pakistan
- Hyperbilirubinemia in 4/15 (27%) vs 2/18 (11%) of non-Pakistani patients
- Jaundice observed in 3/15 (20%) vs 0/18 (0%) of non-Pakistani patients
- Patients with bilirubin elevations had no symptoms of decompensation
    - Bilirubin levels were responsive to dose reduction/interruption
- Incidence/severity in non-Pakistani cohort consistent w/ prior Lambda and Alfa data in HBV[1]
- Transporter-based mechanism for bilirubin elevations[2]

[1] Chan et al J. Hepatology 2016; Pegasys® package insert; [2] Determined by DILISYM® modeling of ALT and bilirubin dynamics

LIMT STUDY OBSERVATIONS

- 33 patients were randomized to Lambda 180 μg (N=14) or 120 μg (N=19)
- ITT rates of durable virologic response (DVR=BLQ at 24 wks post-tx) for Lambda 180 μg = 5 of 14 (36%)
- Lambda was well tolerated overall
- Increased incidences of clinical jaundice and bilirubin elevations were observed in the Pakistani cohort
  - Led to lower than expected rate of study completion (9 of 15, 60%) for Pakistan site
  - Israel and New Zealand sites had completion rates (15 of 18, 83%) comparable to prior Alfa studies
- None of the patients with elevations in bilirubin showed symptoms of decompensation
  - All responded favorably to dose reduction or dose discontinuation

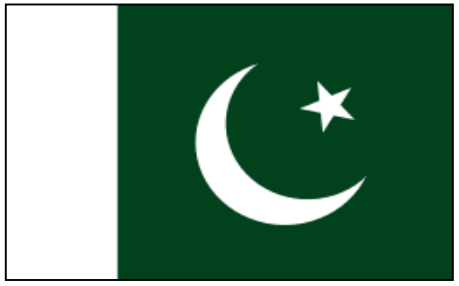
ITT = intent to treat

LIMT STUDY CONCLUSIONS

- Durable BLQ virologic responses have been observed 24 weeks post-treatment
- ITT rates of DVR of Lambda (36%) compares favorably to historic rates for Alfa 180 μg (28%)*
- Common on-treatment AEs included mild to moderate flu-like symptoms and elevated transaminase levels
- Patients previously treated with Alfa noted significantly less side effects on Lambda
- No patients requested discontinuation of treatment
- Lambda is a promising agent for mono and/or combination drug development in the treatment of HDV
- Phase 2 **LIFT** combination study with Lambda + Lonafarnib is on-going at NIH

* Wedemeyer et al; NEJM, 2011
DVR = BLQ at 24 wks post-treatment

ACKNOWLEDGEMENTS



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