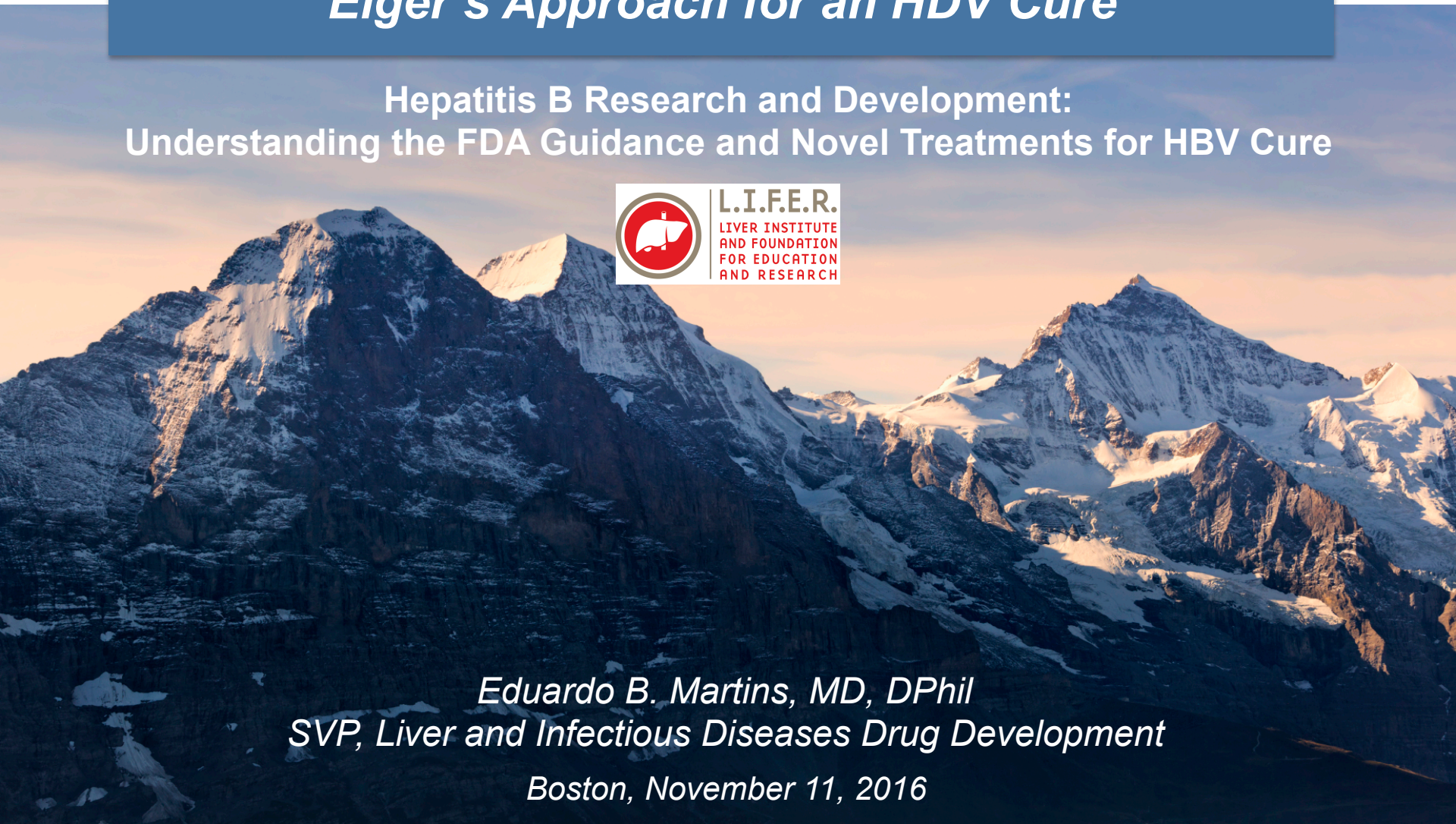
Eiger's Approach for an HDV Cure

Hepatitis B Research and Development: Understanding the FDA Guidance and Novel Treatments for HBV Cure



Eduardo B. Martins, MD, DPhil
SVP, Liver and Infectious Diseases Drug Development

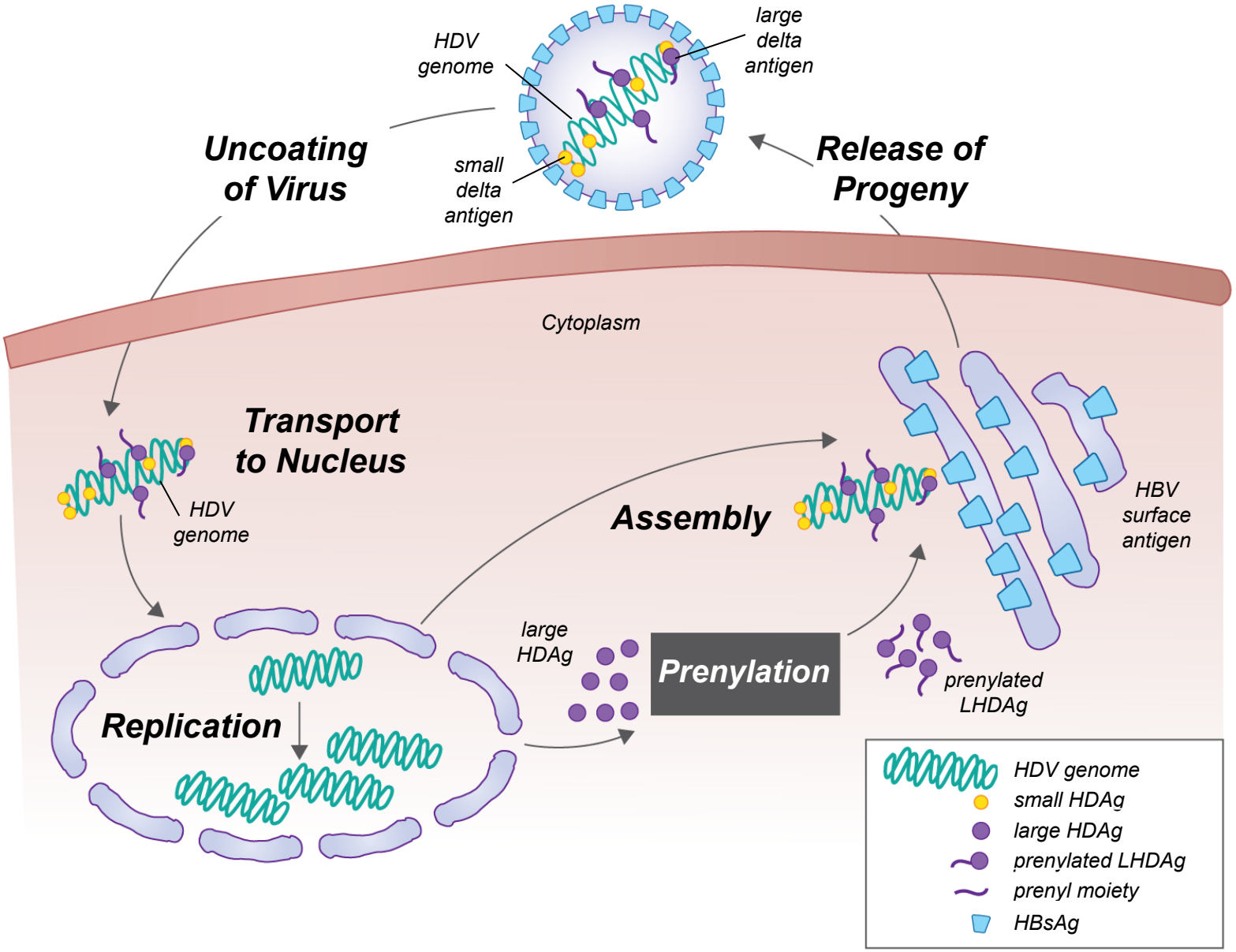
Boston, November 11, 2016

Overview

- *Lonafarnib*
  - *Prenylation inhibition for HDV*
  - *Clinical trials*
  - *Milestones*
- *Pegylated interferon lambda*
  - *Scientific rationale*
  - *Clinical trials*
  - *Milestones*
- *Perspective on HDV cure*

Lonafarnib

The HDV Life Cycle



Prenylation Inhibitors as Antivirals

HDV is a Genetically Validated Target

Identification of a Prenylation Site in Delta Virus Large Antigen

Jeffrey S. Glenn,* John A. Watson, Christopher M. Havel, Judith M. White

SCIENCE • VOL. 256 • 29 MAY 1992

→ *Proof of Concept*

Use of a Prenylation Inhibitor as a Novel Antiviral Agent

JEFFREY S. GLENN,[1]* JAMES C. MARSTERS, JR.,[2] AND HARRY B. GREENBERG[1,3]

Division of Gastroenterology,[1] and Department of Microbiology and Immunology,[3] Stanford University School of Medicine and Veterans Administration Medical Center, Palo Alto, California 94305-5487, and Bioorganic Chemistry, Genentech Inc., South San Francisco, California 94080[2]

JOURNAL OF VIROLOGY, Nov. 1998, p. 9303–9306

→ *Virus Like Particle (VLP)*

A Prenylation Inhibitor Prevents Production of Infectious Hepatitis Delta Virus Particles

Bruno B. Bordier,[1,2] Patricia L. Marion,[1] Kazuo Ohashi,[3] Mark A. Kay,[3] Harry B. Greenberg,[1,2,4]† John L. Casey,[5] and Jeffrey S. Glenn[1,2]*

Division of Gastroenterology and Hepatology,[1] Department of Microbiology and Immunology,[4] and Program in Human Gene Therapy, Departments of Pediatrics and Genetics,[3] Stanford University School of Medicine, and Veterans Administration Medical Center,[2] Palo Alto, California, and Division of Molecular Virology and Immunology, Georgetown University Medical Center, Rockville, Maryland[5]

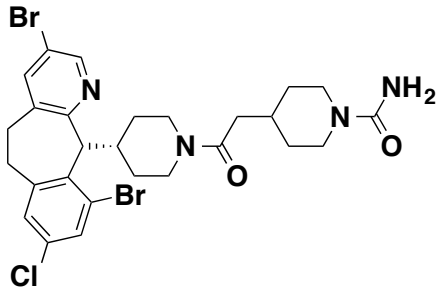
→ *Infectious Virus*

In vivo antiviral efficacy of prenylation inhibitors against hepatitis delta virus

The Journal of Clinical Investigation | August 2003 | Volume 112 | Number 3 I Jeffrey S. Glenn

→ *In Vivo Animal Model*

Lonafarnib for HDV



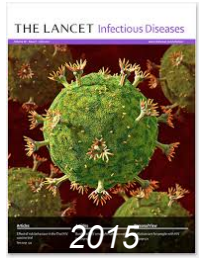
- *Small molecule, oral, prenylation inhibitor*
- *Well-characterized through Phase 3*
  - *>2,000 patients dosed in oncology program by Merck (Schering)*
  - *Dose limiting toxicity is GI (class effect)*
- *Prenylation is a host target; confers high barrier to resistance*
- *Over 100 HDV patients dosed across international sites*
- *Orphan Designation, Fast Track Granted*

Koh et al, Lancet Infect Dis, 2015.

Sarasar® (lonafarnib) Phase 2 HDV Program

111 HDV Infected Patients Dosed

- ***Proof of Concept***
  - *Monotherapy* — *N = 14* — NIH
- ***LOWR HDV – 1***
  - *Combinations +/- PEG IFN α* — *N = 15* — Ankara Üniversitesi 1946
- ***LOWR HDV – 2***
  - *Dose Finding +/- PEG IFN α* — *N = 46* — Ankara Üniversitesi 1946
- ***LOWR HDV – 3***
  - *QD* — *N = 21* — NIH
- ***LOWR HDV – 4***
  - *Dose-Escalation* — *N = 15* — MHH Hannover Medical School



2015 EASL The Home of Hepatology

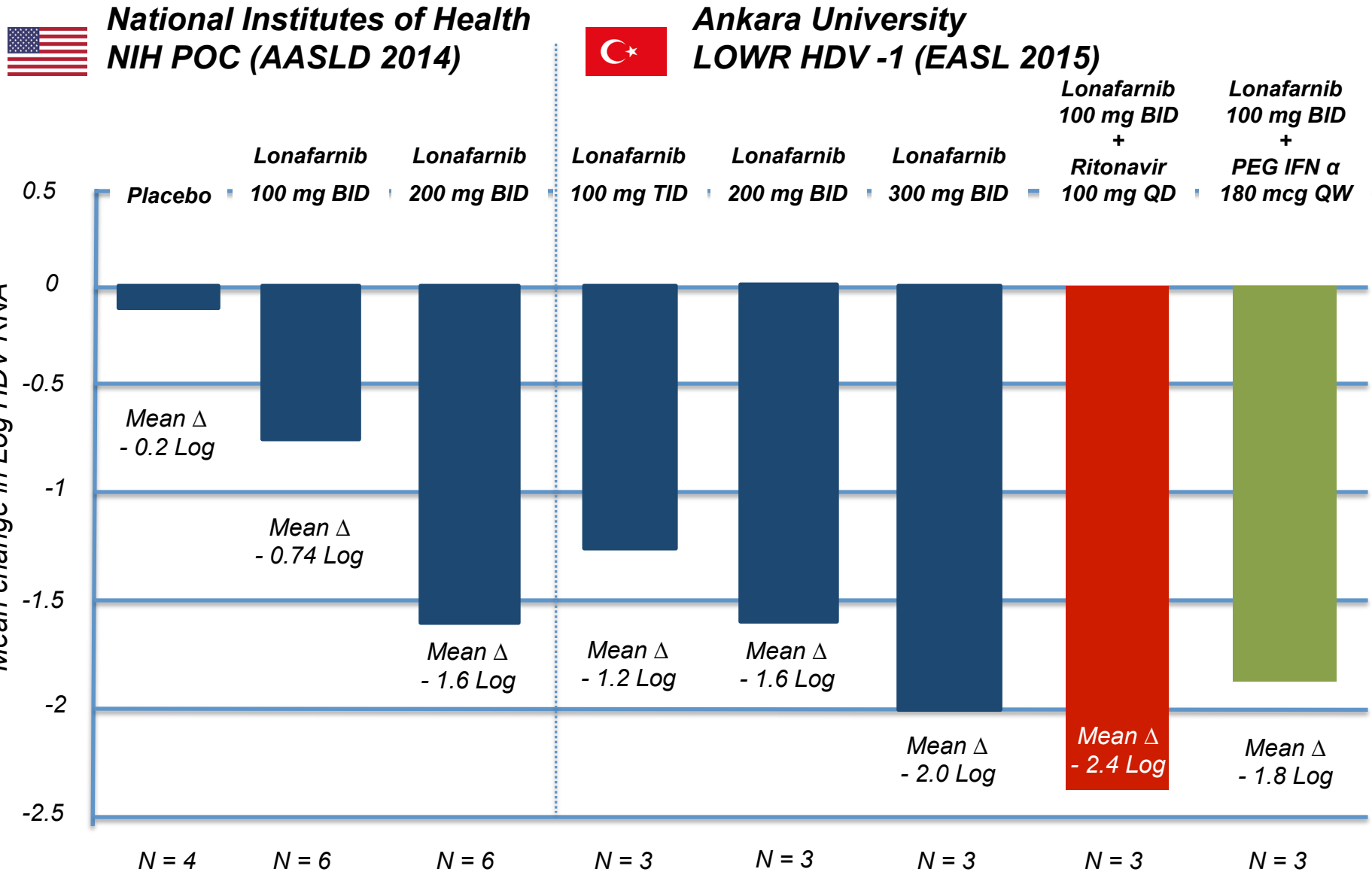
Dosing

Last Patient Dosed

Last Patient Dosed

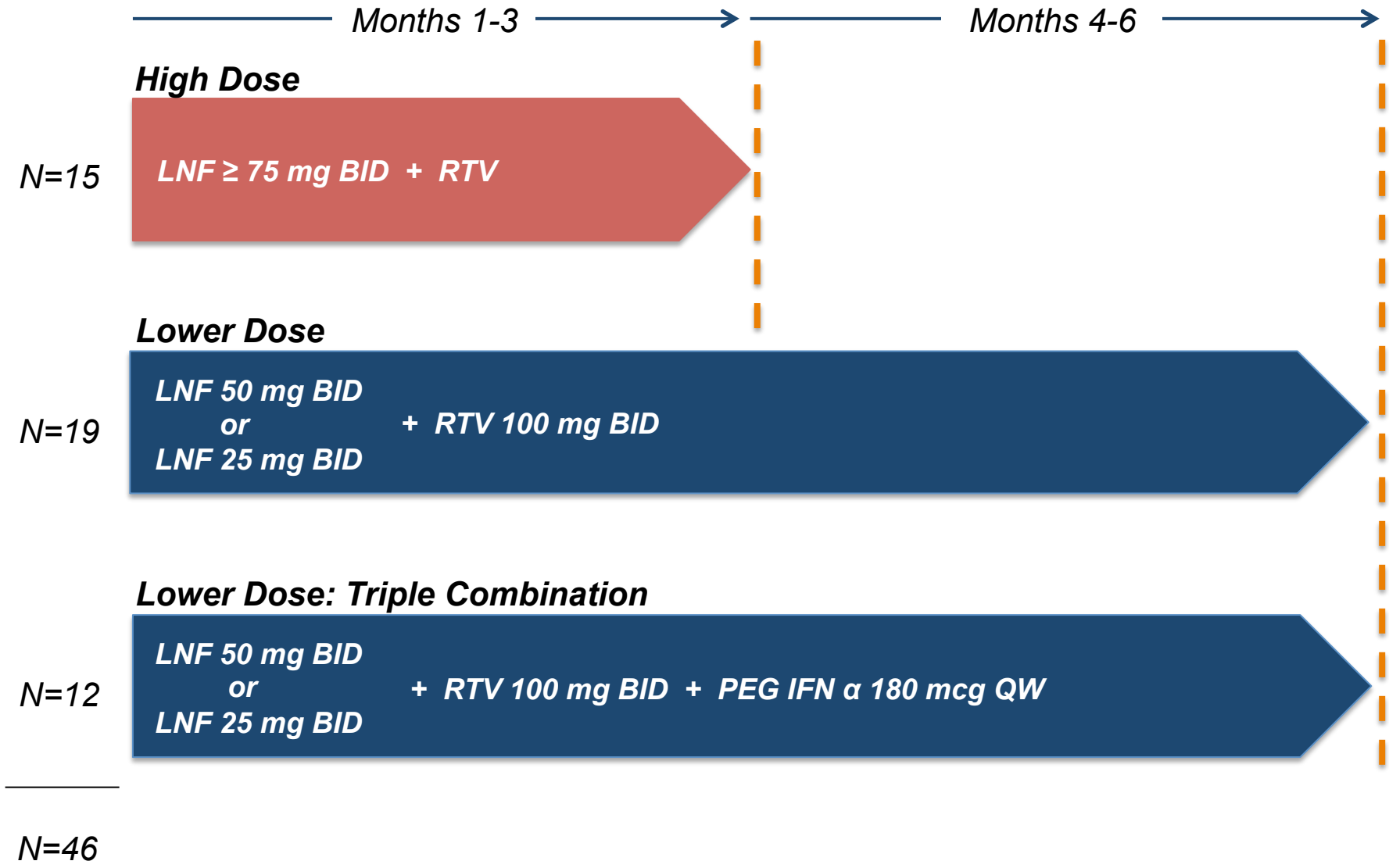
*LOWR HDV = **LO**nafarnib **W**ith **R**itonavir in **HDV***

HDV RNA Decline with 4 Weeks of Lonafarnib



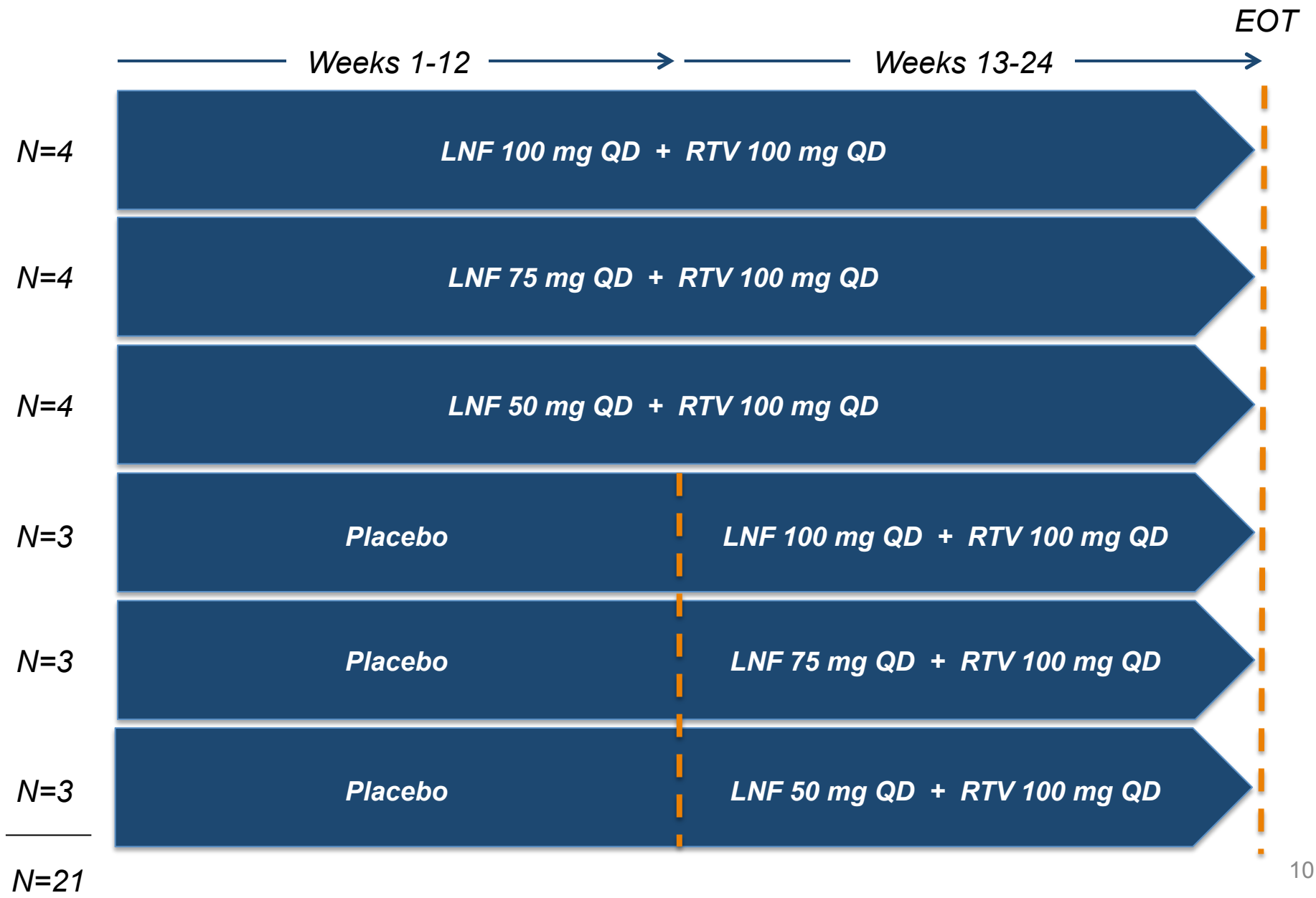
LOWR HDV – 2: "Dose Finding" Study

Tolerability, Longer Dosing, and Triple Combination



LOWR HDV – 3: "QD" Study

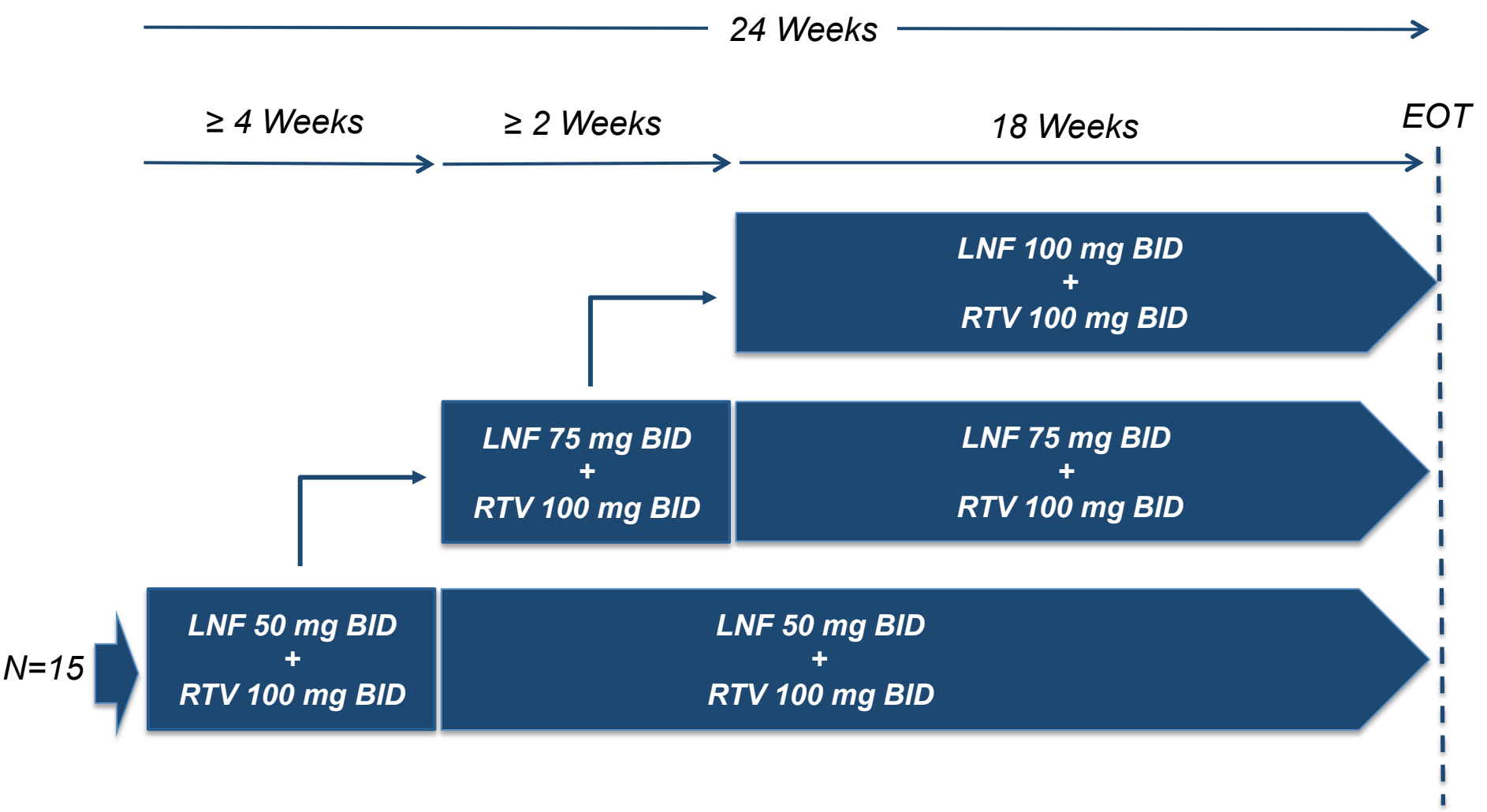
Dosing Completed



MHH
Hannover
Medical
School

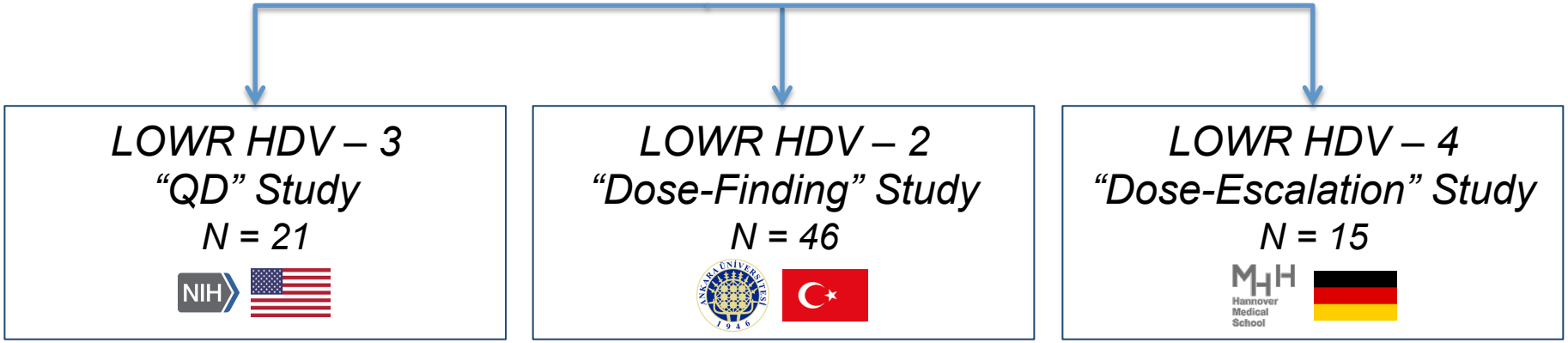
LOWR HDV – 4: "Dose-Escalation" Study

Dosing Completed



LOWR HDV Program

Identifying Dose and Regimen for Registration Program



*LOWR HDV – 2**

- *Dose optimization study to identify optimal LNF-RTV combinations +/- PEG IFN*

*LOWR HDV – 3***

- *Is once-daily dosing sufficient?*

*LOWR HDV – 4****

- *Is rapid dose-escalation possible?*

** Yurdaydin, C. et al, AASLD Abstract #1845; ** Koh, C. et al, 12th HDIN Meeting; *** Wedemeyer, C. et al, AASLD Abstract #230.*

LOWR HDV Program Data Presentations

2015	2016	2017

Phase 2 LOWR HDV – 2

N = 46

Interim Data — EASL The International Liver Congress™ 2016, April 13-17, Barcelona, Spain

Data — AASLD American Association for the Study of Liver Diseases — 2016

Post TRx Data — EASL The Home of Hepatology — 2017

Phase 2 LOWR HDV – 3

N = 21

Data — AASLD American Association for the Study of Liver Diseases — 2016

Post TRx Data — EASL The Home of Hepatology — 2017

Phase 2 LOWR HDV – 4

N = 15

Data — AASLD American Association for the Study of Liver Diseases — 2016

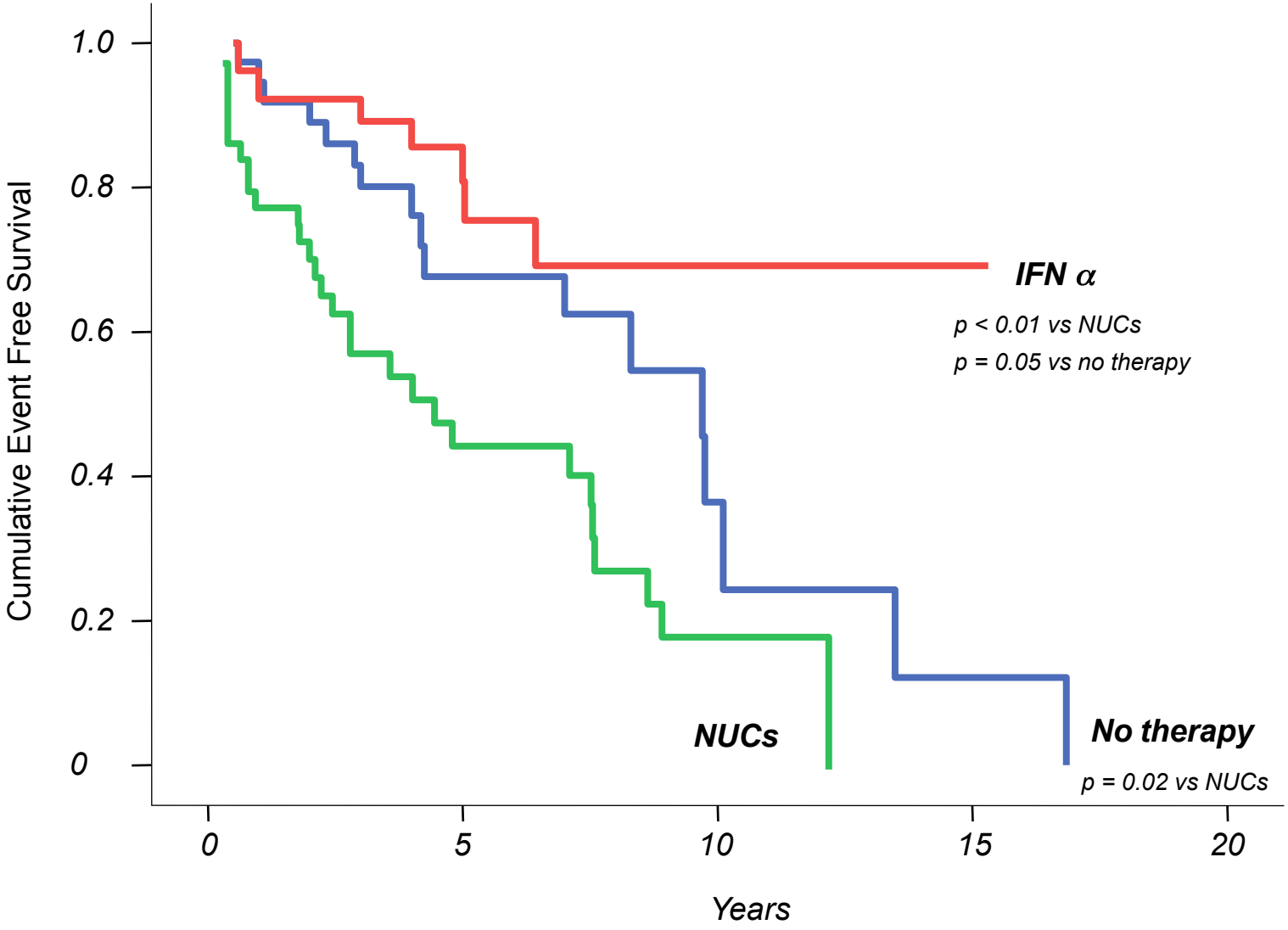
Post TRx Data — EASL The Home of Hepatology — 2017

Pegylated Interferon Lambda 1-a

Hannover Medical School

Fewer Clinical Events with IFN Alfa

Decompensation, HCC, Transplant, Death



Wranke, A. et al. EASL 2016. J Hepatol, accepted manuscript

PEG IFN Lambda

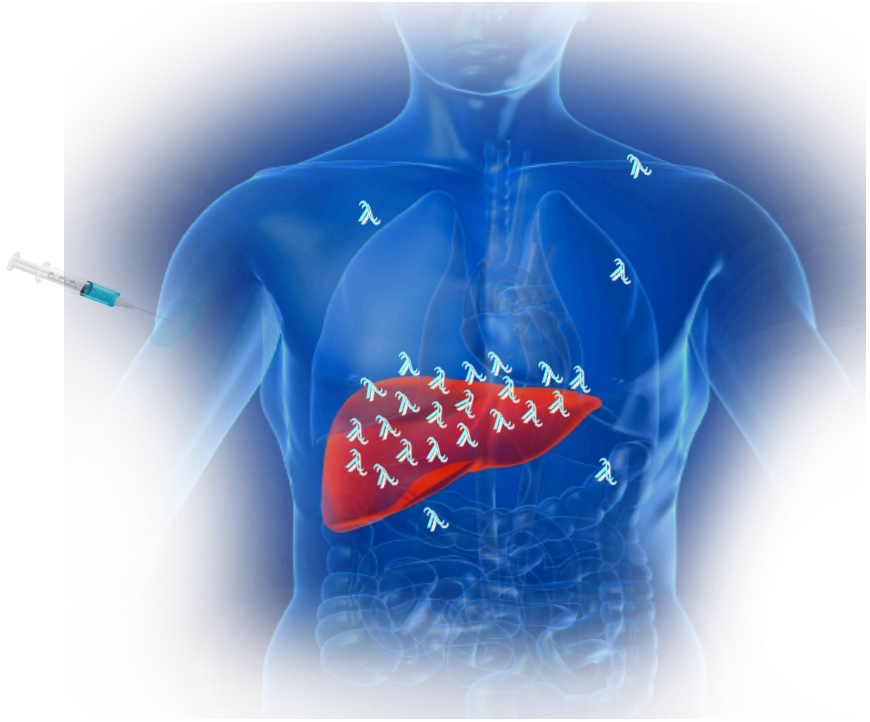
A targeted interferon for HDV

- *A novel, first in class Type III interferon*
  - *Lambda secreted in response to viral infections*
- *Binds to a unique receptor versus Type I interferons*
  - *Highly expressed on hepatocytes*
  - *Limited expression on hematopoietic cells and CNS cells*
- *Similar downstream signaling pathway as Type I interferons*
- *Greater than 3,000 patients in 17 clinical trials*
- *HCV antiviral activity with less of the typical IFN alfa related side effects*
- *Anti-HDV activity in humanized liver mouse model*

PEG IFN Lambda Safety vs PEG IFN Alfa

Results in HCV-Infected Patients: EMERGE 2b Study

Lambda associated with fewer systemic adverse events, such as myalgia, arthralgias, pyrexia and chills, as compared with alfa



AEs, % (≥ 20% in any arm)	Lambda 180 µg (N = 102)	Alfa 180 µg (N = 103)
Fatigue	**46.1**	**42.7**
Headache	**27.5**	**41.7**
Myalgia	**5.9**	**33.0**
Pyrexia	**7.8**	**33.0**
Nausea	**21.6**	**30.1**
Pruritus	**17.6**	**29.1**
Insomnia	**17.6**	**25.2**
Rash	**14.7**	**24.3**
Chills	**3.9**	**21.4**
Arthralgia	**5.9**	**20.4**

*GT1,4 through 48 week treatment**

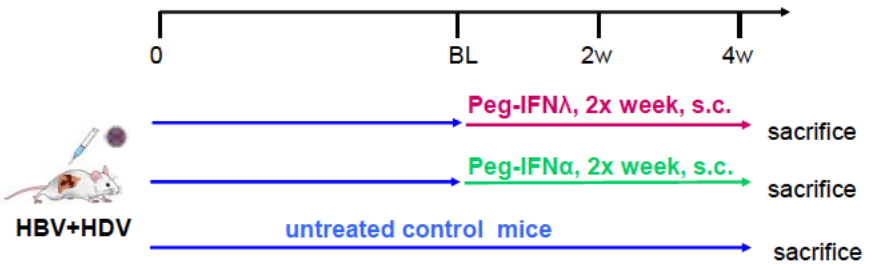
* *GT2,3 patients on 24 week treatment showed similar safety profile*

Zeuzem S, et al. 47th EASL; Apr 18-22, 2012; Barcelona, Spain. Oral 1435.
Muir AJ, et al. 63rd AASLD; Nov 9-13, 2012; Boston, MA, USA. Oral 214.

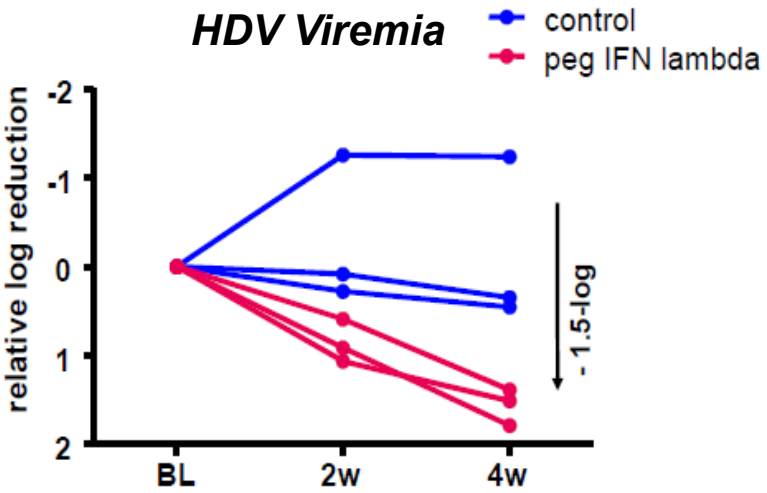
PEG IFN Lambda Suppression of HDV RNA

Induction of Innate Immune Response in Human Hepatocytes

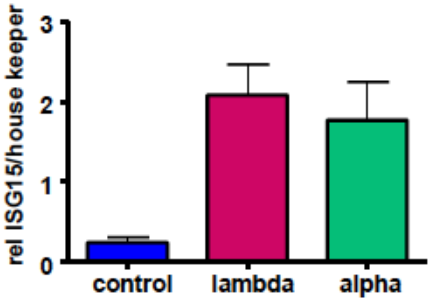
Experimental Design



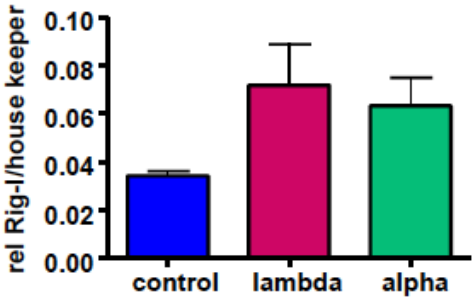
HDV Viremia



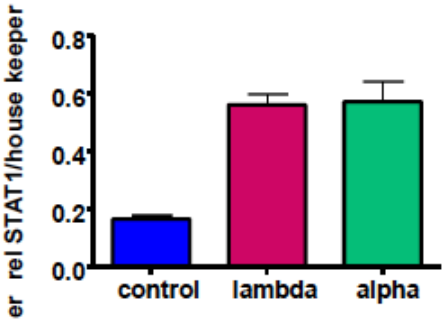
ISG15 = 6.2 Fold



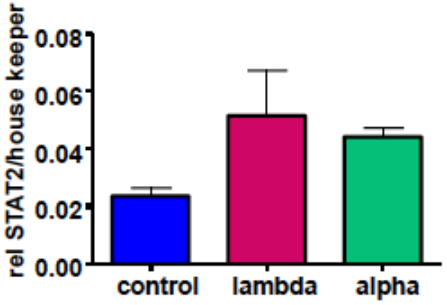
Rig-I = 1.9 Fold



STAT1 = 6.2 Fold



STAT2 = 11.2 Fold



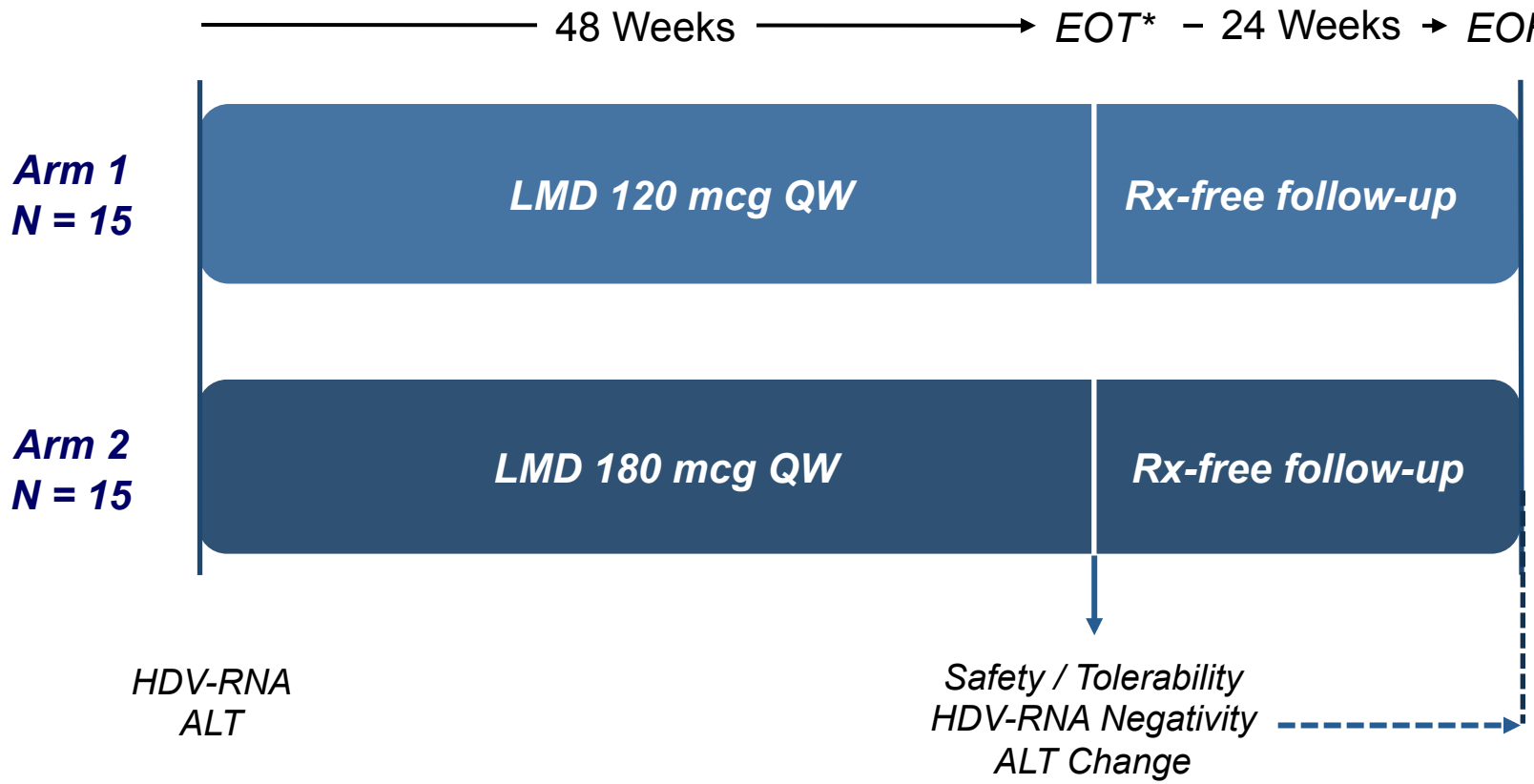
Dandri et al, EASL 2013 Monothematic Conference, Poster

LIMT HDV Phase 2 Study

Lambda Interferon MonoTherapy Study in HDV

Lambda Proof of Concept in HDV

Enrolling

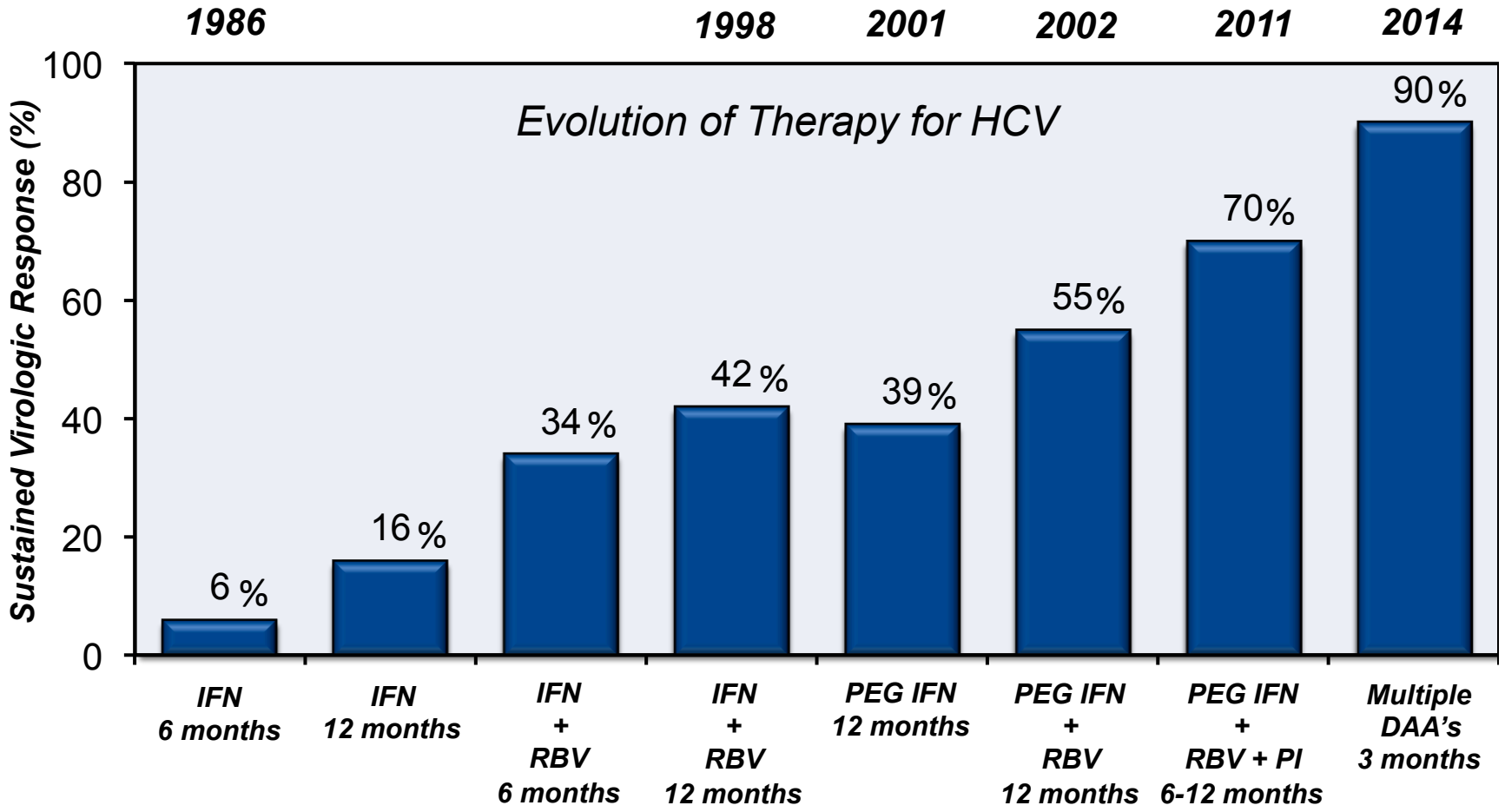


* HDV-RNA negative at EOT and 3-6 months post cessation of therapy

HDV Cure

Over 25 Years to Optimally Cure HCV

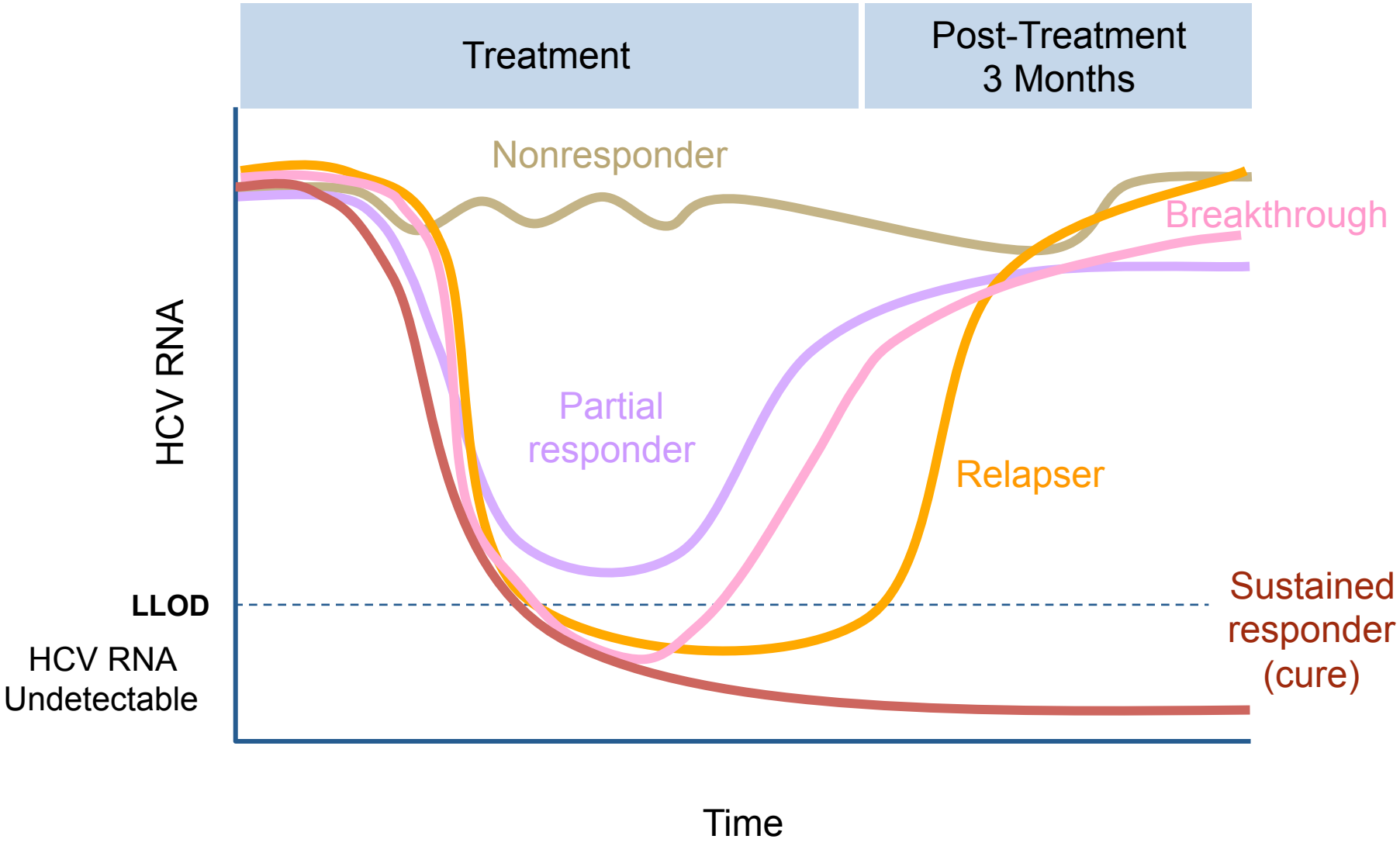
Response Rates Increased Over Time



** Frost and Sullivan HCV Reports, Manns et al Nat Rev Drug Dis 12 (2013), Spach HIV, HCV, and HBV Update*

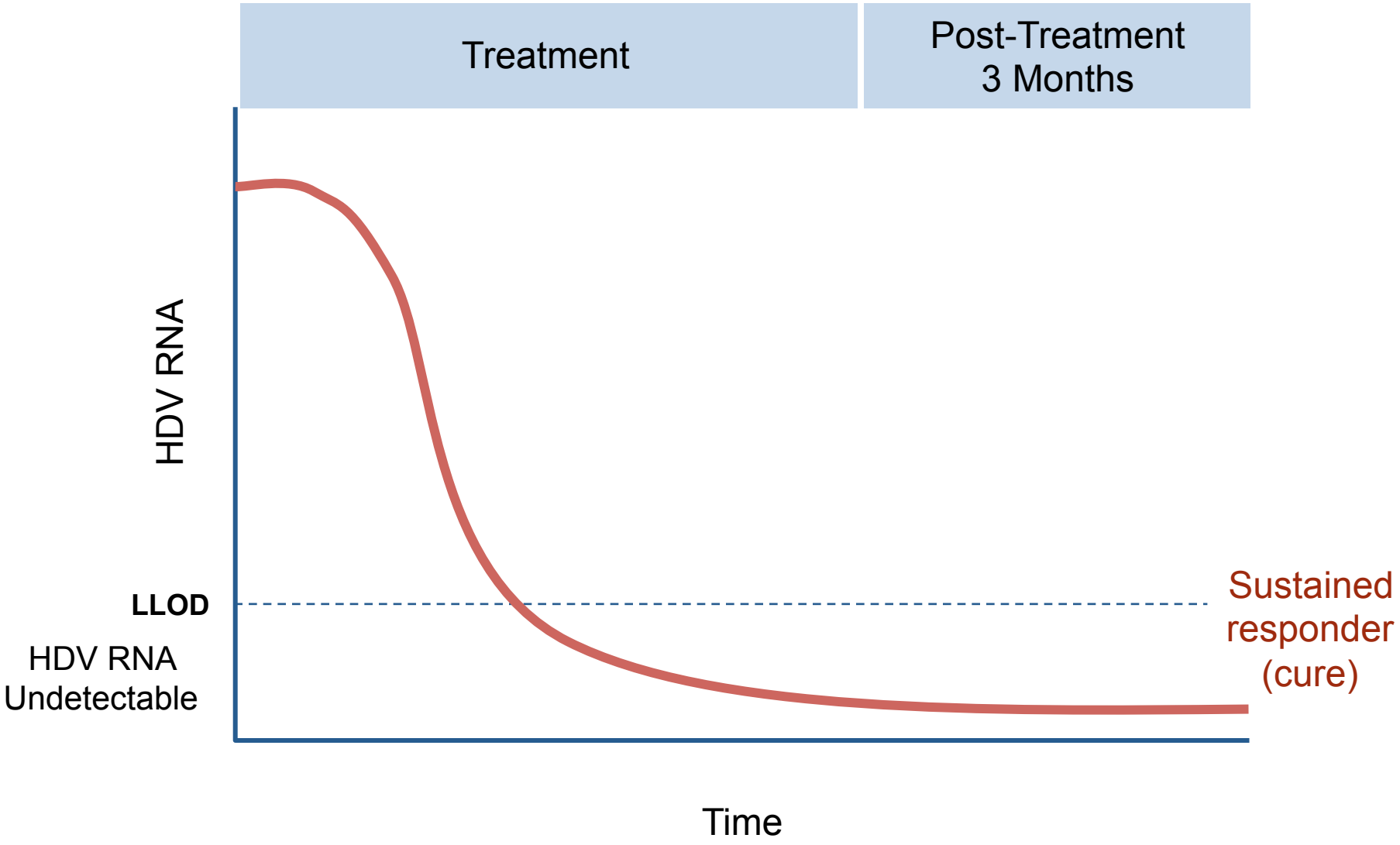
Patterns of HCV Response

Lessons for HDV Cure



HDV Cure

Lessons from HCV

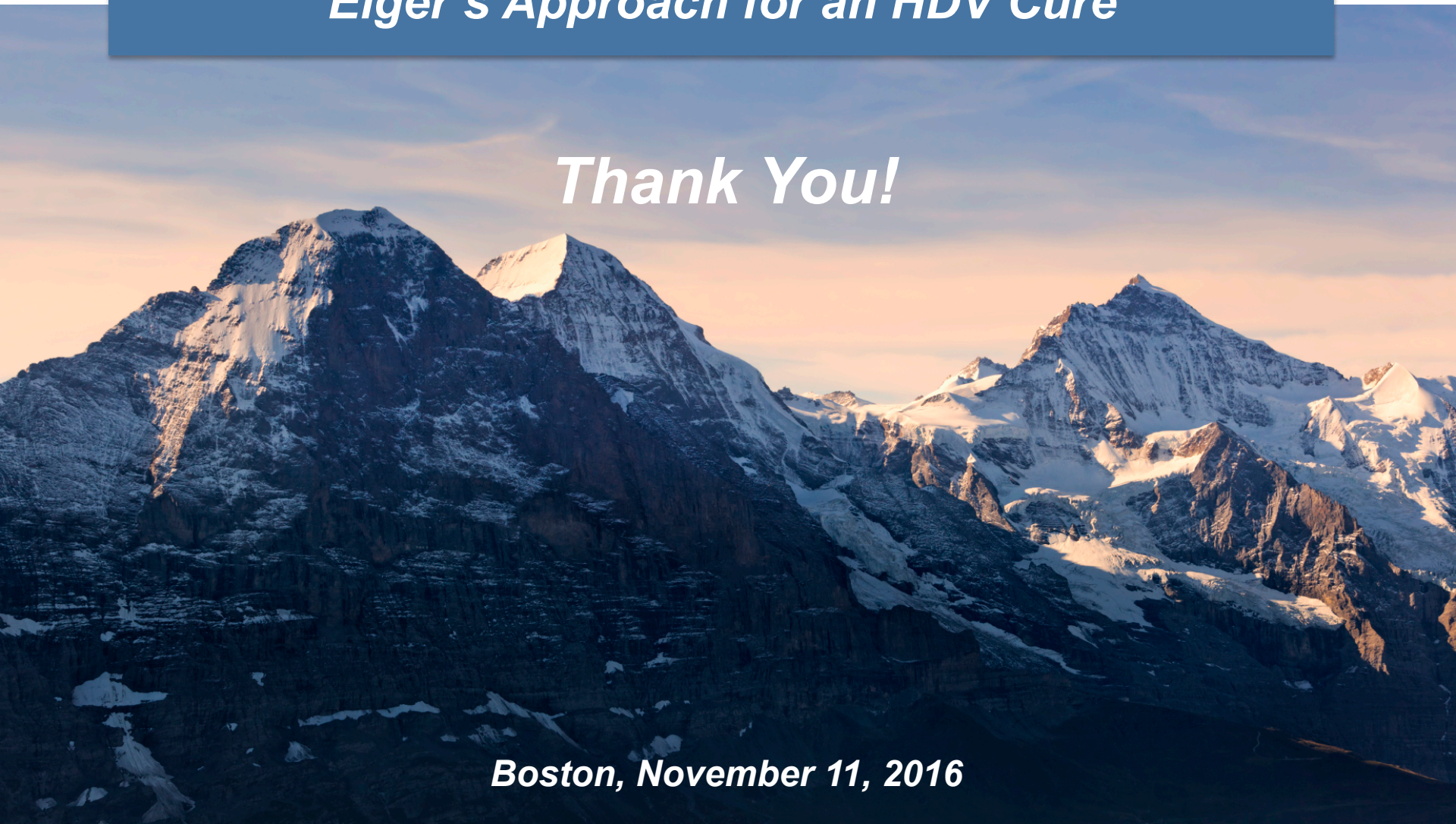


Eiger's Approach For HDV Cure

Summary

- ***Lonafarnib***
  - *POC data published The Lancet ID 2015*
  - *LOWR HDV – 2, – 3, – 4 EOT data at AASLD 2016*
  - *LOWR HDV – 2, – 3, – 4 EOFU data at EASL 2017*
- ***Pegylated Interferon Lambda***
  - *SVR induction in HCV equivalent to pegylated interferon alfa*
  - *Better tolerability profile*
  - *Supportive in vivo data*
  - *Phase 2 study enrolling*
- ***HDV Cure***
  - *SVR 12: HDV-RNA undetectable 12 weeks EOT*

Eiger's Approach for an HDV Cure



Thank You!

Boston, November 11, 2016