A Phase 2 Dose-Escalation Study of Lonafarnib Plus Ritonavir in Patients with Chronic Hepatitis D: Final Results from the **Lo**nafarnib **W**ith **R**itonavir in **HDV - 4** (LOWR HDV - 4) Study

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Disclosures

Heiner Wedemeyer

Honoraria for consulting or speaking (last 5 years):

Abbott, AbbVie, Biolex, BMS, Boehringer Ingelheim, Eiger, Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, MyrGmbH, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV

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Kerstin Port: No conflicts of interest to declare

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Janina Kirschner: No conflicts of interest to declare

Eduardo B Martins: Employee; Shareholder; Eiger BioPharmaceuticals

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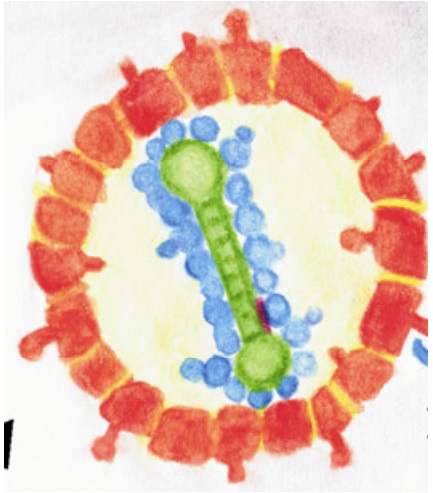
Michael P Manns: Honoraria or grant support by AbbVie, BMS, Gilead, Merck/MSD, Novartis, Roche, Roche Diagnostics

Hepatitis D (Delta) - Virus



Serrano et al, Semin Liver Dis. 2012

- Defective virus that needs HBsAg for its propagation
- 10-20 million individuals are anti-HDV positive
- Causes the most severe form of chronic viral hepatitis

  More rapid progression to liver cirrhosis and liver cancer;
  5-7x more likely to develop cirrhosis and HCC vs HBV

Treatment Options for Hepatitis Delta

48 wks of PEG IFN-α leads to 25-30% undetectable HDV-RNA

Wedemeyer, Yurdaydin et al., NEJM 2011; 364: 322-31

Late relapses occur in 56% of patients with initial response

Heidrich et al., Hepatology 2014; 60:87-97

HDV-RNA suppression is associated with improved long-term clinical outcome

Wranke et al., Hepatology 2016 epub, Oct 22

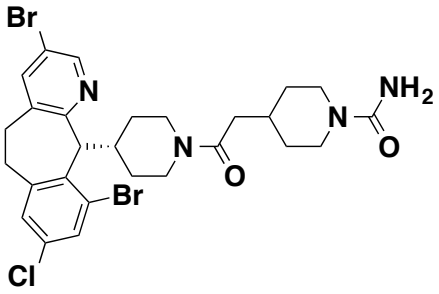
Final step in HDV replication involves prenylation (i.e. farnesylation):

- Farnesyl transferase is a host enzyme which can be targeted by drugs
- Lonafarnib for 28 days induced a dose-dependent HDV-RNA decline

Koh et al., Lancet Infect. Dis. 2015; 15: 1167-74

Lonafarnib for HDV

- Small molecule, oral, prenylation inhibitor



- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering-Plough) (RAS and HDV large antigen share the same farnesyl modification)
  - Dose limiting GI toxicity (class effect)

- Over 120 HDV patients dosed across international sites

LOWR HDV Program

Identifying Dose and Regimen for Registration Study

LOWR HDV – 2
"Dose-Finding" Study
N = 58

LOWR HDV – 3
"QD" Study
N = 21

LOWR HDV – 4
"Dose-Escalation" Study
N = 15

LOWR HDV – 2*

- LNF-RTV +/- PEG IFN
  - Yurdaydin et al. EASL 2017 Abstract #GS-008

LOWR HDV – 3**

  - Koh et al., EASL 2017 Abstract #LBP-519

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LOWR HDV – 4: Dose-Escalation Study

Objectives

Primary Objectives

- Dose-escalation / maintenance up to LNF 100 mg BID + RTV for 24 weeks
- Safety and tolerability of LNF + RTV dose-escalation for 24 weeks
- HDV-RNA decline over 24 weeks

Secondary Objectives

- Pharmacokinetics
- ALT normalization
- Change in HBV-DNA levels
- Post-treatment HDV-RNA levels

HDV-RNA quantified by Robogene 2.0: LLOD = 14 IU/mL

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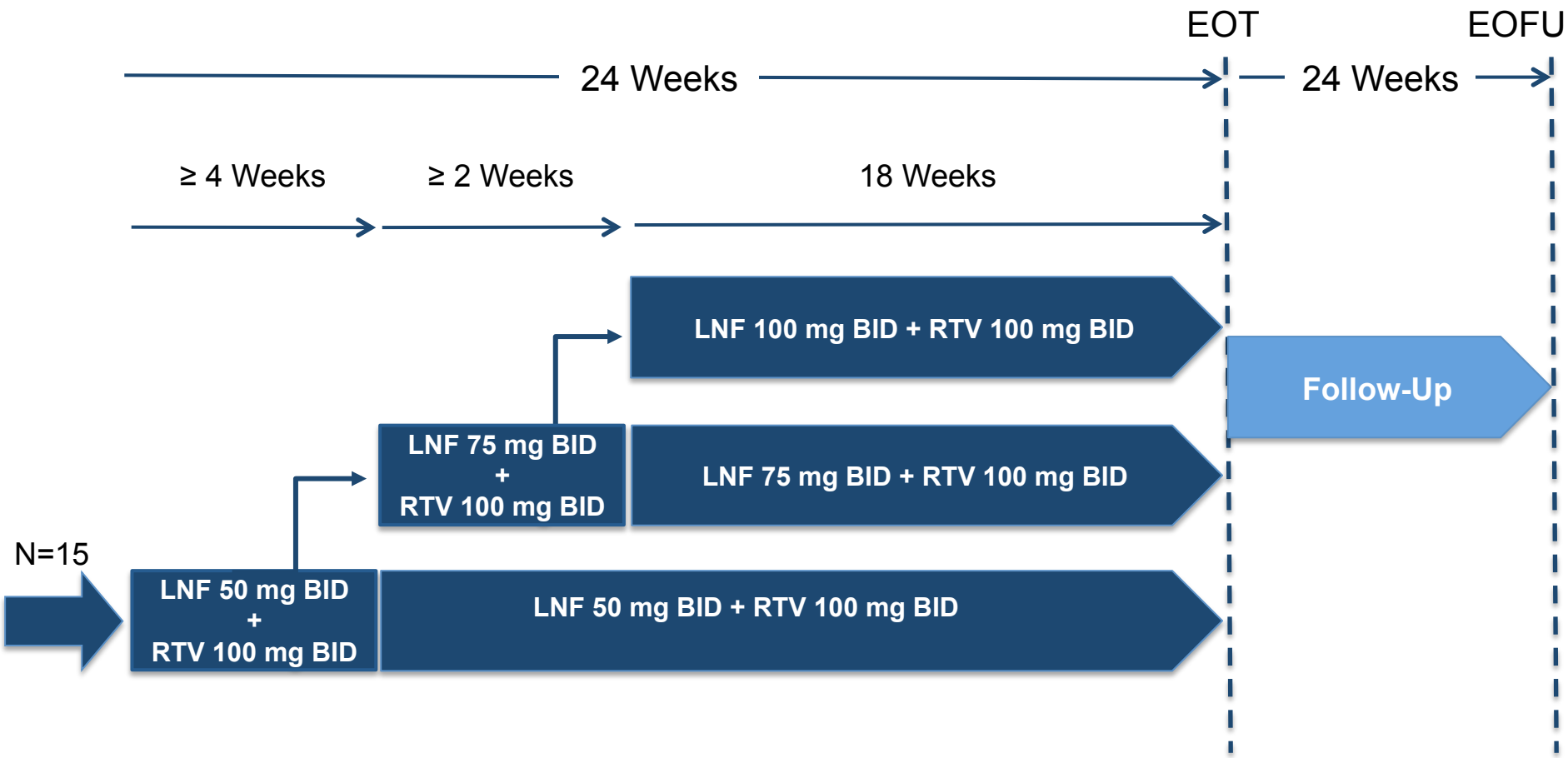
LOWR HDV – 4: Dose-Escalation Study

Study Completed: 24 Weeks Rx + 24 Weeks Follow-Up



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Baseline Characteristics

LOWR HDV - 4

Characteristic	Values
N	15
Median age, years (range)	40 (25 - 66)
Male, n (%)	11 (73.3%)
Race, n (%)	
White	12 (80%)
Asian	2 (13.3%)
Black	1 (6.7%)
BMI, kg/m^2 (range)	26.1 (20.8 - 34.3)
HDV-RNA, $\log_{10}$ IU/mL (range)	4.58 (2.76 - 6.28)
ALT, U/mL (range)	118 (54 - 362)
Fibroscan, kPa (range)	14.4 (3.6 - 35.3)
Prior interferon treatment, n (%)	10 (73%)
NUC treatment from baseline, n (%)	12 (80%)

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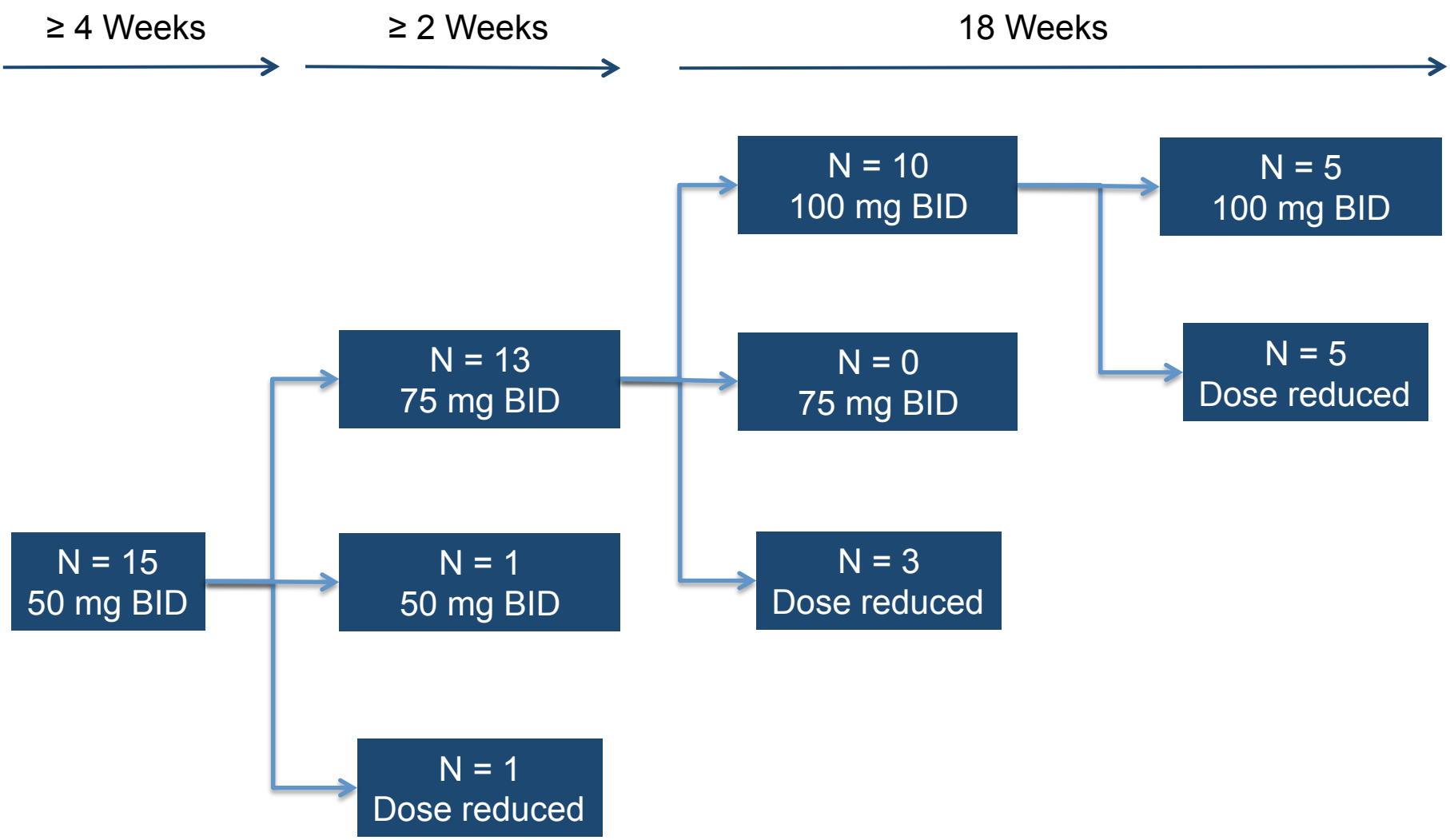
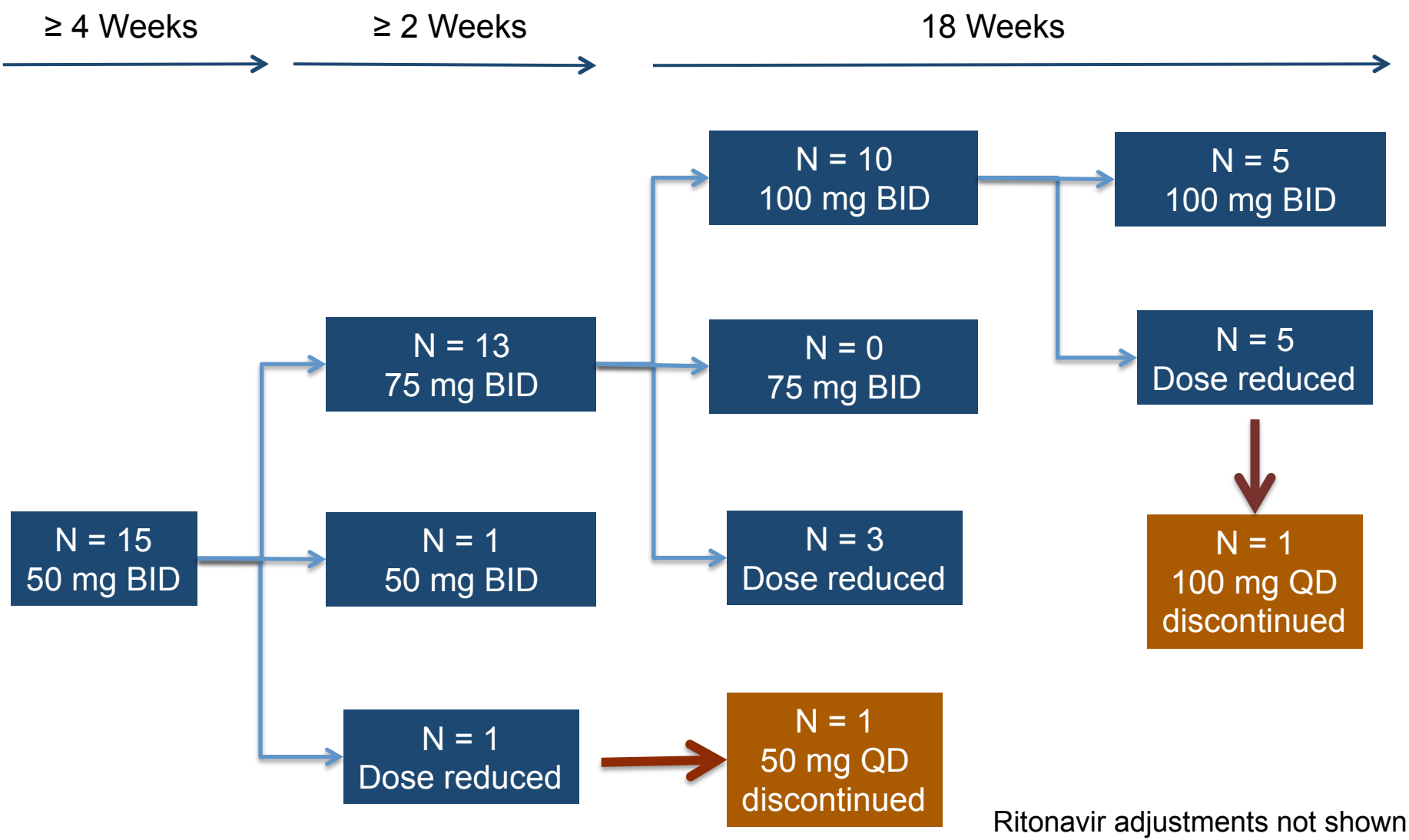
Lonafarnib Doses



Ritonavir adjustments not shown

LOWR HDV – 4: Dose-Escalation Study

Patient Disposition



Ritonavir adjustments not shown

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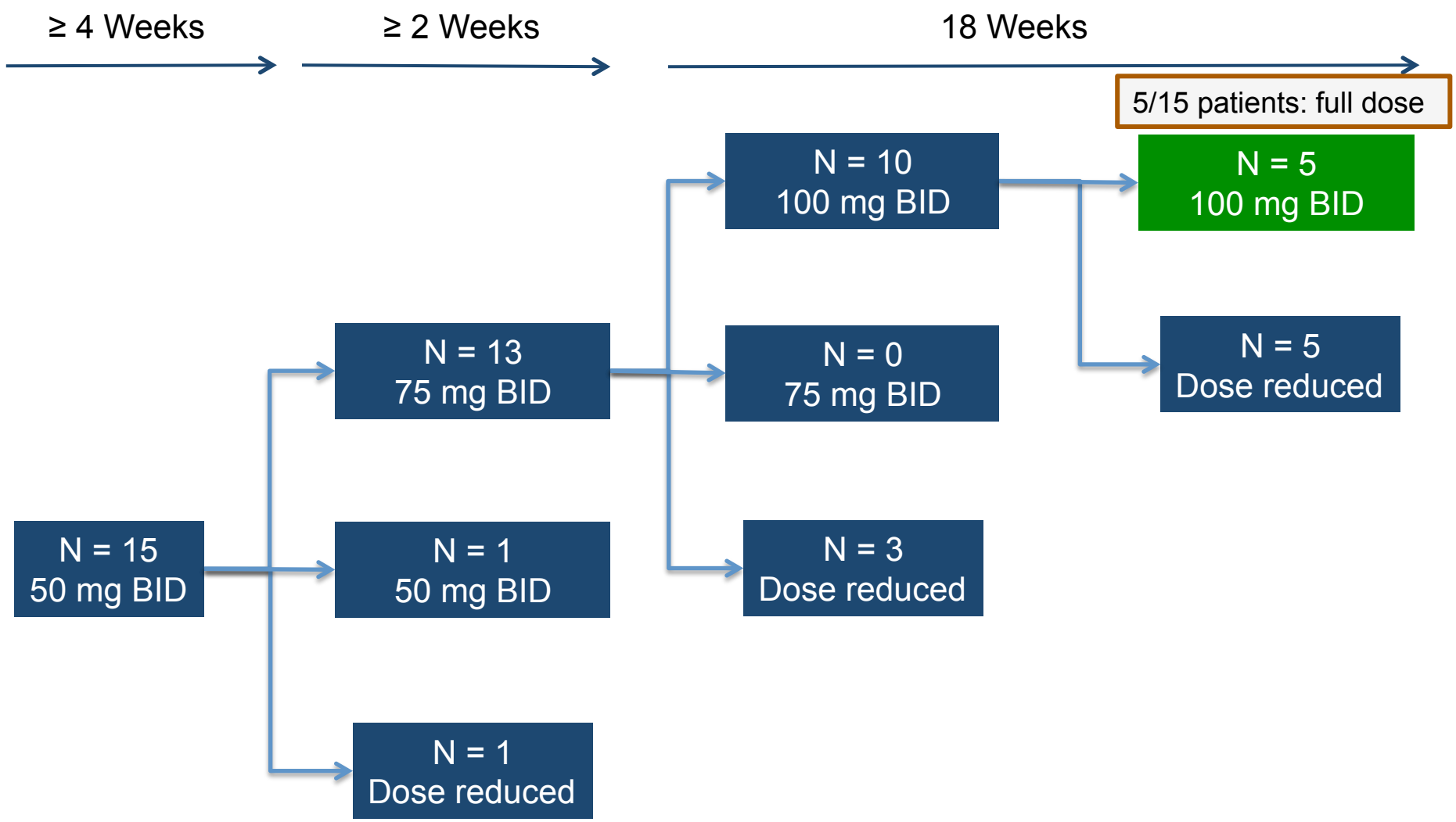
5 Patients Maintained on LNF 100 mg BID

Through Week 24



Ritonavir adjustments not shown

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Safety

GI Adverse Events and Weight Through Week 48

AE Grade	1	2	3	4
Abdominal Pain	2	4	0	0
Anorexia	1	7	0	0
Diarrhea	7	6	2	0
Nausea	2	6	0	0
Vomiting	5	3	0	0
Wt Loss	3	4	1	0

	Baseline	Week 24
Mean Wt (SD)	82.7 kg (12.5)	77.1 kg (10.1)
Mean Wt change from BL	-	-5.6 kg

- 8 GI/weight loss AEs present at Week 48 (end of follow-up)
- 1 SAE: traumatic broken jaw during follow-up (unrelated to treatment)

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Safety

GI Adverse Events and Weight Through Week 48

AE Grade	1	2	3	4
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Diarrhea	7	6	2	0
Nausea	2	6	0	0
Vomiting	5	3	0	0
Wt Loss	3	4	1	0

	Baseline	Week 24	Week 48
Mean Wt (SD)	82.7 kg (12.5)	77.1 kg (10.1)	80.5 kg (9.1)
Mean Wt change from BL	-	-5.6 kg	-2.2 kg

- 8 GI/weight loss AEs present at Week 48 (end of follow-up)
- 1 SAE: traumatic broken jaw during follow-up (unrelated to treatment)

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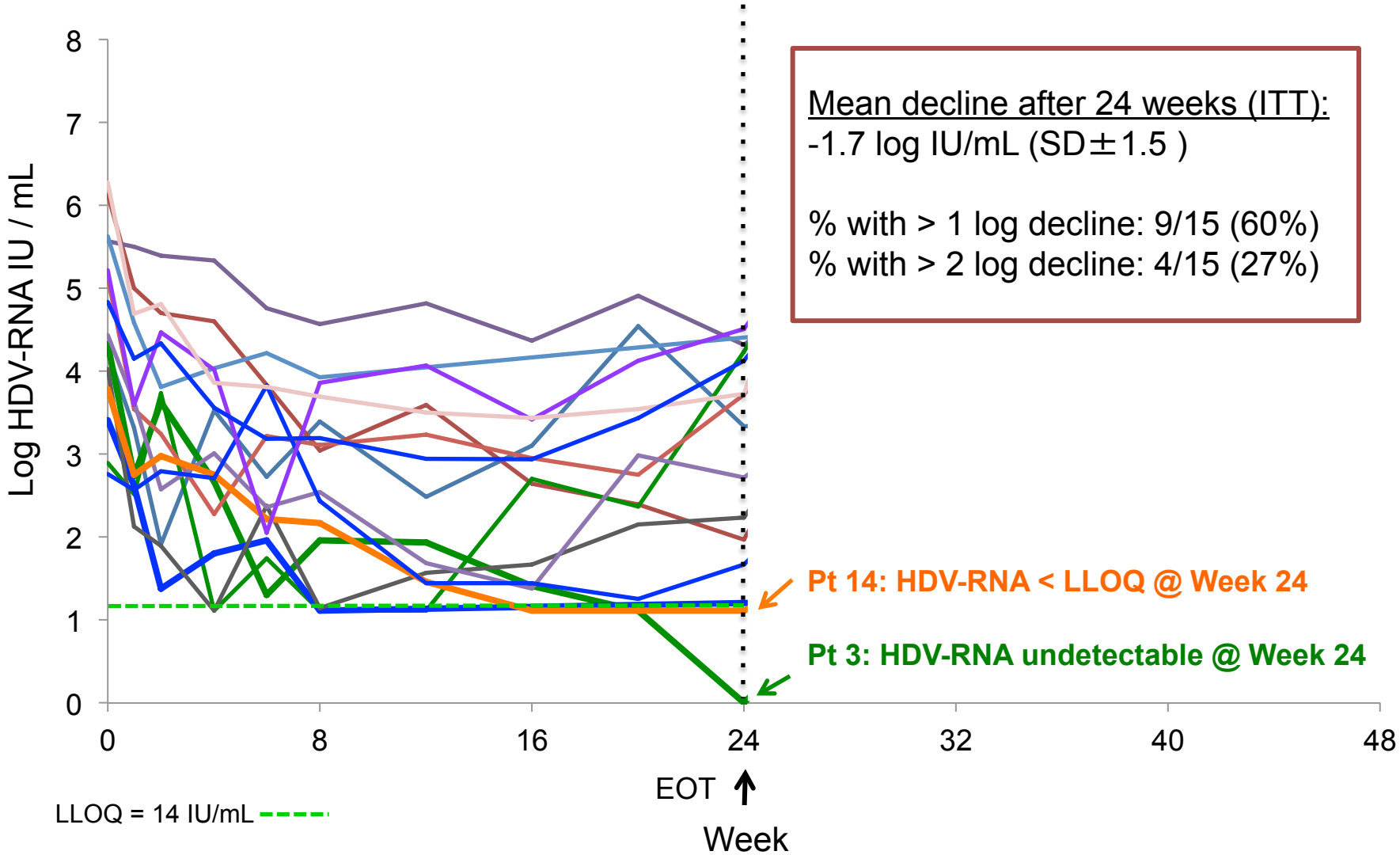
HDV-RNA Drop From Baseline

13 Patients Across 24 Weeks



Mean decline after 24 weeks (ITT):
-1.7 log IU/mL (SD±1.5)

% with > 1 log decline: 9/15 (60%)
% with > 2 log decline: 4/15 (27%)

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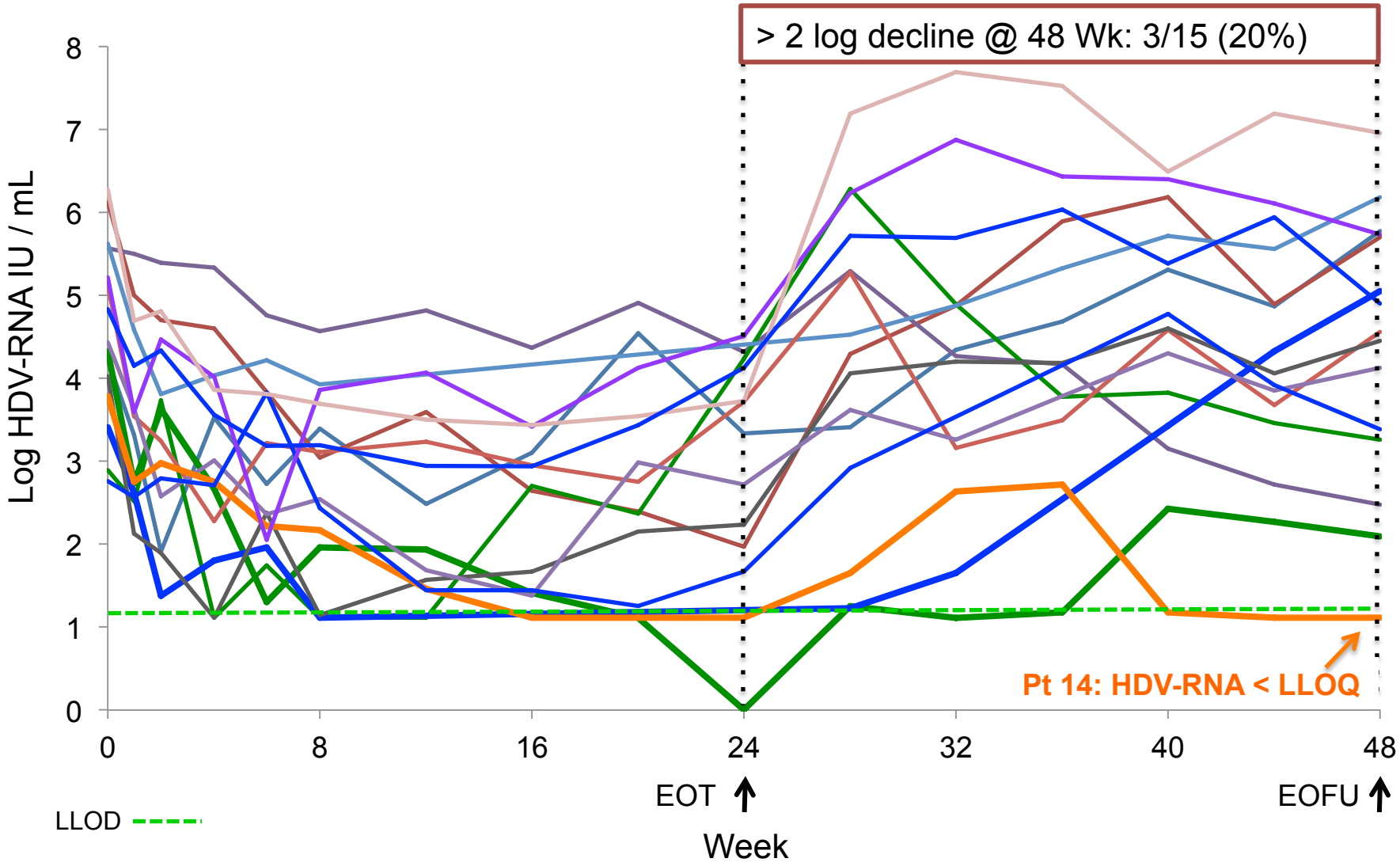
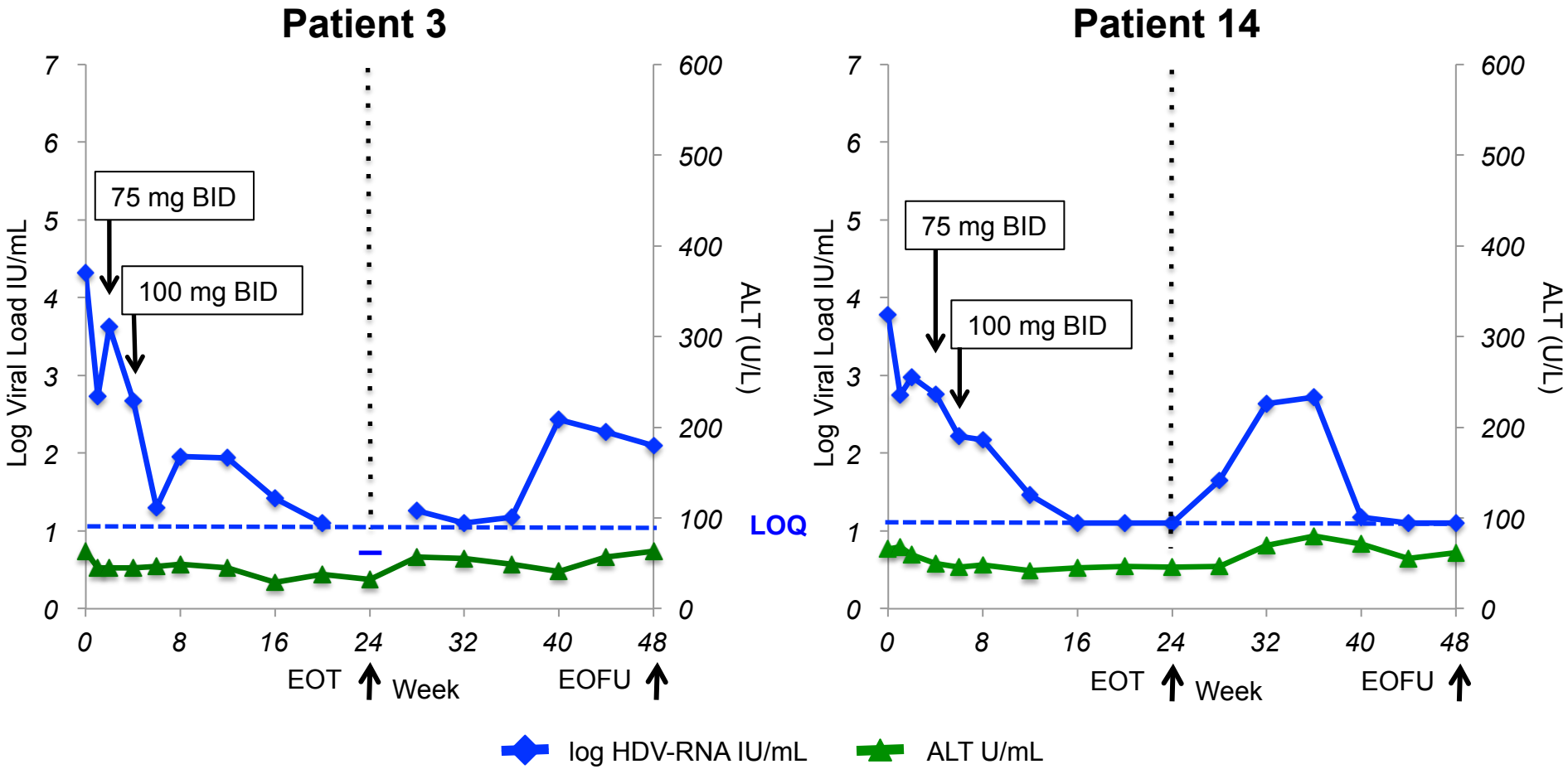
HDV-RNA Drop From Baseline

13 Patients Across 48 Weeks



Responders

Maintained LNF 100 mg BID Through Wk 24



- HDV-RNA PCR negative @ Week 24

- HDV-RNA <LLOQ @ Week 16-24
- HDV-RNA <LLOQ @ Week 48

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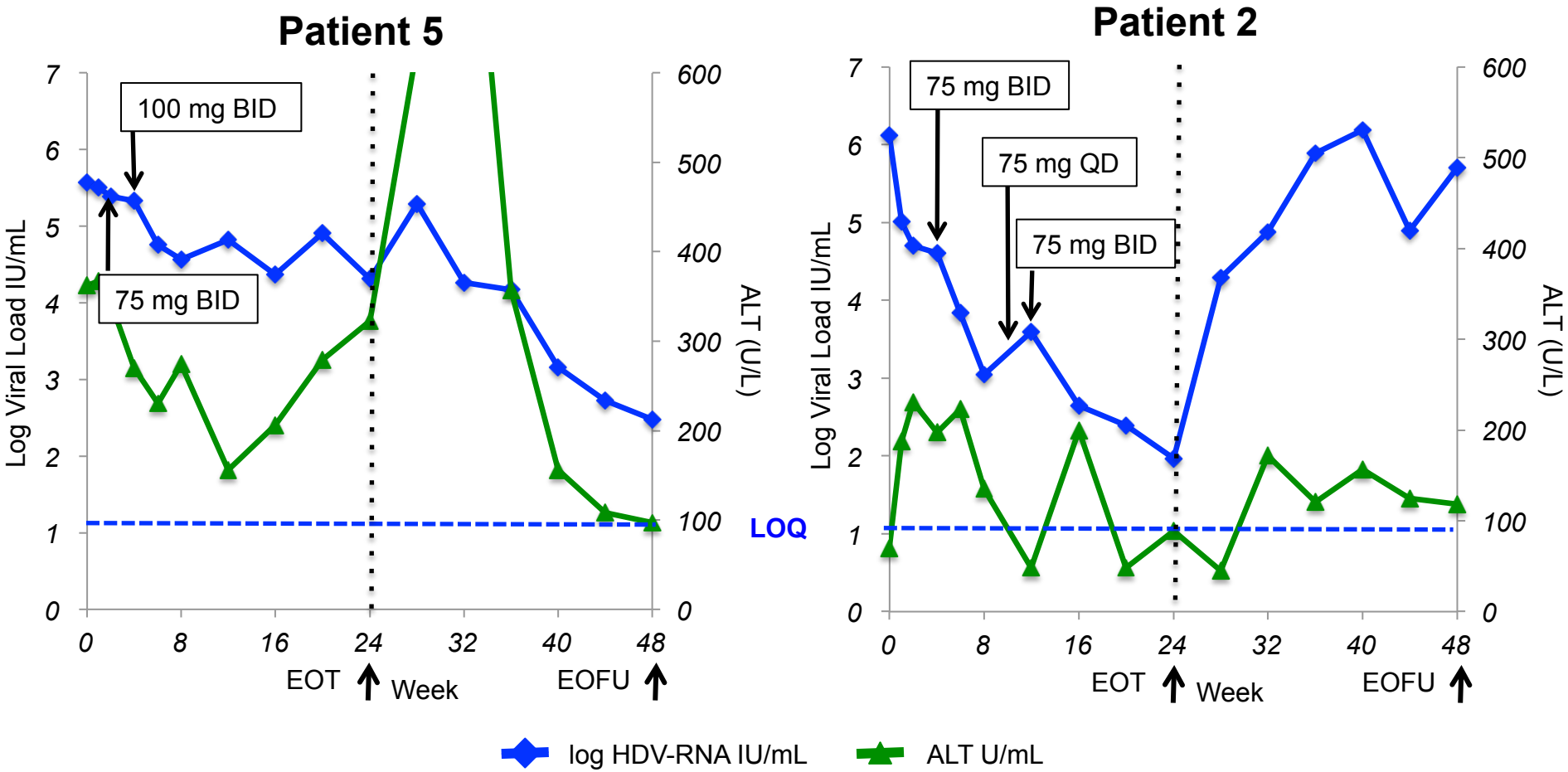
Post-treatment Responder & Relapser



- VL continues to decline post-treatment
- ALT flare = 938 U/L @ Week 32

- 4-log decline @ Week 24

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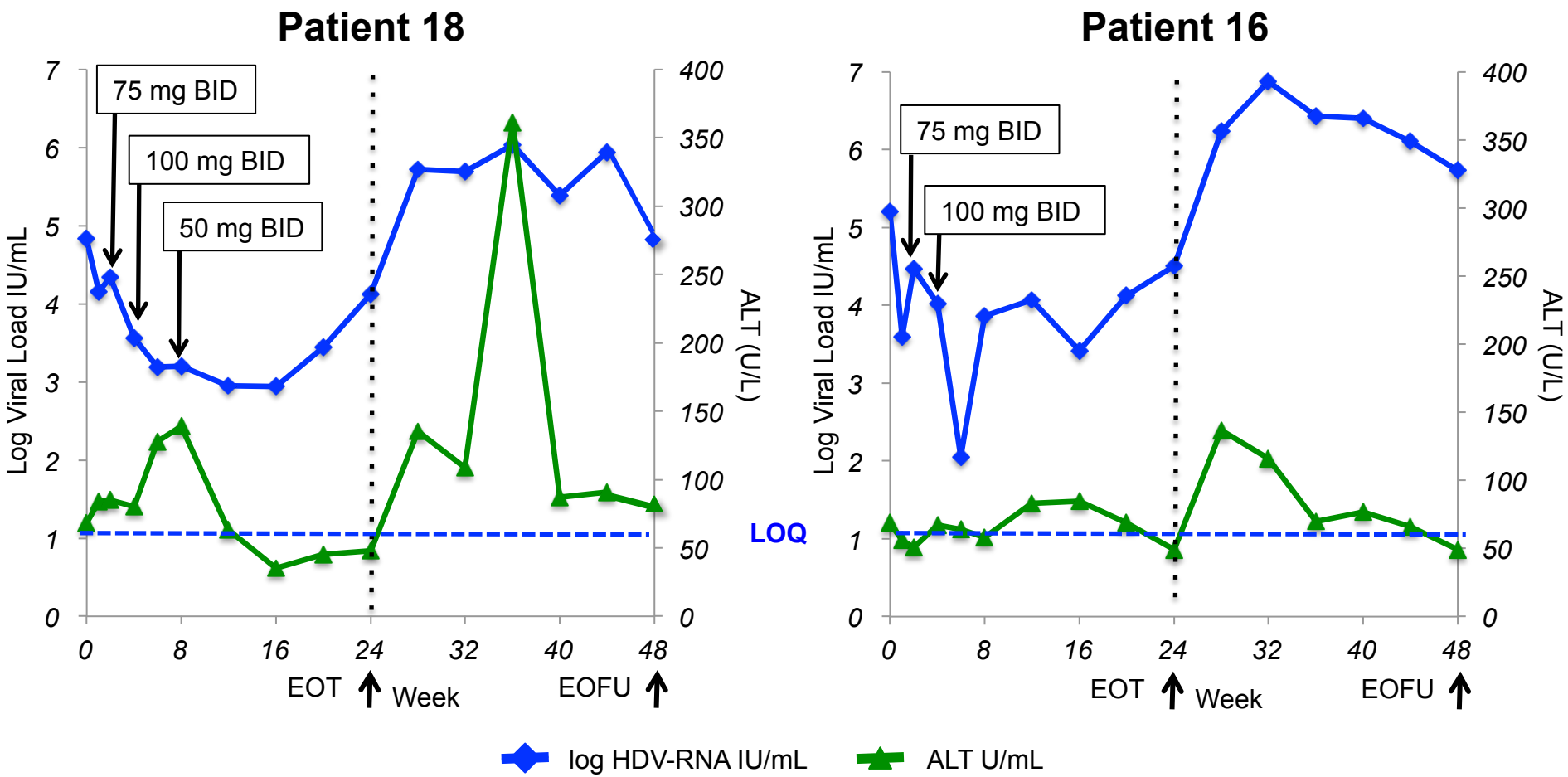
Non - Responders



- HDV RNA < 1 log decline at Week 24

- HDV RNA < 1 log decline at Week 24

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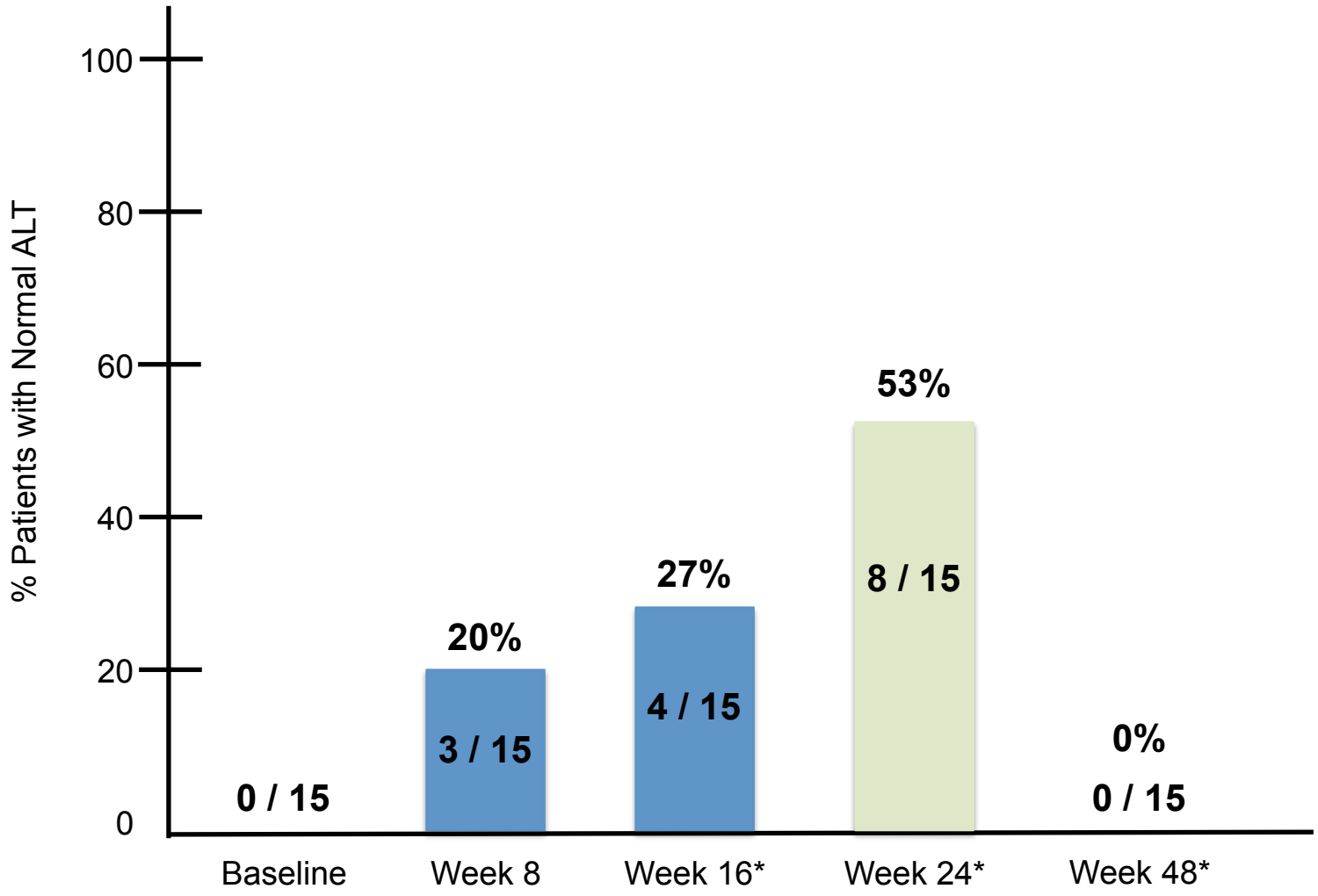
ALT Normalization

53% Patients Normalized ALT at End of Treatment
All Patients with Elevated ALT at End of Follow-Up



* ITT is shown including 2 early terminations

LOWR HDV – 4: Summary

At Week 24 – End of Treatment:

- 5/15 (33%) reached and maintained LNF 100 mg BID + RTV through EOT
  - 1/5 HDV-RNA undetectable; 1/5 dropped < 14 IU/mL (LLOQ)
- 53% patients normalized ALT

At Week 48 – End of Follow-up:

- 1/15 (7%) HDV RNA < 14 IU/mL (LLOQ)
- 3/15 (20%) dropped > 2 logs from baseline

Gastrointestinal AEs

- mostly grade 1-2
- 8/15 (53%) required dose reduction and 2/15 (13%) were discontinued

Inter-patient variability in efficacy and tolerability of LNF

Ongoing analysis:

- Role of host polymorphisms to explain interindividual variability in viral responses
- Role of host immune responses against HDV explaining long-term control

Conclusions

- This study confirmed an antiviral efficacy of lonafarnib over a period of 24 weeks
- Off-treatment HDV RNA control is possible in a proportion of patients
- Longer therapies and combination therapies need to be explored

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