ONLINE EXPERT POSTER REVIEW AND DISCUSSION

REPORTING FROM

The 47th Annual Meeting of the European Association for the Study of the Liver (EASL)

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Efficacy and safety of protease inhibitors for sever hepatitis C recurrence after liver transplantation: a first multicentric experience

A. Coilly, B. Roche, J. Dumortier, D. Botta-Fridlund, V. Leroy, G.P. Pageaux, S.N. Si-Ahmed, T.M. Antonini, D. Samuel, J.-C. Ducios-Vallee

Abstract #47

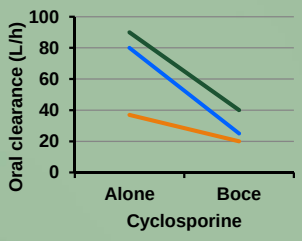
Background

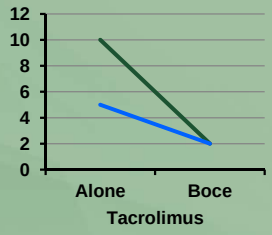
- One limitation is the potential drug-drug interaction with calcineurin inhibitors (CNI), mainly inhibiting the CYP 3A4

  Chariton, Hepatology, 2011
- The administration of telaprevir in healthy volunteers increased cyclosporine exposure 4.6-fold and tacrolimus exposure 70-fold

  Garg, Hepatology, 2011
- The administration of boceprevir in healthy volunteers increased cyclosporine exposure 2.7-fold and tacrolimus exposure 9.9-fold

  xxxx Annual meeting of HEP DART, 2011
- Boceprevir in 5 transplant patients: the estimate oral clearance decreased
  - cyclosporine: 50%
  - tacrolimus: up to 80%





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Patients and Methods

- Cohort study n=28
- 5 French transplant centers
- Inclusion criteria:
  - Active genotype 1 HCV chronic hepatitis
  - HCV recurrence, ≥ F2 (n=200 or cholestatic hepatitis (n=8)
  - Steady-state of immunosuppressive regimen
  - No contraindication for protease inhibitors

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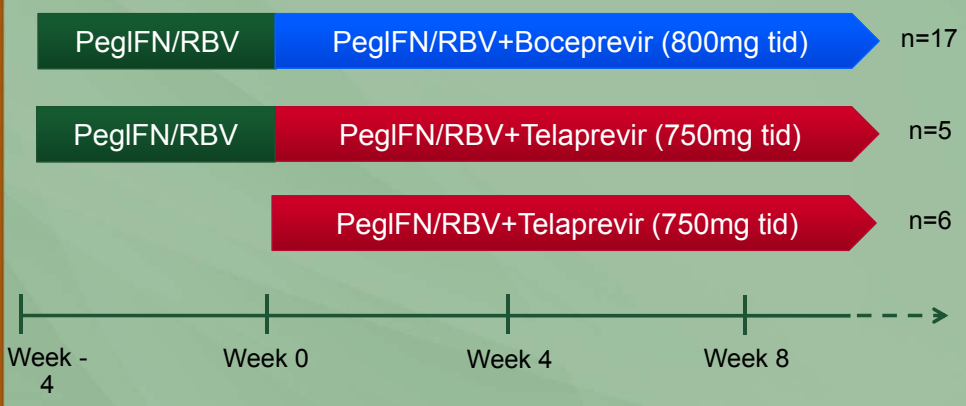
Patients and Methods



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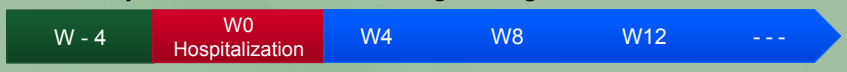
Patients and Methods

- Clinical and biological parameters (liver function, blood count, renal function, AE)
- Trough blood concentrations (C0) of immunosuppressive drugs. For initiation of PI, patients were hospitalized and C0 of CNI were daily monitored to reach target range



- HCV viral Load
- At week 4: rapid virological response
  - RVR+: reduction of <2log of HCV viral load
  - cRVR+: undetectable
- At week 8: virological response
  - VR+: reduction of <2log of HCV viral load
  - cVR+; undetectable

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General Characteristics

	Boceprevir (n=17)	Telaprevir (n=11)	*P*
Age (years)	53 ± 11 [34-75]	55 ± 11 [31-74]	ns
Gender (M/F)	16 (94%)/ 1 (6%)	9 (82%)/ 2 (18%)	ns
Body mass Index (Kg/m²)	23.0 ± 3.2 [17.8-28.4]	23.7 ± 5.2 [18.0-36.9]	ns
Indication for LT: Cirrhosis/HCC/HCV ReLT	6 (35%)/ 9 (53%)/2 (12%)	2 (18%) / 8 (73%) / 1 (9%)	ns
Co-infection HIV	3 (18%)	1 (9%)	ns
Co-infection HBV	1 (6%)	1 (9%)	ns
MELD score at listing	18 ± 11 [6-40]	17 ± 10 [6-33]	ns
Donor age (years0	51 ± 18 [16-84]	47 ± 18 [16-62]	ns
kidney transplantation	0	1 (9%)	ns
Acute rejection/ steroids bolus	1 (6%)/ 0 (0%)	3 (27%)/ 3 (27%)	ns/ 0.05
Cyclosporine/tacrolimus	11 (65%)/ 6 (35%)	5 (45%)/ 6 (55%)	ns
CT/MMF/everolimus	8 (47%)/7 (41%)/ 1 (6%)	1 (9%)/ 3 (27%)/0 (0%)	ns

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Baseline Characteristics

	Boceprevir (n=17)	Telaprevir (n=11)	*P*
Interval between LT and triple therapy (months)	124 ± 144 [7-449]	82 ± 89 [4-317]	ns
METAVIR score			
Activity (<A2/≥A2)	4 (24%)/ 13 (76%)	3 (27%)/ 8 (73%)	ns
Fibrosis stage ≥F3 F4	 9 (53%) 5 (29%)	 6 (55%) 0	ns
Cholestatic hepatitis	4 (24%)	4 (36%)	ns
Biological parameters			
Total bilirubin (µmol/L)	52 ± 86 [8-372]	47 ± 101 [8-333]	ns
ALT (IU/L)	191 ± 209 [40-801]	99 ± 53 [26-186]	0.01
INR	1.06 ± 0.12 [0.9-1.31]	1.08 ± 0.12 [1.0-1.35]	ns
Creatinine clearance (mL/min)	83 ± 31 [38-168]	73 ± 19 (39-113)	ns
Hemoglobin (g/dL)	13.1 ± 1.9 [8.7-16.3]	13.5 ± 1.9 [9.5-16.8]	ns
Neutrophil count (G/L)	2.9 ± 1.7 [1.1-5.9]	2.10 ± 1.4 [0.9-5.2]	ns
Platelet count (G/L)	142 ± 68 [54-136]	145 ± 60 [34-212]	ns

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Virological Characteristics

	Boceprevir (n=17)	Telaprevir (n=11)	*P*
Genotype: 1a/1b	11 (65%)/ 6 (35%)	4 (36%)/ 7 (64%)	ns
Pre-LT anti-HCV dual therapy			
Naïve	8 (47%)	4 (36%)	ns
Non-responders	9 (53%)	7 (64%)	ns
Post-LT anti-HCV dual therapy			
Naïve	8 (47%)	5 (45%)	ns
Non-responders	5 (30%)	6 (55%)	ns
Af baseline			
Baseline HCV viral load (log_{10} IU/mL)	7.0 ± 0.8 [5.9-8.5]	7.1 ± 1.0 [5.2-8.3]	ns
Peg-IFNa 2a/2b	4 (24%)/ 13 (76%)	8 (73%)/ 3 (27%)	0.03
RBV dosage (mg/kg/day0	12 ± 3 [7-17]	11 ± 5 [3-19]	ns
Recipient IL-28b polymorphism			
CC	6 (35%)	1 (9%)	0.05
CT/TT	4 (24%)/ 4 (24%)	4 (36%)/ 0 (0%)	ns

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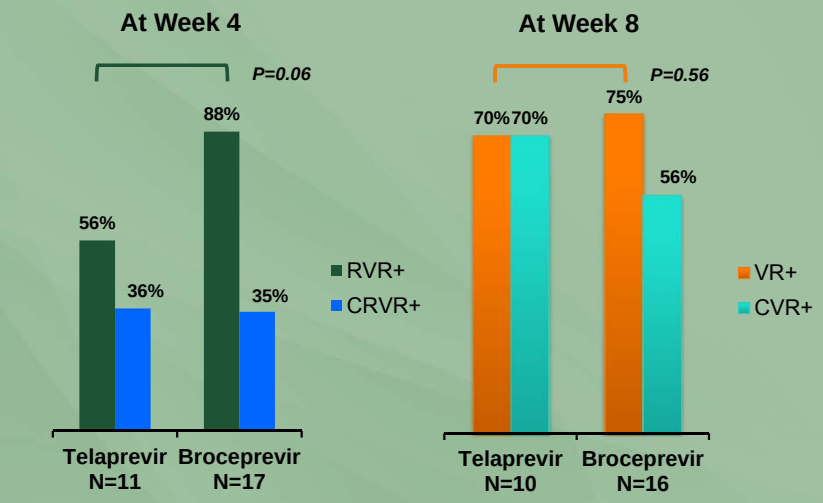
Virological Response



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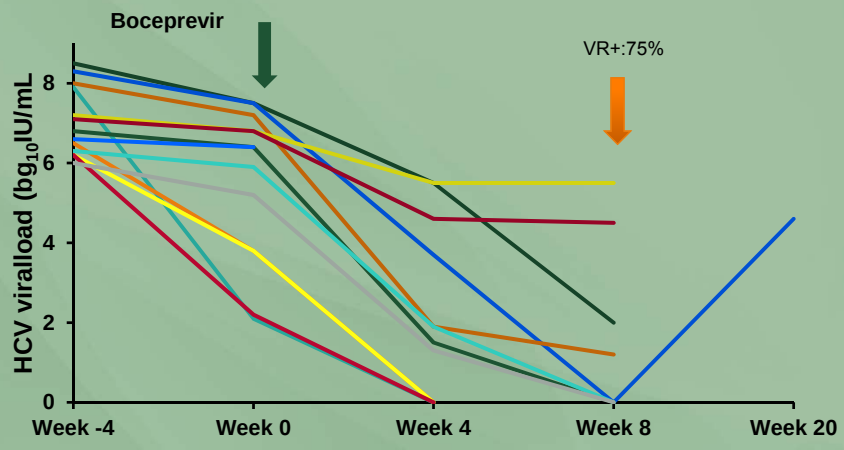
Virological Response in Boceprevir Group (n=17)

Mean time of triple therapy: 15 ± 7 wk (4-27)



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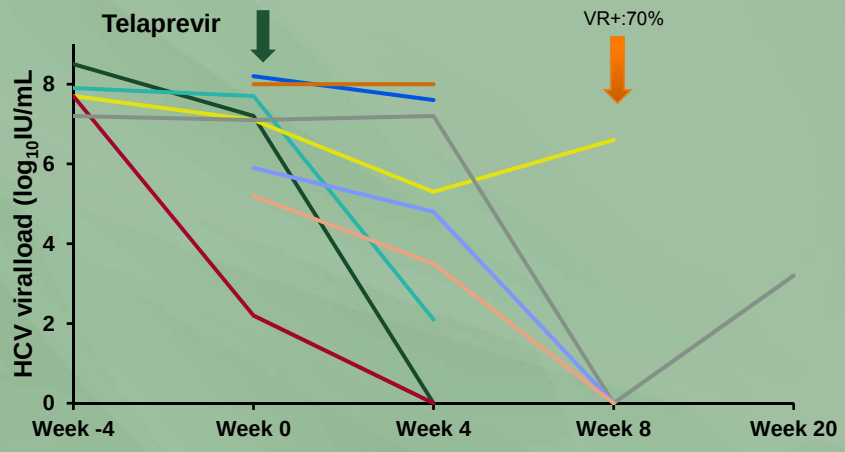
Virological Response in Telaprevir Group (n=11)

Mean time of triple therapy: 13 ± 4 wk (6-22)



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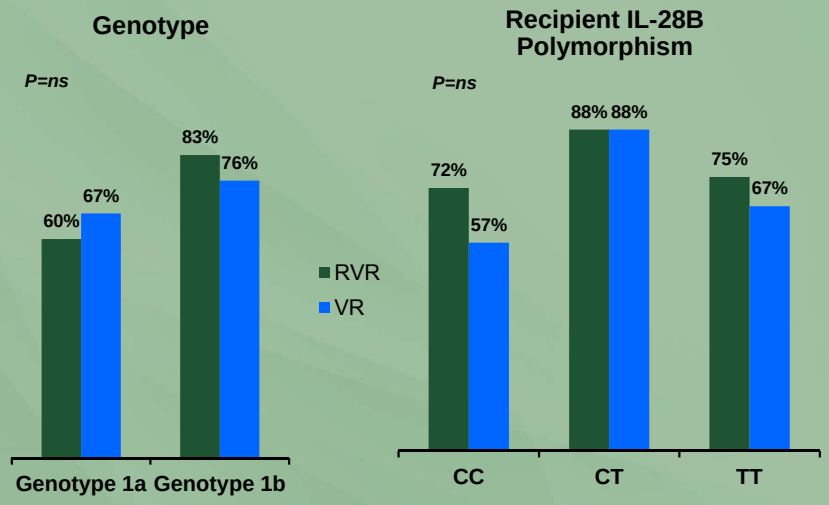
Virological Response According to...



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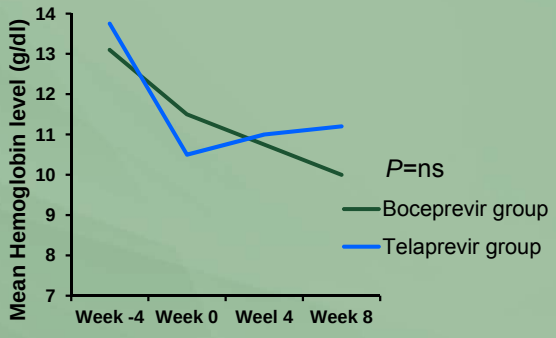
Adverse Events

	Boceprevir (n=17)	Telaprevir (n=11)	*P*
Death	**0 (0%)**	**1 (9%)**	**ns**
Infections	2 (12%)	2 (18%)	ns
Myelotoxicity Anemia <10g/dl <8g/dl Neutropenia (<1 G/L) Thrombocytopenia (<50 G/L)	 12 (71%) 3 (18%) 4 (24%) 0	 6 (55%) 1 (9%) 2 (18%) 1 (9%)	ns
Dermatological AE	1 (6%)	1 (9%)	ns
Renal failure	0	1 (9%)	ns
Diabetes mellitus	2 (12%)	0	ns

Hemoglobin Level During Triple Therapy Anemia Management

- 26 (93%) of patients were treated by EPO
  - Delay administration: 31 days
- 4 (14%) requiring red blood cell transfusion (boce=; tela=1)
- Mean RBV reduction: 25% [-33-90]
- No impact of MMF use



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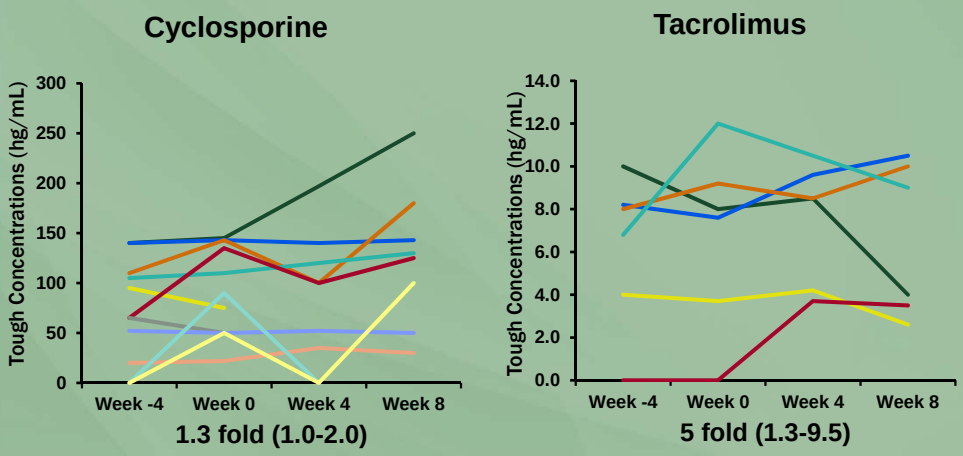
Management of Drug-drug Interactions: Boceprevir Group



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Conclusions

- Efficacy:
  - At Week 4, 35% of boceprevir patients and 36% of telaprevir patients achieved a complete rapid virological response
  - At Week 8, 56% of boceprevir patients and 70% of telaprevir patients achieved a complete virological response
- Safety:
  - Anemia is the main AE Boce: 71%, Tela: 55%
  - >90% of patients were treated by EPO
  - CNI dosage reduction was constantly required:
    - 1.3 fold with cyclosporine and 5 fold with tacrolimus, in boceprevir group
    - 4 fold with cyclosporine and 35 fold with tacrolimus, in telaprevir group

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Safety of Telaprevir or Boceprevir in Combination with Peginterferon Alfa/Ribarvirn, in Cirrhotic Non Responders. First Results of the French Early Access Program (ANRS CO20-CUPIC)

C. Herzode, C. Dorival, F Zoulim, T Poynard, R. Mathurin, S. Pol, D. Larrey, P. Cacoub, V de Ledinghen, M. Bouliere, PH Bernard, G. Riachi, Y. Barthe, H. Fontaine, F. Carrat, JP Bronowicki, the CUPIC Study Group (ANRS CO 20)

Abstract #8

Background

- In Phase III trials adverse events were reported:
  - Rash, pruritus and anemia with Telaprevir (TVR)
  - Anemia and dysgeusia with Boceprevir (BOC)
- Only few patients with cirrhosis were included:
  - Telaprevir:
    - ADVANCE[1] = 47
    - ILLUMINATE[2] =61
    - REALIZE[3] = 139

    } **247**
  - Boceprevir:
    - SPRINT-2[4] = 76 (F3F4)
    - RESPOND-2[5]=39

    } **115**

1 Jacobson IM. et al. N Engl J Med 2011:364:2405-16
2 Sherman K. et al. N Engl J Med 2011:365:1014-24
3 Zeuzem S. et al. N Engl J Med 2011:364:2417-28
4 Poordad F. et al. N Engl J Med 2011:364:1195-206
5 Bacon BR. et al. N Engl J Med 2011:364:1207-17

French Early Access Program

ATU

The Temporary authorization of Use (ATU) is an early access program for medicinal products which have undergone full clinical development and are waiting for marketing authorization by the French Health Products Safety Agency (Afssaps)

CUPIC

Compassionate Use of Protease Inhibitors in viral C cirrhosis

National multicenter observatory in the setting of the ATU

Promoter: ANRS

Aim: to prospectively collect clinical data and biological specimen

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Objective of CUPIC Cohort

- Primary objective
  - Determine the rate of SVR
- Interim analysis
  - Evaluate safety and tolerability among patients included in the CUPIC cohort who received at least 16 weeks of antiviral treatment
    - From February 15th 2011 to march 31st 2012:
      - 651 patients were included in 55 sites
      - 455 patients were included in this analysis

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CUPIC Patients

- Treated in the French early access program
- HCV genotype 1 patients
- Compensated cirrhosis (Child Pugh A)
- Non-responders
  - Relapsers
  - Partial responders
  - (↓ >2 log10 HCV RNA decline at Week 12)
  - Null responders theoretically excluded

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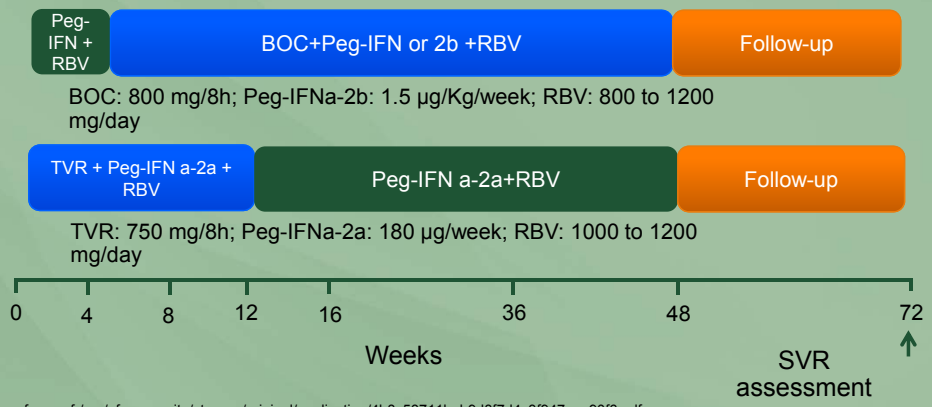
Treatment Regimen



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Telaprevir: Patient Characteristics

	Telaprevir n=296
Male (%)	68
Mean age (years)	57.0
Median follow-up duration (days)	140
Median telaprevir duration (days)	84.0
Mean neutrophils (10^9/mm^3)	3.3
Mean hemoglobin (g/dl)	14.4
Mean platelets (/mm^3)	150.000

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Telaprevir: Patient Characteristics

	Telaprevir n=296
Genotype 1b / 1a (%)	61 / 39
Mean Baseline HCV RNA (log_{10} IU/mL)	6.5
Mean Prothrombin Time (µmol/L)	88
Mean Total Bilirubin (µmol/L)	15
Mean Albumin (g/dL)	40
Esophageal varices (%)	15
Previous treatment response (%) Partial responders Relapsers Nulls responders	 52 40 8
Patients with Realize exclusion criteria (%)	34

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Telaprevir: Preliminary Safety Findings

Patients, n (%) patients with at least one event)	Telaprevir n=296
Serious adverse events (SAEs)*	144 (48.6%)
Premature discontinuation Due to SAEs	77 (26.0%) 43 (14.5%)
Death ***Septicemia, Septic shock, Pneumopathy, Oesophageal varices Bleeding, Encephalopathy, Lung carcinoma***	6 (2.0%)
Infection (Grade 3/4)	26 (8.8%)
Asthenia (Grade 3/4)	14 (4.7%)
Rash Grade 3 Grade 4 (SCAR)	20 (6.8%) 2 (0.7%)
Pruritus (Grade 3/4)	11 (3.7%)
Hepatic decompensation (Grade 3/4)	13 (4.4%)

* 407 SAEs in 144 patients, SCAR = severe cutaneous adverse reaction

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Telaprevir: Preliminary Safety Findings

Patients, n(% patients with at least one event)	Telaprevir N=296
Anemia Grade 2 (8.0 - <10.0 g/dL) Grade ¾ (<8,0 g/dL) EPO use Blood transfusion	 58 (19.6%) 30 (10.1%) 168 (56.8%) 45 (15.2%)
Neutropenia Grade 3 (500 - <1000/mm^3) Grade 4 (<500/mm^3) G-CSF use	 12 (4.0%) 2 (0.7%) 7 (2.4%)
Thrombopenia Grade 3 (25000 -<50000) Grade 4 (<25000) Thrombopoietin Use	 35 (11.8%) 4 (1.3%) 5(1.7%)

EPO: Erythopoietin, G-CSF: granuloctye-colony stimulating factor

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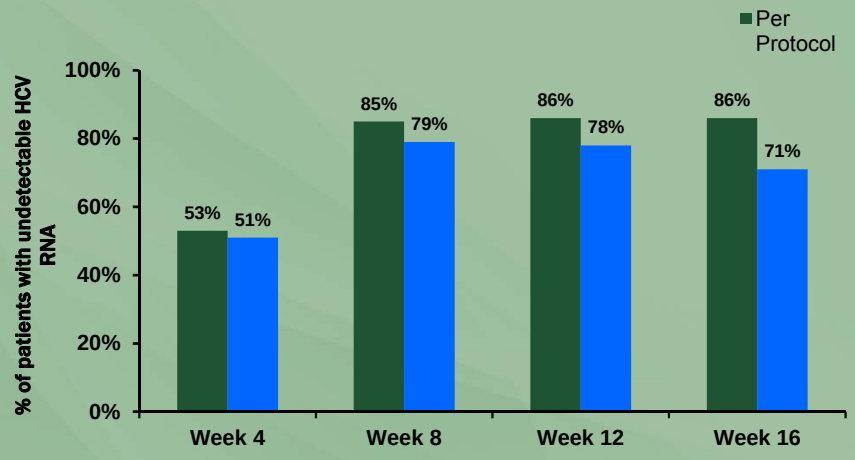
Telaprevir: Preliminary Efficacy Data



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Boceprevir: Patient Characteristics

	Boceprevir n=159
Male (%)	67.5
Mean age (years)	56.8
Median follow-up duration (days)	168
Median boceprevir duration (days)	140
Mean Neutrophils (10^9/mm^3)	3.2
Mean Hemoglobin (g/dl)	14.8
Mean Platelets (/mm^3)	150 000

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Boceprevir: Preliminary Safety Findings

Patients, n (%) patients with at least one event)	Boceprevir n=159
Serious adverse events (SAEs)*	61 (38.4%)
Premature discontinuation Due to SAE	38 (23.9%) 12 (7.4%)
Death ***Bronchopulmonary infection, Sepsis***	2 (1.3%)
Infection (Grade 3/4)	4 (2.5%)
Asthenia (Grade 3/4)	9 (5.7%)
Rash Grade 3 Grade 4 (SCAR)	 0 0
Pruritus (Grade 3/4)	1 (0.6%)
Hepatic decompensation (Grade 3/4)	7 (4.4%)

* 158 SAEs in 81 patients, SCAR = severe cutaneous adverse reaction

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Boceprevir: Preliminary Safety Findings

Patients, n(% patients with at least one event)	Boceprevir n=296
Anemia Grade 2 (8.0 - <10.0 g/dL) Grade ¾ (<8,0 g/dL) EPO use Blood transfusion	 36 (22.6%) 16 (10.1%) 105 (66.0%) 17 (10.7%)
Neutropenia Grade 3 (500 - <1000/mm^3) Grade 4 (<500/mm^3) G-CSF use	 7 (4.4%) 1 (0.6%) 6 (3.8%)
Thrombopenia Grade 3 (25 000 -<50 000) Grade 4 (<25 000) Thrombopoietin Use	 10 (6.3%) 1 (0.6%) 3(1.9%)

EPO: Erythopoietin, G-CSF: granuloctye-colony stimulating factor

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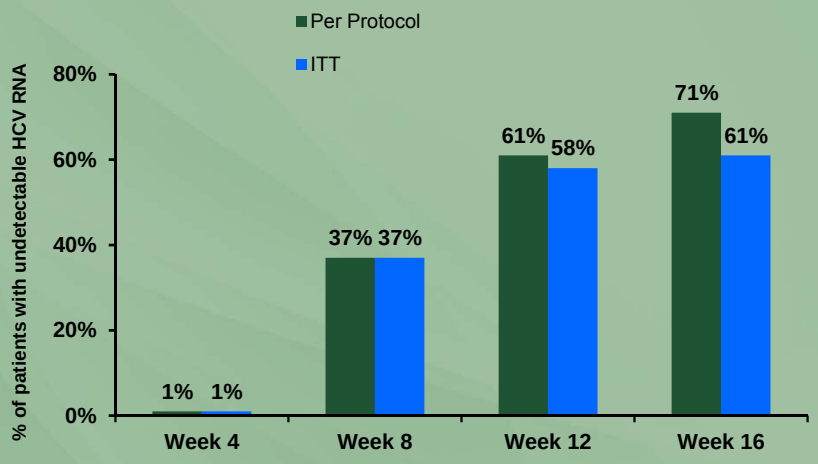
Boceprevir: Preliminary Efficacy Data



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Preliminary Conclusions

- The safety profile of DAAs among compensated cirrhotic patients treated in the CUPIC cohort was poor, however associated with high rates of on treatment virologic response
  - Compatible with the use in real-life practice
- We observed a high rate of SAEs (38.4 to 48.6%) compared to phase III trails results (9 to 14%) and high rate of discontinuation due to SAEs (7.4 to 14.5%)
- Based on preliminary results of the CUPIC cohort, patients with cirrhosis should be treated cautiously and should be carefully monitored especially because of a high incidence of anemia with poor response to EPO
- SVR rates in real-world setting are awaited in this population

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