Welcome to Medivir breakfast presentation at EASL 2009

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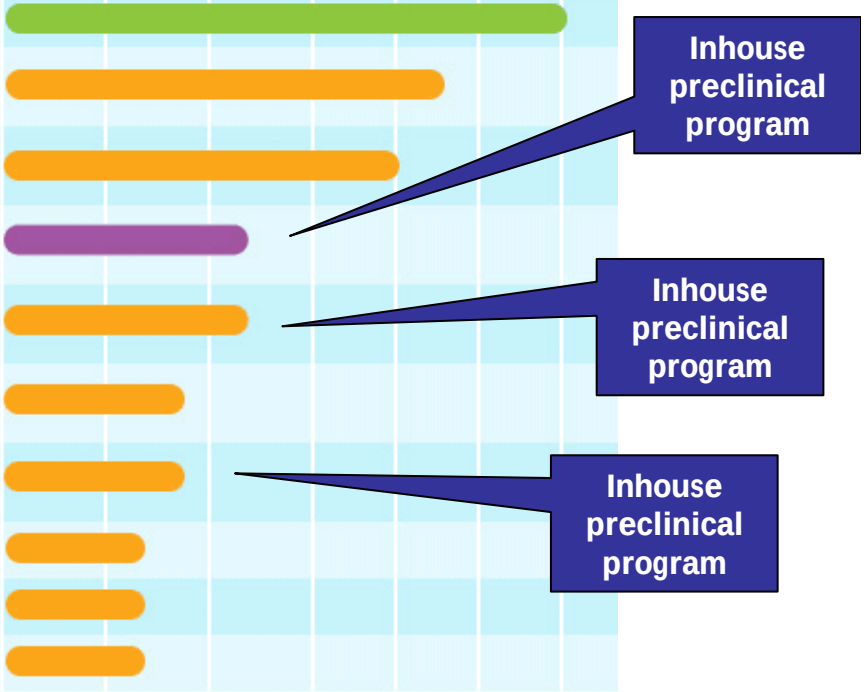
Medivir Pipeline April 2009

- ”We has a large interest and strong commitment in HCV drug development”

Prioritized projects

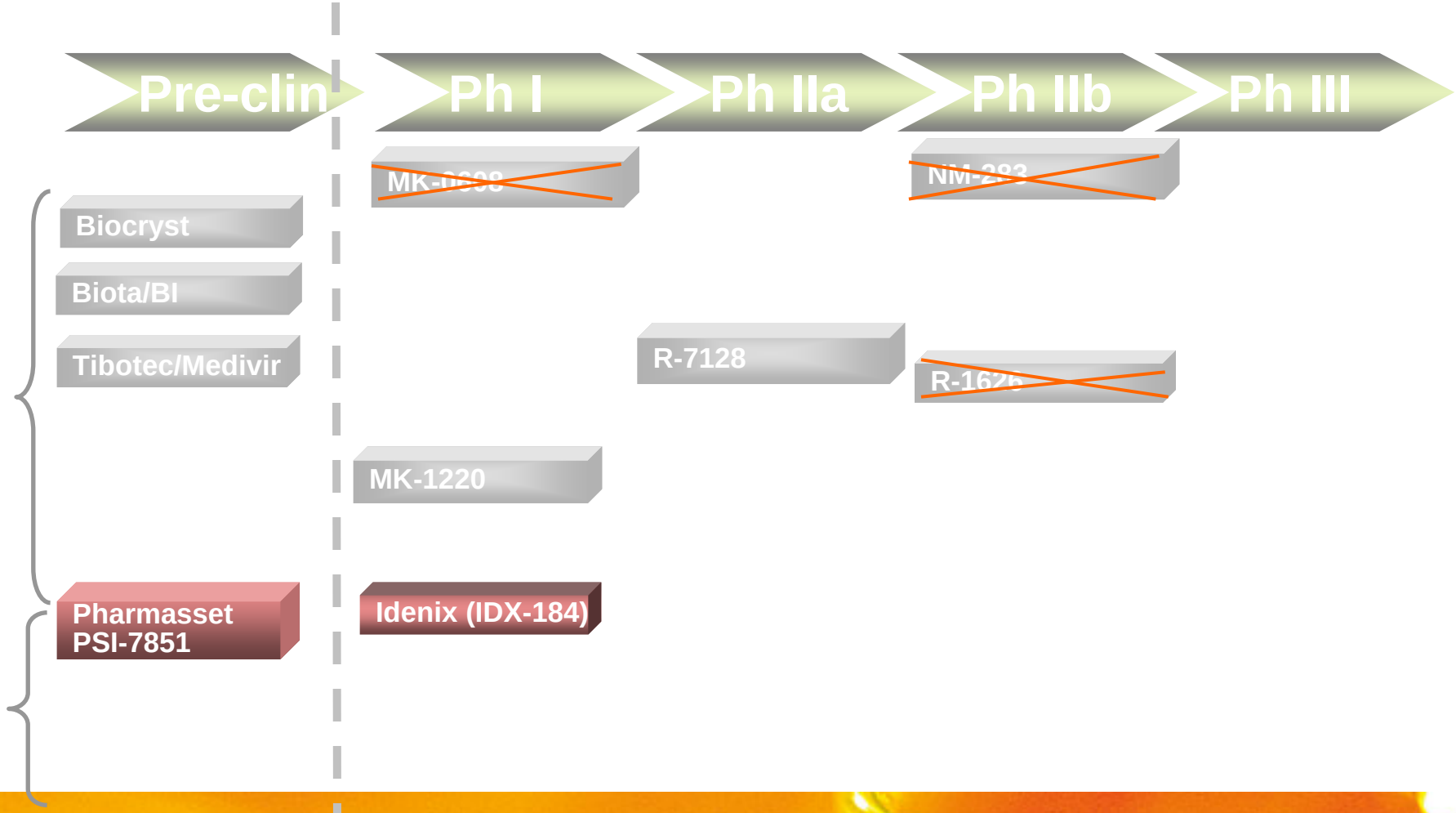
Project	Indication(s)	Partners/ Date of agreement	Terms	Medivir's markets
Lipsovir® (ME-609)	Labial herpes	In-house		
TMC435 (HCV-PI)	Hepatitis C	Tibotec / 2004	EUR 80.5 m + royalties and FTE funding	Nordic region
MIV-701 (Cath K)	Osteoporosis, osteoarthritis, bone metastases	In-house		
HCV POL	Hepatitis C	Tibotec / 2008	EUR 142-272 m + royalties and FTE funding	Nordic region
MIV-710 (Cath K)	Osteoporosis, osteoarthritis, bone metastases	In-house		
HIV PI	HIV	Tibotec / 2006	EUR 64 m + royalties and FTE funding	Nordic region
BACE	Alzheimer's	In-house		
Cathepsin S	Rheumatoid arthritis, multiple sclerosis	In-house		
COPD PI	COPD	In-house		World
Renin	Hypertension	In-house		



HCV POL - In collaboration with Tibotec / JNJ

Nucleoside HCV Polymerase Inhibitors

HCV Nucleoside Competitive Landscape



Hepatitis C Polymerase – Medivir/J&J program

Status

- Partnership with Tibotec / Johnson & Johnson since May 15 2008
- Candidate Drug selected on December 9th, 2008, triggering a milestone of € 2.6m
- Selected CD in preclinical development phase towards phase I

Patents

- Extensive and non-limiting IP filed

Licensing agreement

- Remaining milestones of € 137m + royalties on sales for one product reaching market.
- Additional € 130m for second compound and indication reaching market + royalties on sales.
- FTE Funding for one year, ends May 2009
- All development costs covered by JNJ
- Nordic rights retained by Medivir

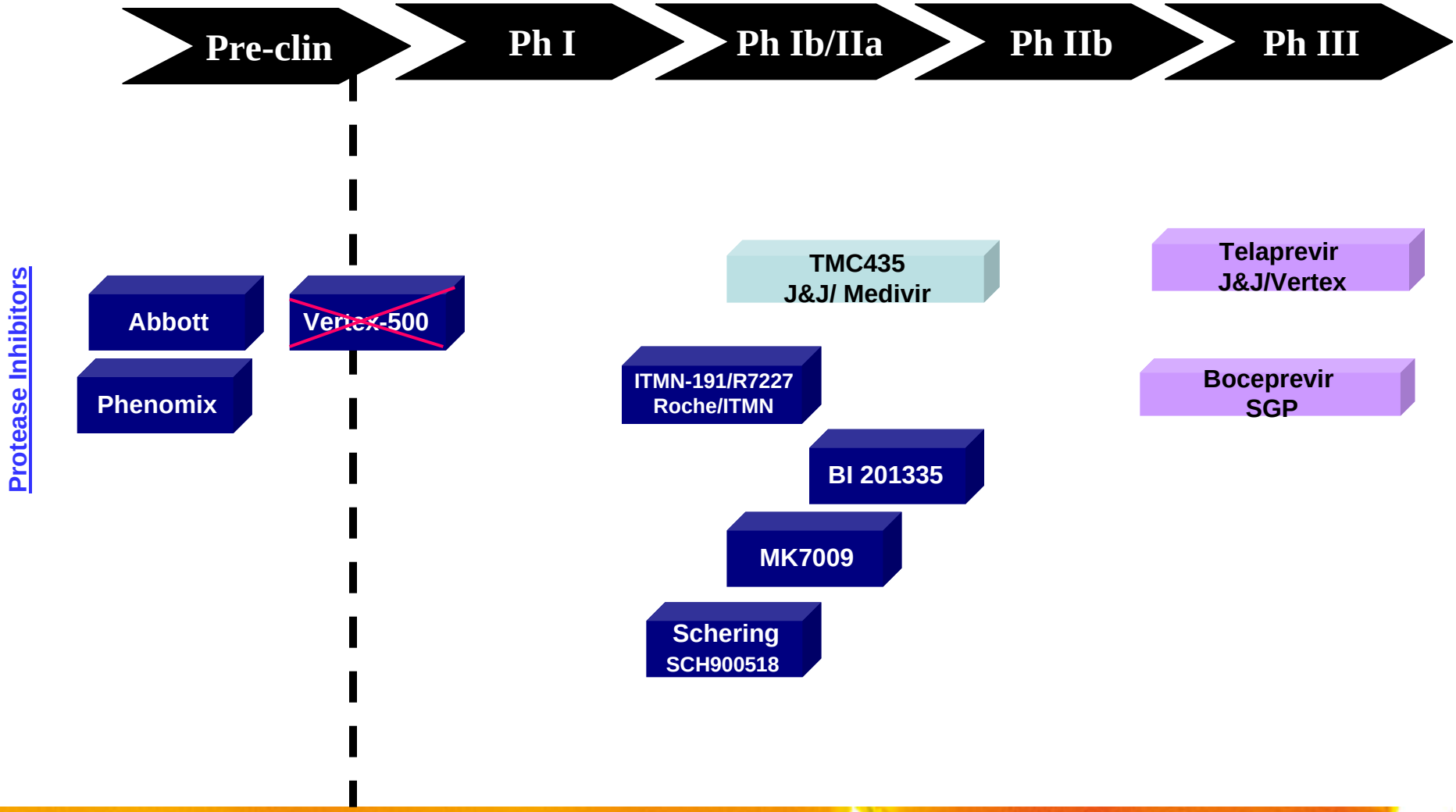
TMC435 – in collaboration with Tibotec / J&J

Presently in final stage of phase IIa for genotype 1 treatment naïve patients and treatment experienced patients

Data from Opera-1 (Phase IIa) in treatment naïve and treatment experienced patients presented

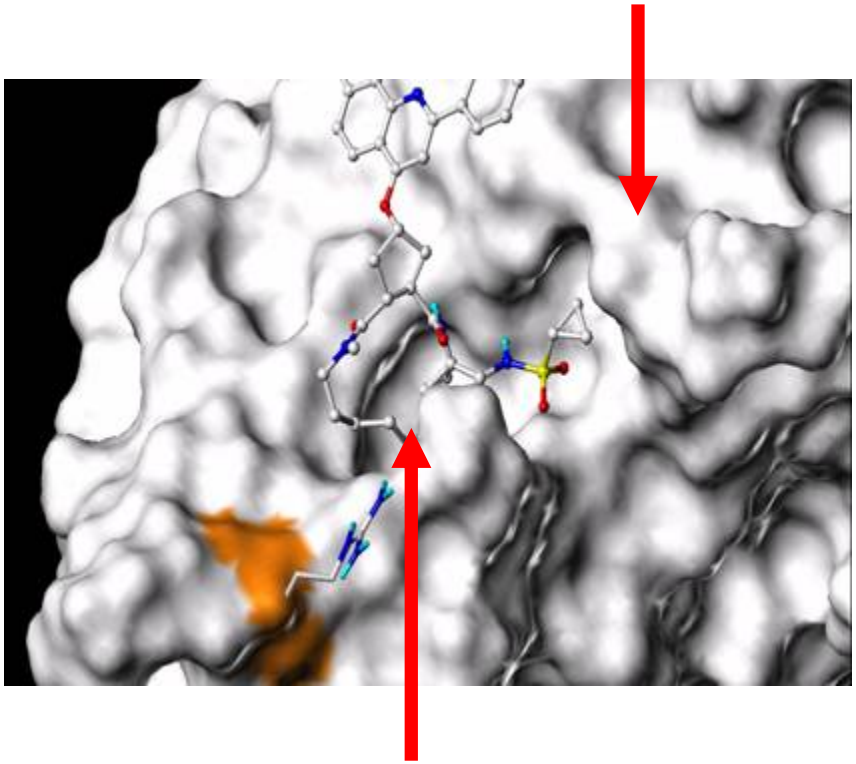
Phase IIb will start in Q2

HCV PI Competitive Landscape



Hepatitis C protease – TMC435 - Medivir/Tibotec

- Non-covalent binding NS3/4A protease inhibitor
- EC_{50} = 8 nM in genotype 1 replicon
- In vitro: Synergistic with IFNα and additive with RBV



Hepatitis C protease – TMC435 - Medivir/Tibotec

Status

- Phase IIb will start Q2 2009

Results from IIa

- Data from 25 and 75 mg dose groups in treatment naïve patients presented in November 2008.

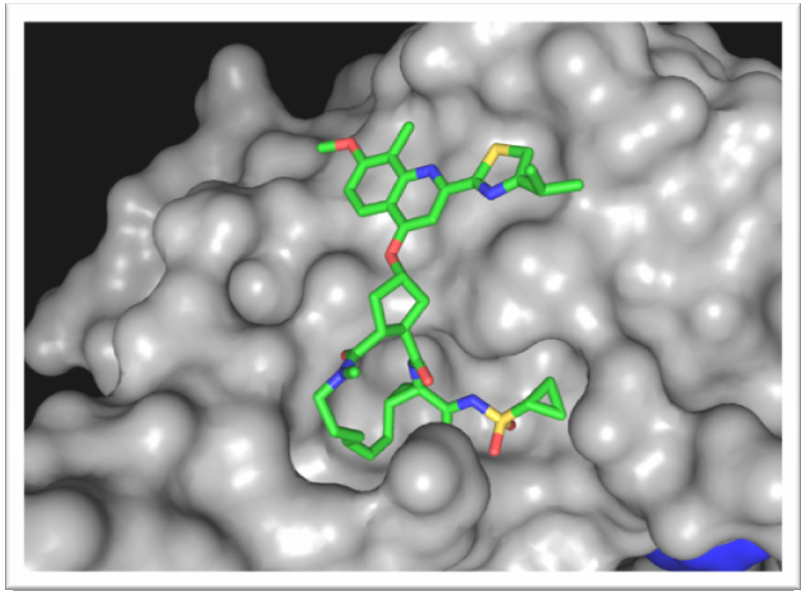
New data presented at EASL in April 23-25 2009

- Data from 25 mg, 75 mg and 200 mg at week 12 in treatment naïve patients
- Data in previous non-responders and relapsers from the 75, 150 and 200mg dose groups at week 4

Licensing agreement

- Upfront & milestones of EUR 80.5m (EUR 47m remains)

  + royalties on sales
- All development costs covered by Tibotec
- Nordic rights retained by Medivir

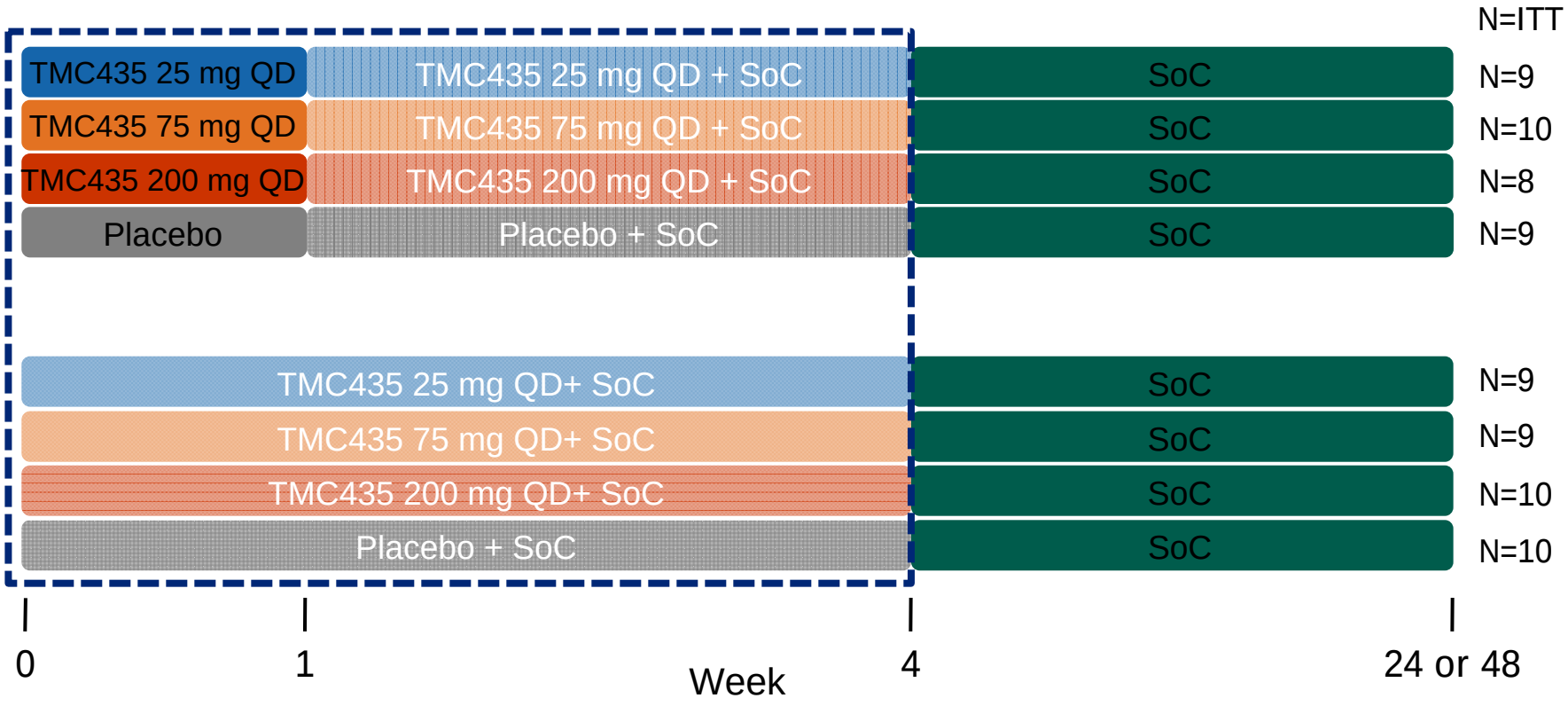


OPERA-1 (Study TMC435-C201)

- Phase IIa, double-blind, placebo-controlled, proof-of-concept trial
  - treatment-naïve and treatment-experienced patients, genotype-1 infection
- Data presented for treatment-naïve patients
  - Cohort 1: TMC435 25 and 75 mg QD
  - Cohort 2: TMC435 200 mg QD
- Standard entry criteria for PEG-IFN/RBV studies
  - documented chronic HCV infection
  - compensated liver disease including cirrhosis

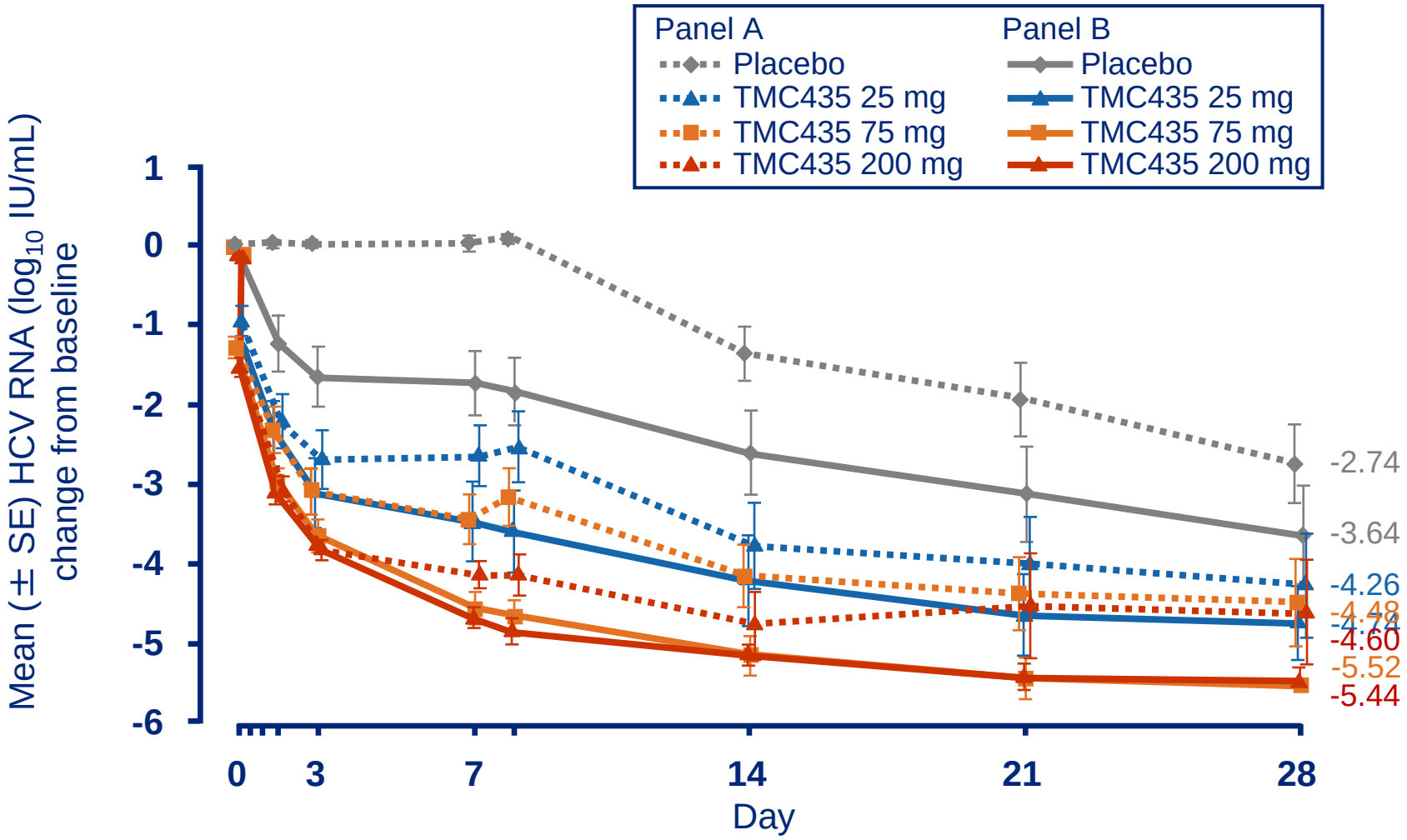
OPERA-1 (Cohorts 1 and 2): study design
Treatment-naïve, genotype-1 HCV-infected patients

- Cohort 1: TMC435 25 and 75 mg QD
- Cohort 2: TMC435 200 mg QD



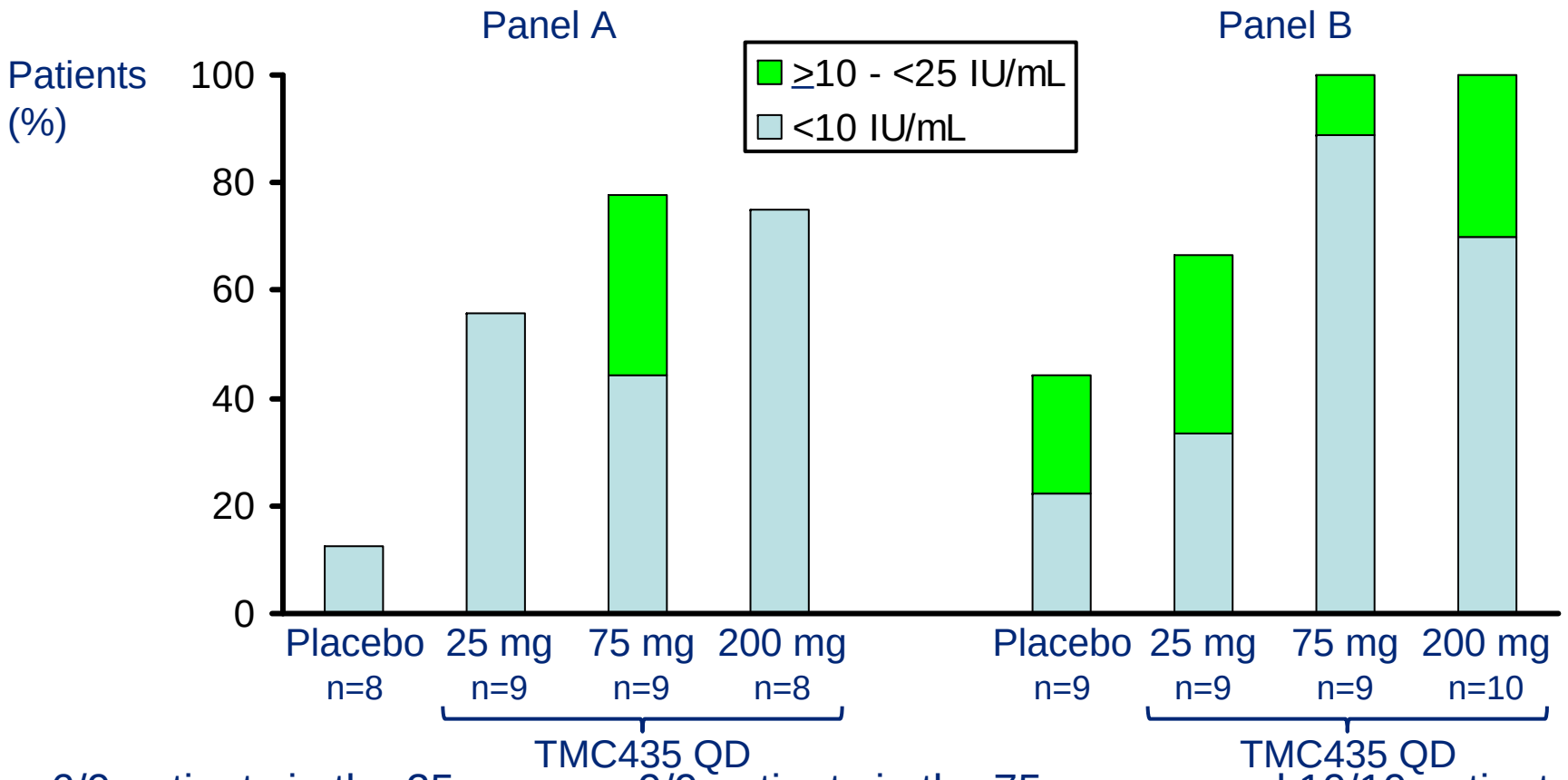
SoC = pegylated interferonα-2a + ribavirin (PEG-IFNα-2a + RBV)
ITT, intent-to-treat population

OPERA-1 (Cohorts 1 and 2): mean change in HCV RNA from baseline to Day 28 (mono- and triple therapy)



Panel A: 1 week of TMC435 monotherapy followed by 3 weeks combined with SoC
Panel B: 4 weeks of TMC435 combined with SoC

OPERA-1 (Cohorts 1 and 2): response to treatment at Day 28



- 6/9 patients in the 25 mg arm, 9/9 patients in the 75 mg arm and 10/10 patients in the 200 mg arm of Panel B had HCV RNA <10 IU/mL at Week 12 (4-weeks TMC435 + SoC, 8-weeks SoC only)

Panel A: 1 week of TMC435 monotherapy followed by 3 weeks combined with SoC
Panel B: 4 weeks of TMC435 combined with SoC

OPERA-1 (Cohorts 1 and 2): virology findings during the first 4 weeks of treatment

- No viral breakthroughs were observed in Panel B (4 weeks TMC435 + SoC)
- 5 viral breakthroughs were observed in Panel A (1 week TMC435 monotherapy followed by 3 weeks TMC435 + SoC)
- 2 patients in 25 mg group
- 2 patients in 75 mg group
- 1 patient in 200 mg group

- Among the viral breakthroughs in Panel A, emerging NS3 mutations† were observed in all 5 patients
- R155K (intermediate FC‡)
- R155K + D168N (intermediate FC‡)
- D168E (intermediate FC‡)
- Q80R/K + D168E (high FC‡)
- D168V (high FC‡)

Viral breakthrough: >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir or >100 IU/mL in patients with previous HCV RNA <10 IU/mL
FC, fold change; intermediate FC: >10-100; high FC: >100
†based on in vitro passage experiments; ‡based on in vitro replicon SDM data for TMC435

OPERA-1 (Cohorts 1 and 2): adverse event (AE) summary

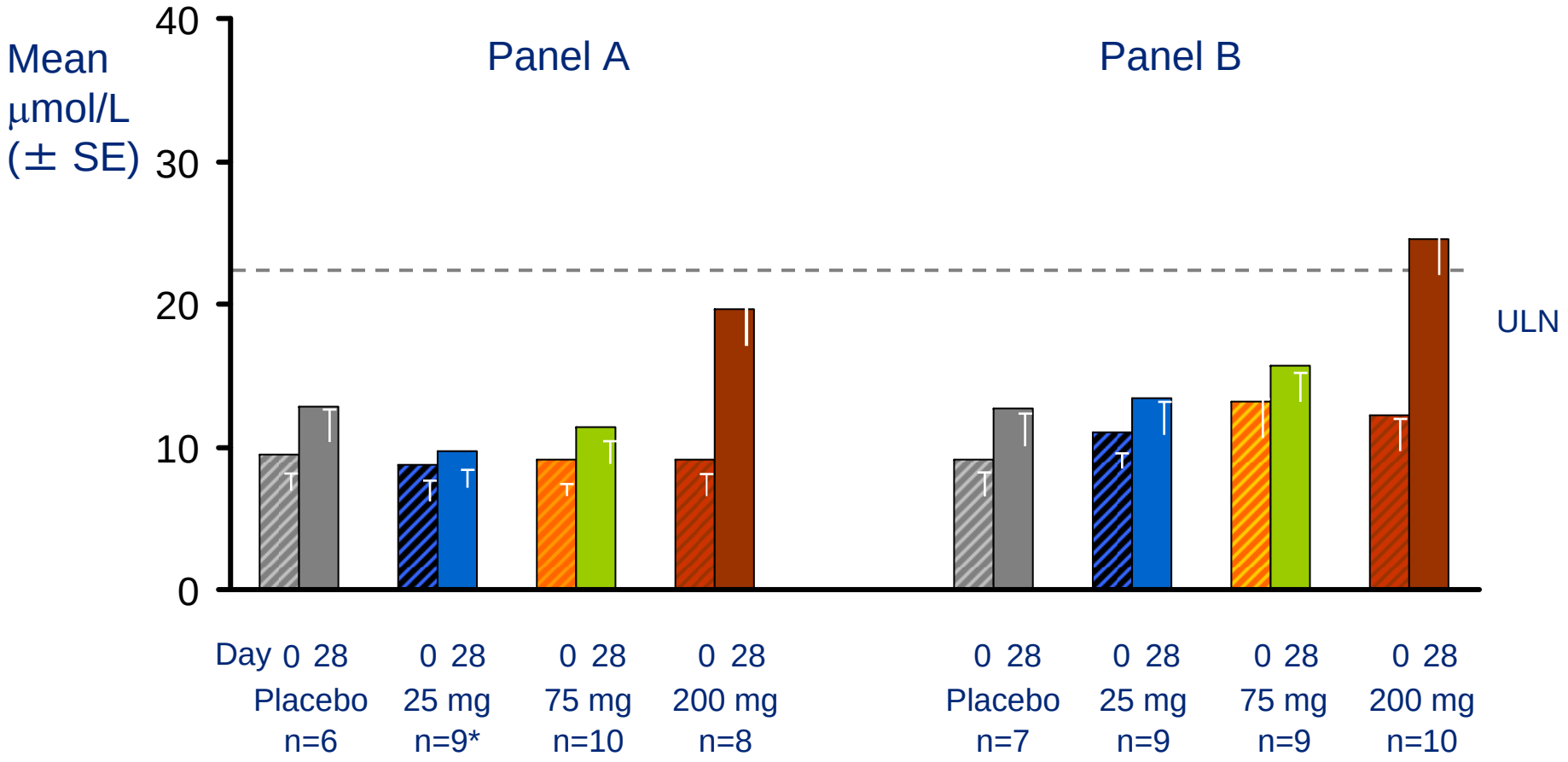
Parameter, %	Cohort 1			Cohort 2	
	Placebo (N=13)	25 mg QD (N=18)	75 mg QD (N=19)	Placebo (N=6)	200 mg QD (N=18)
Any AE					
Grade 3 or 4	0	0	10.5*	0	11.1*
Discontinuation due to AE	0	0	0	0	0
Serious AE	7.7	0	0	0	0
Death	0	0	0	0	0
Most common AEs†					
Headache	38.5	50.0	47.4	50.0	16.7
Fatigue	30.8	44.4	21.1	16.7	27.8
Nausea	7.7	27.8	26.3	16.7	27.8
Influenza-like illness	15.4	27.8	31.6	0	22.2

No evidence of hepatobiliary, renal, haematopoietic or cardiac disturbances

*Neutropenia in 4 subjects, related to PEG-IFNα -2a, not or doubtfully related to TMC435

†Reported in >10 patients (all TMC435 groups combined)

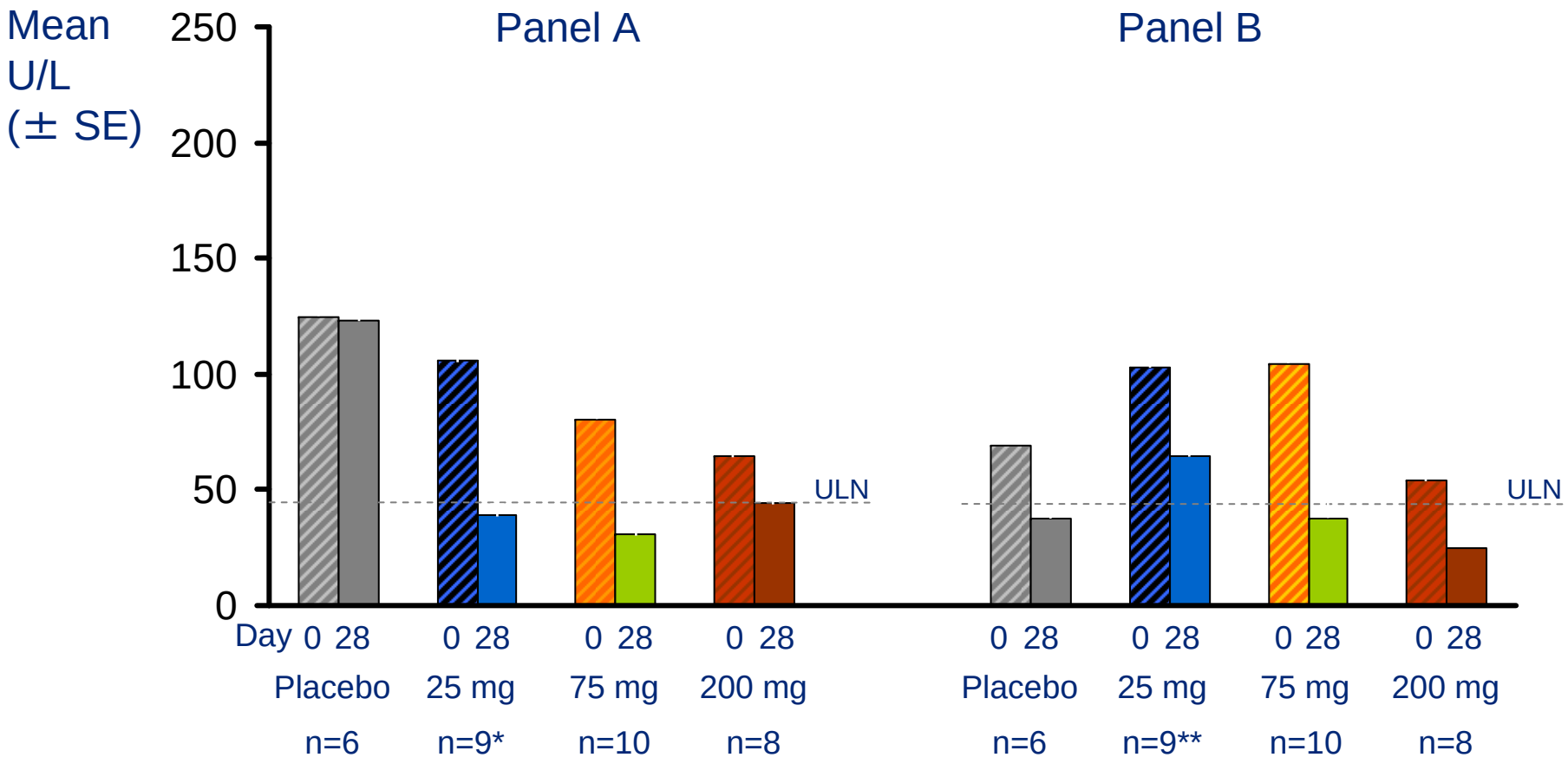
OPERA-1 (Cohorts 1 and 2): Total bilirubin at baseline (Day 0) and Day 28



- Bilirubin levels decreased after the end of treatment with TMC435
- Elevations in direct and indirect bilirubin levels were also observed, particularly in the highest dose group

*Baseline sample missing from 1 patient; ULN, upper limit of normal = 21 μmol/L

OPERA-1 (Cohorts 1 and 2): ALT at baseline (Day 0) and Day 28



*Baseline sample missing from 1 patient; **baseline sample missing from 2 patients

ALT, alanine aminotransferase

OPERA-1 (Cohorts 1 and 2): summary

TMC435 demonstrated potent antiviral activity in monotherapy and in combination with SoC over 4 weeks of treatment

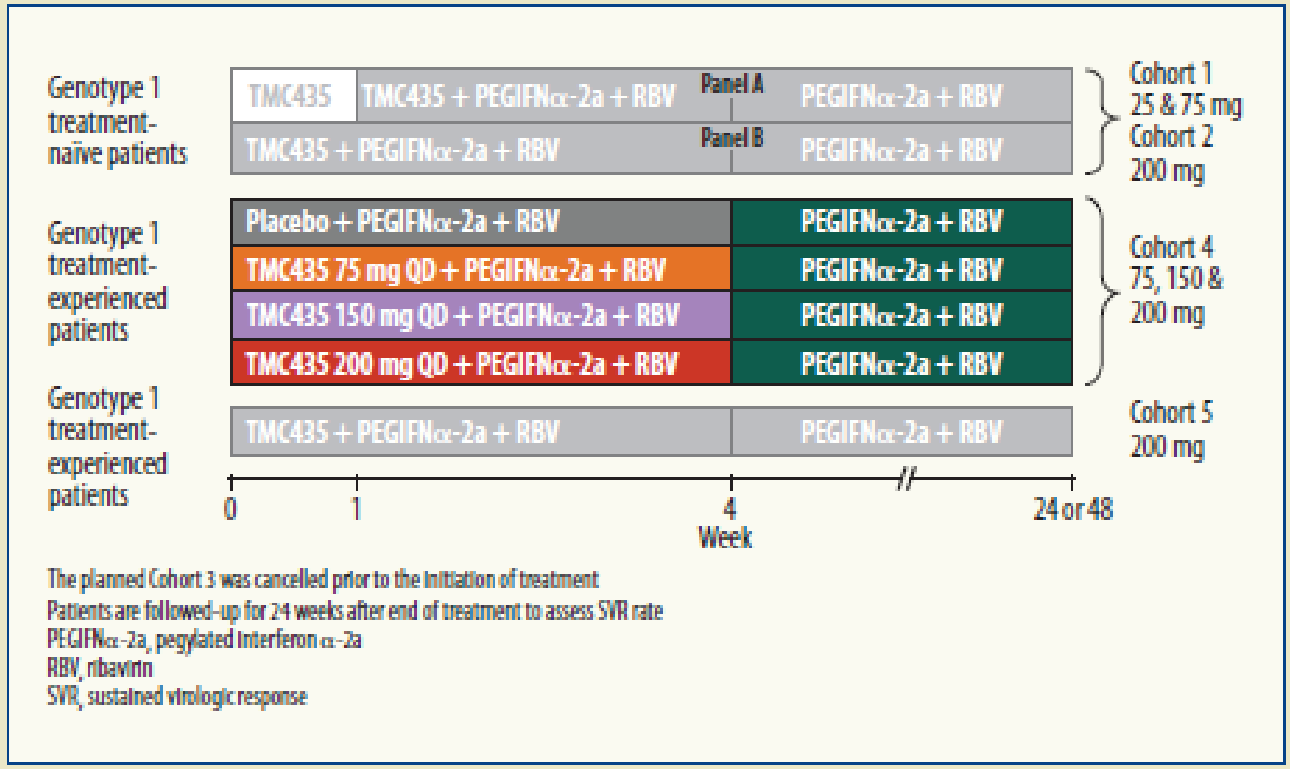
- TMC435 25, 75 and 200 mg QD resulted in marked HCV RNA reductions
- In the 75 and 200 mg groups, all patients achieved HCV RNA levels <25 IU/mL and 7/10 and 8/9 respectively were undetectable at the end of 4-week triple therapy (Panel B)
- After 4 weeks triple + 8 weeks SoC, all patients (9/9 and 10/10) in 75 and 200 mg groups achieved non-detectable HCV RNA levels

Once-daily administration of TMC435 in combination with SoC in treatment-naïve genotype-1 patients over 28 days was generally safe and well tolerated

- TMC435 was not associated with AE-related treatment discontinuations
- Most reported AEs were mild to moderate
- Most common AEs included headache, fatigue, nausea and influenza-like illness
- Bilirubin elevations were observed in some patients receiving TMC435, mostly with the 200 mg dose, and were generally mild and reversible in nature
- Substantial decreases in transaminases were observed in patients receiving TMC435

Opera-1: Data in treatment experienced HCV G1 patients

Figure 1. OPERA-1 study design.



4 weeks triple (TMC + SoC) therapy, no lead in.
Lowest dose of 75 mg

Demographics

Table 1. Patient demographics and baseline characteristics.

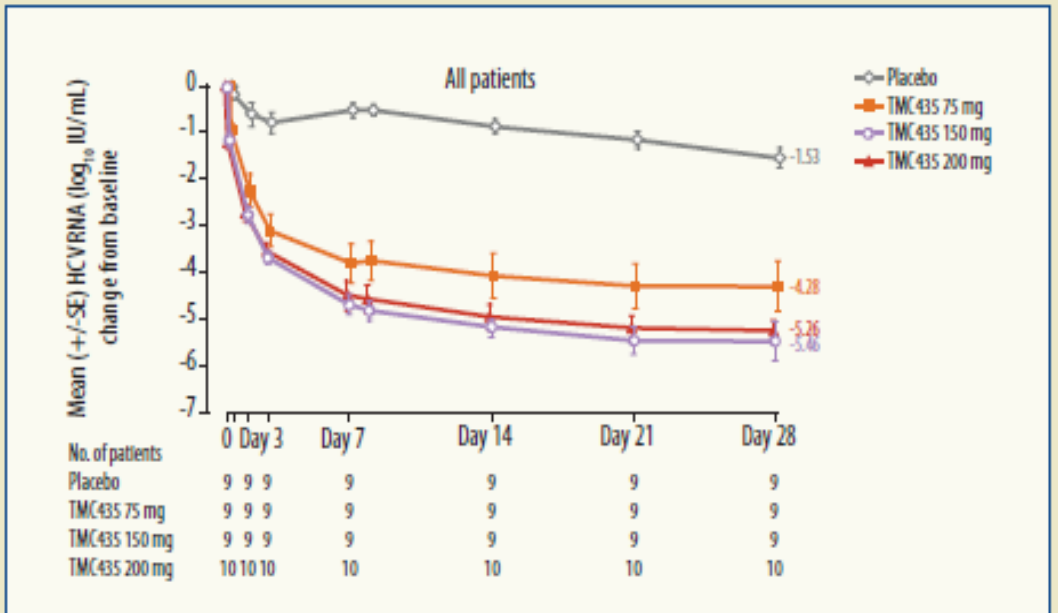
	Placebo	TMC435		
	N=9	75 mg QD N=9	150 mg QD N=9	200 mg QD N=10
Gender, n (%)				
Female	0	3 (33.3)	1 (11.1)	2 (20.0)
Male	9 (100)	6 (66.7)	8 (88.9)	8 (80.0)
Race, n (%)				
Caucasian	9 (100)	9 (100)	9 (100)	10 (100)
Age, years				
Median	47.0	53.0	56.0	55.5
(Range)	(21–57)	(38–62)	(32–67)	(28–69)
Body weight, kg				
Median	78.0	74.0	75.0	92.5
(Range)	(67–94)	(55–92)	(50–99)	(54–101)
HCV subtype (NS5B), n (%)				
1a	2 (22.2)	2 (22.2)	4 (44.4)	3 (30.0)
1b	7 (77.8)	7 (77.8)	5 (55.6)	7 (70.0)
HCV RNA (log_{10} IU/mL)				
Median	6.4	6.9	6.9	6.9
(Range)	(6–7)	(6–7)	(7–8)	(6–7)
Cirrhosis, n (%)				
	5 (55.6)	5 (55.6)	5 (55.6)	6 (60.0)
Response to prior IFN-based therapy* for HCV, n (%)				
Non-responder	6 (66.7)	7 (77.8)	6 (66.7)	6 (60.0)
Relapser	3 (33.3)	2 (22.2)	3 (33.3)	4 (40.0)

*88% of patients received PEGIFN-based therapy

Majority of patients (68%)
Were non-responders

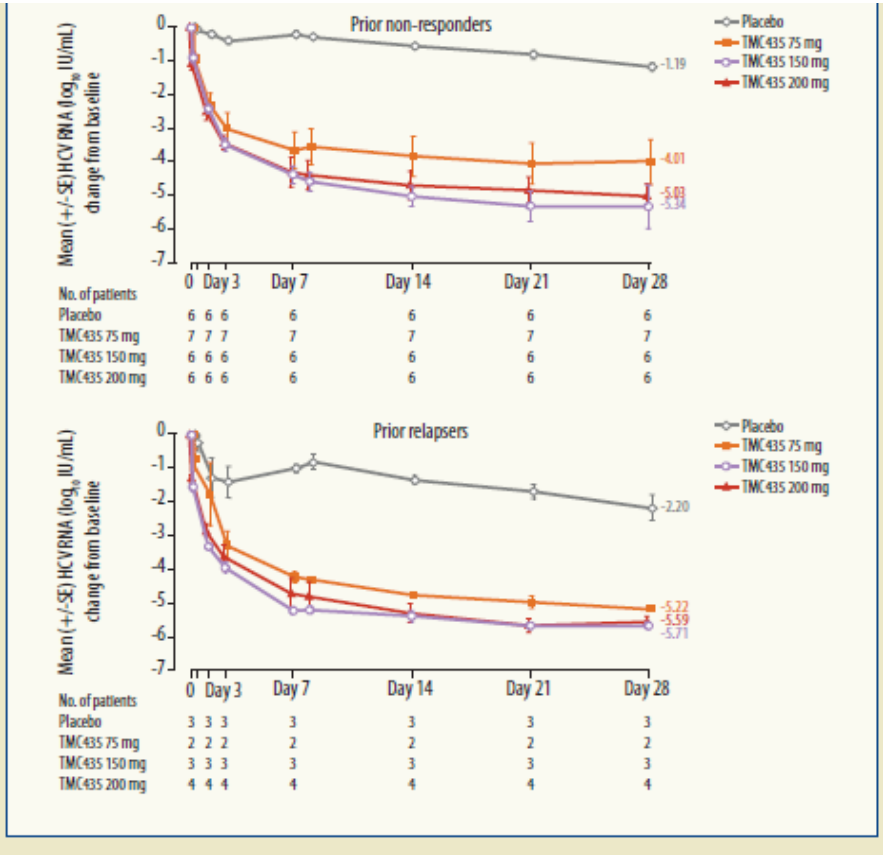
Viral load reduction - All patients

Figure 2. Mean (SE) change in plasma HCV RNA from baseline for treatment-experienced patients receiving once-daily TMC435 75, 150 and 200 mg or placebo over time to Day 28.



Marked viral load reduction that exceeded 5 $\log_{10}$ IU/mL after 4 weeks in highest dose groups

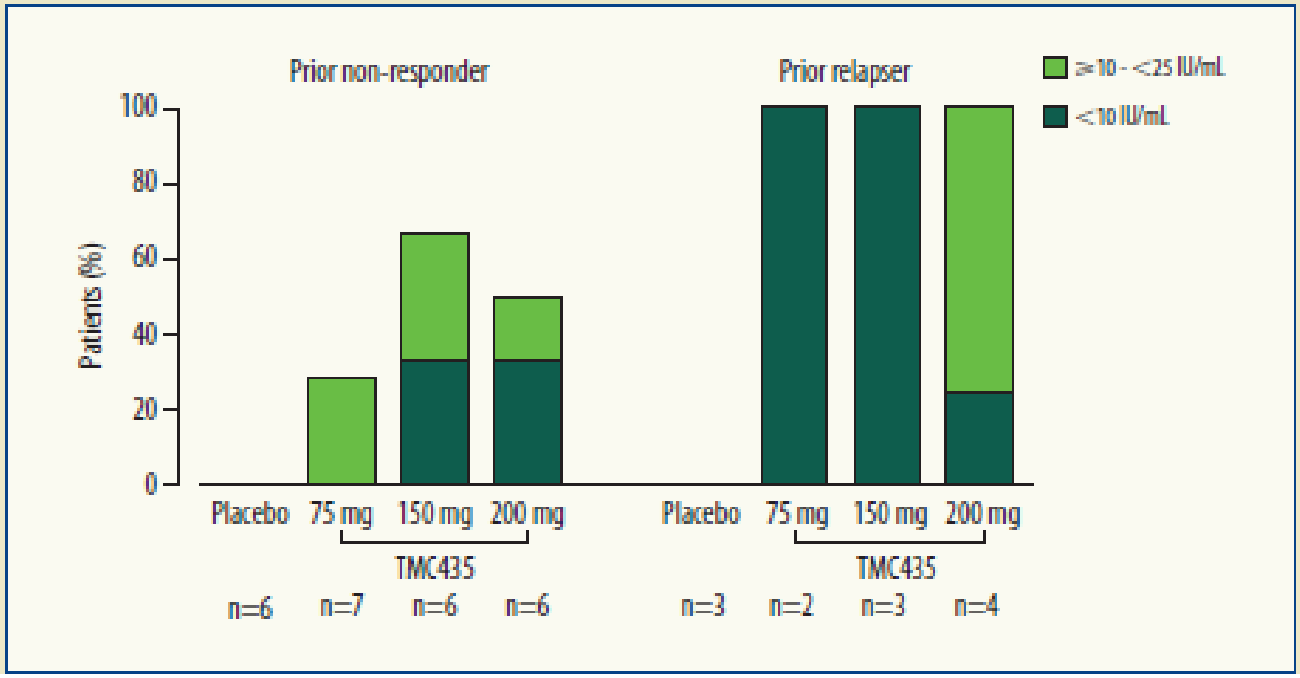
Viral load reduction categorized by previous response



Viral response pronounced in both non-responders and relapsers

Viral load reduction

Figure 3. Response to treatment with once-daily TMC435 75, 150 and 200 mg or placebo in treatment-experienced patients at Day 28.



2/9 (22%), 5/9 (56%) and 3/10 (30%) patients in 75, 150 and the 200 mg groups reached undetectable levels (< 10 IU/mL) after 4 weeks of treatment, compared to 0/9 patients on placebo.

Adverse events

Table 2. Summary of adverse events (AEs).

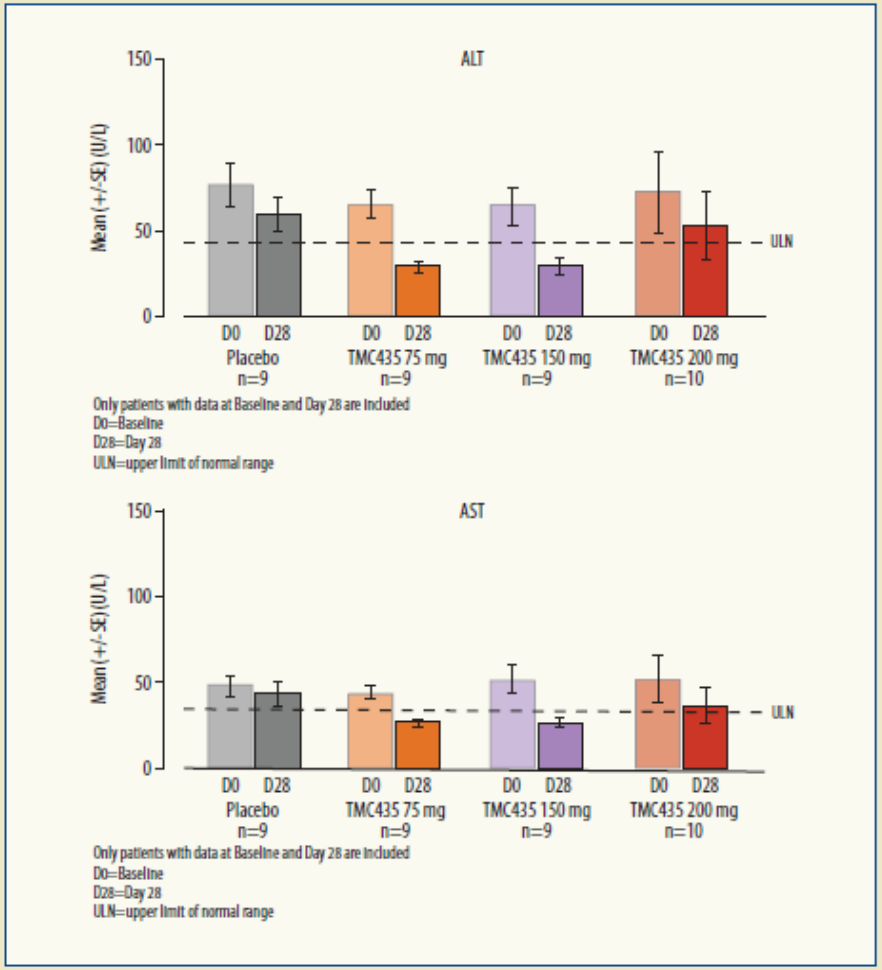
n (%)	Placebo N=9	TMC435 75 mg QD N=9	TMC435 150 mg QD N=9	TMC435 200 mg QD N=10
Patients with:				
Any AE	8 (88.9)	8 (88.9)	9 (100)	10 (100)
Grade 1 AEs	8 (88.9)	7 (77.8)	8 (88.9)	8 (80.0)
Grade 2 AEs	5 (55.6)	3 (33.3)	5 (55.6)	7 (70.0)
Grade 3/4 AEs	0	0	0	2 (20.0)*
Most common AEs§				
Headache	6 (66.7)	5 (55.6)	5 (55.6)	3 (30.0)
Influenza-like illness	1 (11.1)	3 (33.3)	1 (11.1)	5 (50.0)
Dyspnoea	0	2 (22.2)	2 (22.2)	4 (40.0)
Nausea	1 (11.1)	3 (33.3)	2 (22.2)	2(20.0)
Pyrexia	1 (11.1)	2 (22.2)	2 (22.2)	2 (20.0)
Arthralgia	2 (22.2)	1 (11.1)	4 (44.4)	0
Asthenia	2 (22.2)	1 (11.1)	2 (22.2)	2 (20.0)
Fatigue	2 (22.2)	1 (11.1)	2 (22.2)	2 (20.0)
Pruritis	3 (33.3)	1 (11.1)	1 (11.1)	3 (30.0)

*Fatigue and influenza-like illness (1 patient) and hyperbilirubinaemia (1 patient)
§Reported in ≥5 patients (TMC435 treatment groups combined)

There were no treatment discontinuations due to AEs or serious adverse events

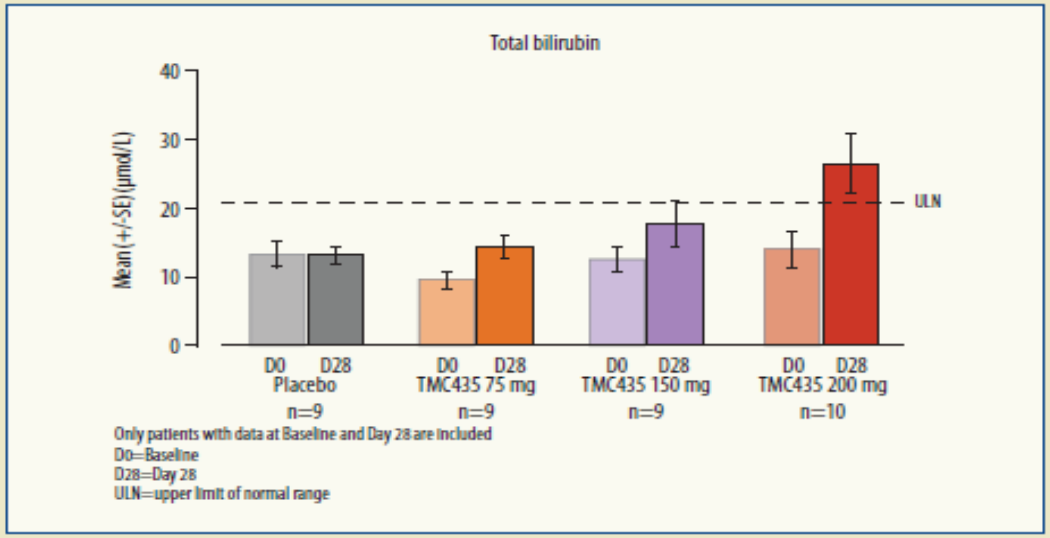
Effect on the liver - transaminases

Figure 4. Serum aminotransferase levels for treatment-experienced patients at baseline and after 28 days of treatment with once-daily TMC435 75, 150 and 200 mg or placebo. a) Alanine aminotransferase, ALT; b) Aspartate aminotransferase, AST.



Bilirubin, total

Figure 5. Total serum bilirubin levels for treatment-experienced patients at baseline and after 28 days of treatment with once-daily TMC435 75, 150 and 200 mg or placebo.



- No dose trends or clinically relevant changes were noted in any other laboratory parameters, ECG parameters or vital signs.

- **Bilirubin elevations were generally mild, and reversible in nature and elevations were most common with the highest dose**
- **Bilirubin elevations have been taken into account with the dose selection for phase 2b**
- **Appropriate measures have been put in place in the protocols for monitoring and management of these changes**
- **The mode of action is being investigated**

Conclusions Opera-1
Treatment naïve and treatment experienced

In both treatment-naïve and treatment experienced patients infected with HCV genotype-1, TMC435 in combination with SoC over 4 weeks of treatment:

- **demonstrated potent antiviral activity**
- **was generally safe and well tolerated**
- **was not associated with AE-related treatment discontinuations.**
- **Mild and reversible increases in bilirubin was observed, most pronounced in the highest dose groups. The mechanism of action is under active investigation.**

These results support the development of TMC435 for both treatment-naïve and treatment-experienced patients infected with HCV genotype-1