ONLINE EXPERT POSTER REVIEW AND DISCUSSION

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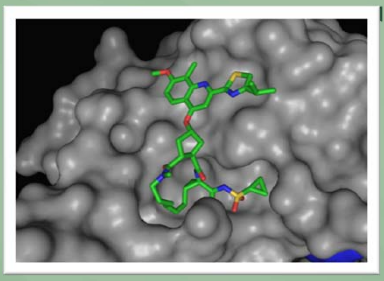
TMC435 with peginterferon and ribavirin in treatment-experienced HCV genotype 1 patients: the ASPIRE study, a randomized Phase IIb trial

Stefan Zeuzem, Thomas Berg, Edward Gane, Peter Ferenci, Graham R. Foster, Michael W. Fried, Christophe Hezode, Gideon Hirschfield, Ira Jacobson, Igor Nikitin, Paul Pockros, Fred Poordad, Oliver Lenz, Monika Peeters, Vanitha Sekar, Goedele De Smedt, Maria Beumont-Mauviel

Abstract #2

TMC435

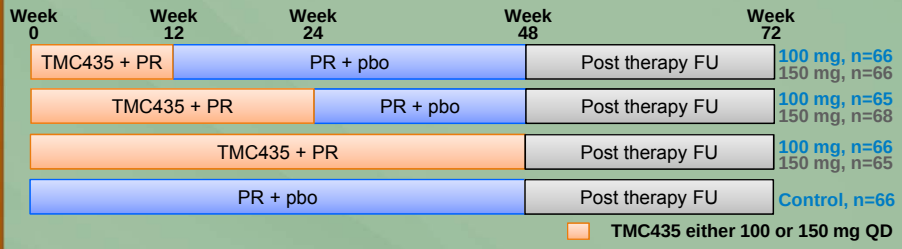


- Investigational, one-pill, once-daily, oral HCV NS3/4A protease inhibitor
  - Potent antiviral activity in patients infected with HCV genotype 1, with antiviral activity demonstrated against genotypes 2, 4, 5, and 6 isolates[1-4]
  - Favourable safety profile[1-4]
- ASPIRE (TMC435-C206)
  - Phase IIb study to assess efficacy and safety of TMC435 administered once-daily in combination with PegIFN/RBV, in patients infected with HCV genotype 1 who have failed previous PegIFN/RBV treatment

EC50, half maximal effective concentration; PegIFN/RBV, pegylated interferon and ribavirin

1Reesink HW et al. Gastroenterology 2010;138:913-921
2Moreno C et al. J Hepatology 2012; in press
3Fried MW et al. Oral presentation at AASLD 2011
4Zeuzem S et al. Poster LB-2998 presented at EASL 2011

ASPIRE Study: International, Phase IIB, Randomised, Double-blind Clinical Trial



- Prior relapser: HCV RNA undetectable EOT and detectable within 24 W of FU
- Prior partial responder: ≥2 log10 HCV RNA reduction from baseline at W12 and detectable EOT
- Prior null responder: <2 log10 HCV RNA reduction from baseline at W12
- Primary endpoint: SVR24 (HCV RNA <25 IU/mL undetectable at W72)
- Key secondary endpoints: Virologic response at other time points, viral breakthrough and relapse rates, safety and tolerability

D, day; EOT, end of treatment; FU, follow-up; pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin; QD, once daily; W, week
Stopping rules: all treatment stopped if HCV RNA <1 log10 reduction from baseline (W4), <2 log10 reduction from baseline (W12), confirmed detectable ≥25 IU/mL (W24 or W36), increased by >1 log10 compared to nadir or >100 IU/mL with previously being <25 IU/mL detectable or undetectable, on treatment (confirmation required) (D1-W48)

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ASPIRE Study: Baseline Demographics And Disease Characteristics

	TMC435 100 mg* PR48 n=197	TMC435 150 mg* PR48 n=199	Pbo PR48 n=66
Patient demographics			
Male, %	68	68	64
Race, white, %	92	93	94
Age, years, median (range)	50.0 (20-69)	50.0 (20-69)	50.5 (22-66)
Body weight, kg, median (range)	80.0 (43-138)	80.5 (50-125)	84.8 (53-112)
IL28B genotype CC†, %	17 (n=136)	17 (n=142)	22 (n=50)
Disease characteristics			
HCV subtype (NS5B) 1a‡, %	41	42	41
HCV RNA ≥800 000 IU/mL at baseline§, %	89	85	83
Metavir score, F3 / F4, %	23 / 18	15 / 20	20 / 16
Prior response to PegIFN/RBV			
Relapser, %	40	40	41
Partial responder, %	35	35	35
Null responder, %	25	26	24

*Duration groups combined; †IL28B, polymorphism on chromosome 19 s12979860 data available for patients who consented to DNA research only; ‡N5SB sequence-based assay; §Roche COBAS TaqMan HCV assay v2; ALT, alanine aminotransferase; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin; pbo, placebo

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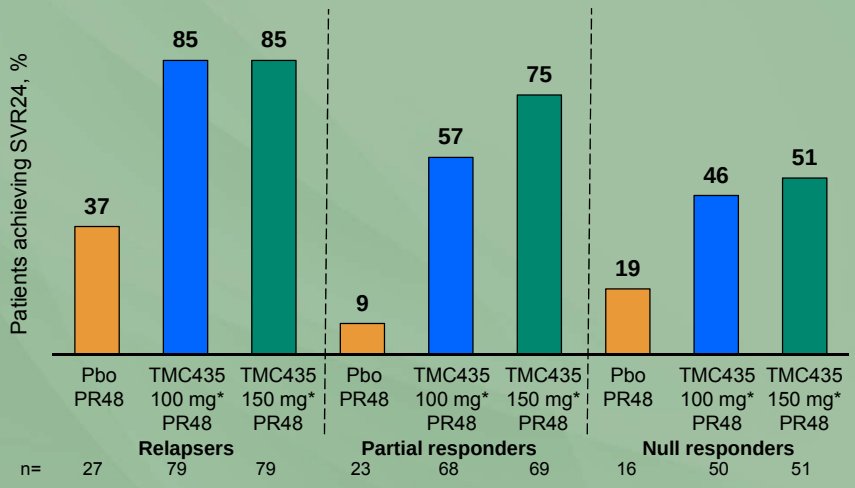
ASPIRE Study: Proportion Of Patients Achieving SVR24 By Prior Response



*Duration pooled
Pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment

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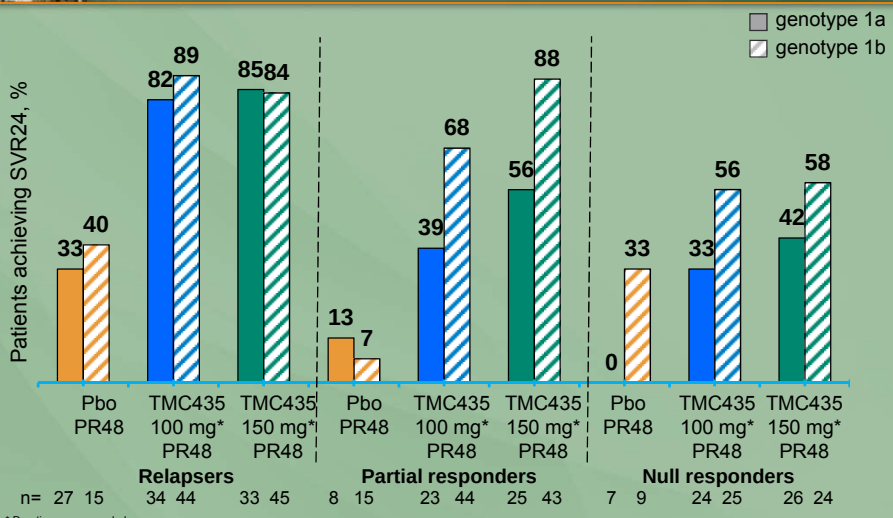
ASPIRE Study: SVR24 By Prior Response And HCV Genotype Subtype



* Duration groups pooled
Pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment

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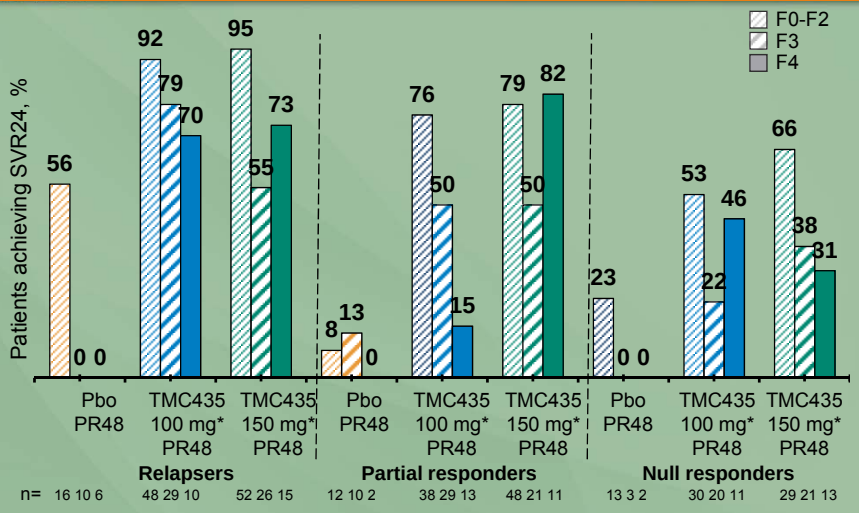
ASPIRE Study: SVR24 By Prior Response And Metavir Score



* Duration groups pooled
Pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin;
SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment

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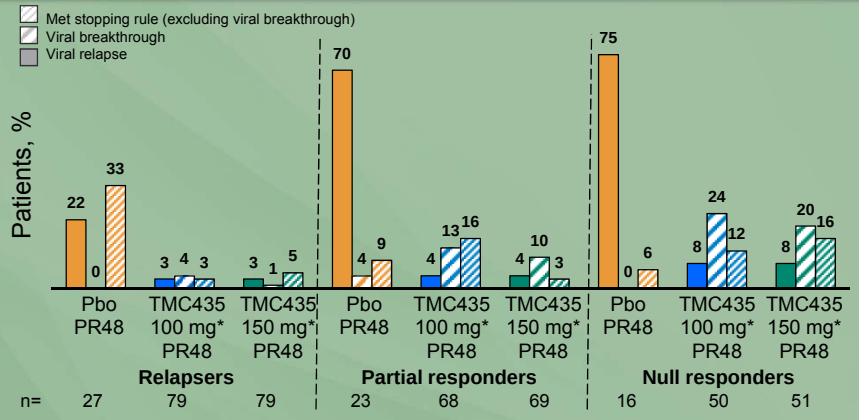
ASPIRE Study: Proportion Of Patients Experiencing Failure (ITT Population)



- Viral breakthrough and relapse was usually associated with emerging mutations at NS3 amino acid positions 80, 122, 155, and/or 168 (Lenz et al. Hepatitis C Therapy session, 19 April, EASL 2012)

* Duration groups pooled; Pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin;
Virologic stopping rule: all treatment stopped if HCV RNA <1 log10 reduction from baseline (W4), <2 log10 reduction from baseline (W12), confirmed detectable (W24 or W36)
Breakthrough: confirmed HCV RNA >1 log10 increase compared to nadir, or confirmed >100 IU/mL in subjects previously <25 IU/mL
Relapse: confirmed detectable HCV RNA during follow-up in subjects <25 IU/mL at end of treatment

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ASPIRE Study: Adverse Events*

	TMC435 100 mg‡ n=197	TMC435 150 mg‡ n=199	Pbo PR48 n=66
Grade 3-4 AEs	28	36	26
Serious AEs, %	6	10	6
AEs leading to TMC435/Pbo discontinuation, %	7	9	5
AEs most frequently reported in TMC435 groups (>25% of patients), %			
Headache	31	40	36
Fatigue	47	41	44
Influenza-like illness	35	24	20
Pruritus	34	35	17
AEs of interest (regardless of severity or causality), %			
Hepatobiliary disorders †	5	10	5
Rash (any type) ‡	23	30	18
Rash (any type), Grade 3	0.5	0.5	0
Photosensitivity AEs	2	6	2

*Potential confounding factor: mean PegIFN/RBV exposure higher for patients in TMC435/PegIFN/RBV groups (41 weeks) compared with placebo/PegIFN/RBV group (27.9 weeks)

Adverse events listed do not include changes in laboratory parameters
‡Duration groups combined; † Mainly increased bilirubin; ‡Combines all types of reported rash
AE, adverse event; pbo, placebo; PR, 180 µg pegylated interferon α-2a + 1000-1200 mg ribavirin

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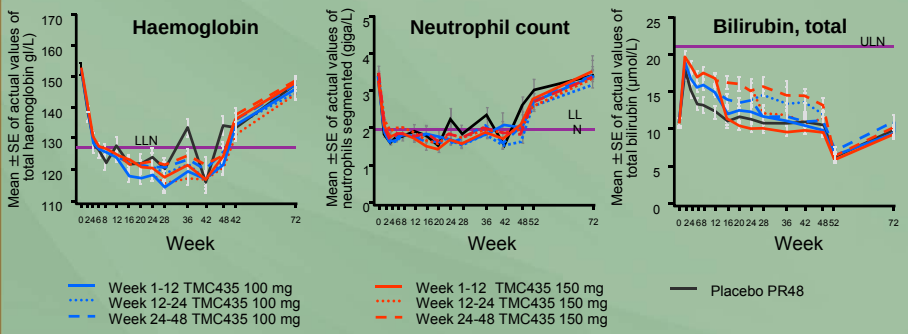
ASPIRE Study: Laboratory Parameters Over Time

- Decreases in haematological parameters comparable to placebo in all TMC435-treated groups
- Mild and reversible increases in bilirubin with TMC435, not accompanied by changes in other liver parameters*



SE, standard error; LLN, lower limit of normal; ULN, upper limit of normal;
*Studies indicate that TMC435 inhibits OATP1B1 and MRP2 transporters (Huisman M et al. Poster 278 presented at AASLD 2010)
1.5% (N=6) of patients in TMC435 arms used ESA during trial compared with 1.5% with placebo (N=1)

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ASPIRE Study: Summary

- In HCV genotype 1 patients who previously failed PegIFN/RBV treatment, once-daily TMC435 administered with PegIFN/RBV was significantly more effective than PegIFN/RBV/placebo
- With TMC435 150 mg in combination with PegIFN/RBV:
  - 85% of prior relapsers achieved SVR24
  - 75% of prior partial responders achieved SVR24
  - 51% of prior null responders achieved SVR24
  - 31-82% in patients with cirrhosis
- Once-daily TMC435 was well tolerated in this population
- Phase III clinical trials for TMC435 150 mg are ongoing

PegIFN/RBV, peginterferon □-2a + ribavirin; SVR24, HCV RNA <25 IU/mL undetectable 24 weeks after planned end of treatment

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