The ASPIRE Trial: TMC435 in treatment-experienced patients with genotype 1 HCV infection who have failed previous PegIFN/RBV treatment: Week 24 interim analysis

LB Poster 2998

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INTRODUCTION

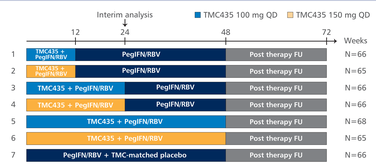
- TMC435 is an investigational potent, once-daily oral NS3/4A protease inhibitor currently in Phase III clinical development for the treatment of hepatitis C virus (HCV) infection.
- Phase I, IIa and IIb studies, in treatment-experienced and/or treatment-naïve patients infected with HCV, have demonstrated that TMC435 is generally well tolerated, has a pharmacokinetic profile that supports a once-daily dosing regimen, and has potent antiviral activity in patients infected with genotypes 1, 2, 4, 5 and 6.[1-7]
- Phase III clinical trials are now underway in treatment-naïve patients and in patients who relapsed after previous treatment.
- ASPIRE (TMC435-C206; NCT00980330) is a Phase IIb, randomised, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including pegylated interferon α-2a and ribavirin (PegIFN/RBV).
- Patients enrolled in the ASPIRE trial were infected with HCV genotype 1, and had failed to respond or relapsed following at least one course of PegIFN/RBV therapy.

METHODS

Study Design

- The study included seven treatment arms, with a total duration of 72 weeks (Figure 1). This interim analysis was performed when all patients had completed 24 weeks of the study.

FIGURE 1: ASPIRE study design.



FU, follow-up

- Inclusion criteria included documented chronic infection with HCV genotype 1, HCV RNA >10,000 IU/mL at screening, and ≥1 prior documented course of PegIFN α-2a or α-2b/RBV for ⩾12 consecutive weeks which had not been discontinued due to intolerability.
- Exclusion criteria included decompensated liver disease and co-infection with HIV or HBV.
- Patients were administered TMC435 (100 or 150 mg once daily [QD]) or placebo in combination with PegIFN/RBV.
- The patient population was stratified by genotype (1a, 1b, and other), and by prior virologic response (relapsers, partial and null responders were included in a 2:2:1 ratio):
  - Relapse: HCV RNA undetectable end of treatment; detectable within 24 weeks post-treatment
  - Partial response: ≥2 log10 reduction HCV RNA at Week 12; detectable HCV RNA at end of treatment
  - Null response: <2 log10 reduction HCV RNA at Week 12

Virologic Stopping Rules

- Patients should stop all medication following lack of on-treatment virologic response or viral breakthrough, defined as:
  - At Week 4: <1 $\log_{10}$ reduction in HCV RNA from baseline
  - At Week 12: <2 $\log_{10}$ reduction in HCV RNA from baseline
  - At Week 24: HCV RNA confirmed detectable
  - At Week 36: HCV RNA confirmed detectable
  - Between Day 1 and Week 48: Confirmed HCV RNA increase >1 $\log_{10}$ compared to nadir; or confirmed HCV RNA >100 IU/mL if HCV RNA was previously <25IU/mL detectable or undetectable.

Antiviral Efficacy

- The primary objective of the trial is to evaluate the efficacy of six different regimens of TMC435 in combination with PegIFN/RBV compared with the placebo/PegIFN/RBV control group.
- Primary endpoint: The proportion of subjects in TMC435 groups with undetectable HCV RNA (<25 IU/mL undetectable; Roche Taqman v2) 24 weeks after the planned end of treatment (SVR24) compared with the control group, who received PegIFN/RBV and TMC435-matched placebo.
  - The primary efficacy endpoint will be assessed at Week 72 and is not available for this Week 24 interim analysis.
  - Here we report the results of the pre-planned Week 24 interim analysis including the proportion of patients with a virologic response at Weeks 4, 12 and 24, HCV RNA change per IL28B genotype, and rates of viral breakthrough.

Safety

- Secondary objectives of the study include evaluation of the safety and tolerability of TMC435 plus PegIFN/RBV compared with placebo/PegIFN/RBV control group, over the trial period. Adverse events (AEs) were recorded, safety laboratory analyses performed, and vital signs measured.

Statistical Analysis

- Selected virologic response parameters were compared between TMC435 groups and placebo/PegIFN/RBV control group using a logistic regression model. The model included baseline HCV RNA as covariate and treatment and the stratification parameters, prior response and genotype 1 subtype, as factors.
- 95% confidence intervals were constructed for the observed response rates, and for the difference between the TMC435 groups and the placebo/PegIFN/RBV control group.

RESULTS

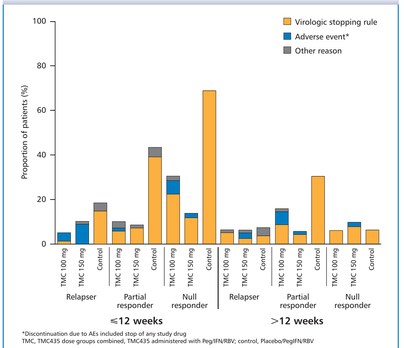
Patient Demographics

- Baseline demographics and characteristics were well balanced between treatment groups (Table 1).

Patient Disposition

- In all subpopulations, more treatment discontinuations were noted in the placebo control group compared with the TMC435 groups. This was noted particularly in null responders, followed by partial responders.
- The primary reason for discontinuation was reaching a virologic stopping rule, which was more commonly observed in placebo control patients during the first 12 weeks of therapy (Figure 2).

FIGURE 2: Discontinuation due to AEs or reaching virologic stopping rule.



*Discontinuation due to AEs included stop of any study drug
TMC, TMC435 dose groups combined, TMC435 administered with PegIFN/RBV; control, Placebo/PegIFN/RBV

Observed Virologic Response

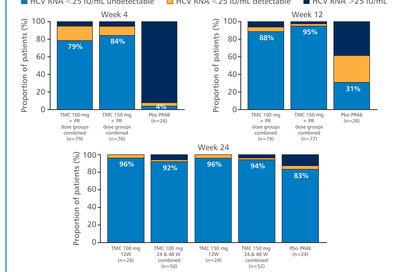
- At Weeks 4, 12, and 24, significantly higher virologic response rates were observed following treatment with TMC435 plus PegIFN/RBV, compared with placebo plus PegIFN/RBV (Figure 3a-c).
- In null and partial responders, somewhat higher virologic response rates were observed in TMC435 150 mg dose groups, compared with 100 mg groups, at early timepoints while differences were less pronounced at Week 24 (Figure 3).

TABLE 1: Baseline demographics and characteristics, per treatment arm.

	TMC12PR48 100 mg N=66	TMC24PR48 100 mg N=65	TMC48PR48 100 mg N=66	TMC12PR48 150 mg N=66	TMC24PR48 150 mg N=68	TMC48PR48 150 mg N=65	Pbo PR48 N=66	All subjects N=462
Patient demographics								
Male, %	66.7	67.7	68.2	68.2	63.2	73.8	63.6	67.3
Race								
White, %	89.4	92.3	93.9	92.4	89.7	96.9	93.9	92.6
Black, %	7.6	3.1	4.5	4.5	7.4	3.1	1.5	4.5
Asian, %	1.5	4.6	1.5	1.5	0	0	3.0	1.7
Other, %	1.5	0	0	1.5	2.9	0	1.5	1.0
Age, years, median	51.5	50.0	50.0	48.0	51.5	50.0	50.5	50.0
Body Mass Index, median	27.55	26.50	26.60	26.40	27.45	27.20	27.95	27.20
IL28B*	N=43	N=46	N=47	N=43	N=50	N=49	N=50	N=328
CC, %	16.3	17.4	17.0	11.6	18.0	20.4	22.0	17.7
CT, %	74.4	65.2	59.6	69.8	64.0	57.1	64.0	64.6
TT, %	9.3	17.4	23.4	18.6	18.0	22.4	14.0	17.7
Disease characteristics								
HCV Subtype (NS5B), %								
1A	39.4	44.4	39.4	45.5	45.5	36.9	40.9	41.7
1B	59.1	54.0	59.1	54.5	51.5	63.1	59.1	57.2
HCV RNA, ⩾800,000 IU/mL at baseline, %	87.9	90.8	87.9	86.4	85.3	83.1	83.3	86.4
Metavir score F4, %	10.8	20.6	21.2	19.7	19.4	20.3	15.6	18.2

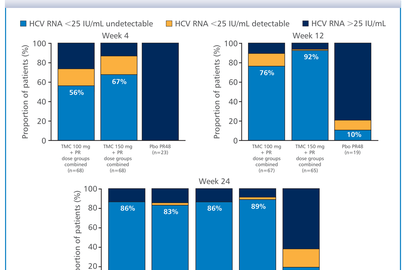
*Data available for patients who consented to DNA research only. IL28B, polymorphism on chromosome 19 rs12979860; PegIFN, pegenterferon; Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; RBV, ribavirin; TMC12PR48, TMC435 for 12 weeks in addition to PegIFN/RBV for 48 Weeks; TMC24PR48, TMC435 for 24 weeks in addition to PegIFN/RBV for 48 Weeks; TMC48PR48, TMC435 for 48 weeks in addition to PegIFN/RBV for 48 Weeks

FIGURE 3a: Observed virologic response rate at Weeks 4, 12, 24, by treatment group: Relapsers.



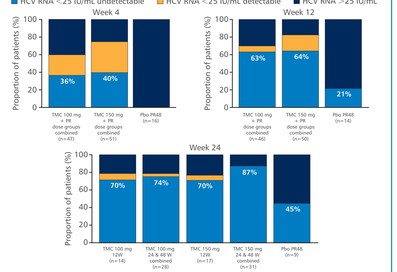
Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PegIFN, pegenterferon; RBV, ribavirin; TMC, TMC435

FIGURE 3b: Observed virologic response rate at Weeks 4, 12, 24, by treatment group: Partial responders.



Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PegIFN, pegenterferon; RBV, ribavirin; TMC, TMC435

FIGURE 3c: Observed virologic response rate at Weeks 4, 12, 24, by treatment group: Null responders.

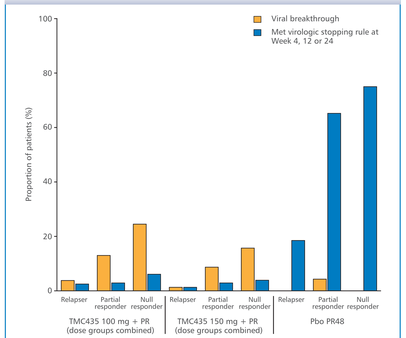


Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PegIFN, pegenterferon; RBV, ribavirin; TMC, TMC435

Viral Breakthrough

- Overall, 6% (12/214) of patients in the TMC435 arm and 49% (32/66) of patients in the control group met a virologic stopping rule (excluding viral breakthrough) at week 4, 12, or 24 due to lack of virologic response.
- Overall, viral breakthrough was observed in 18.2% (39/214) of patients in the TMC435 arms and 1.5% (1/66) in the control group (Figure 4).
- Highest rates of viral breakthrough and virologic failure were observed in null responders, followed by partial responders, with the lowest in relapsers.

FIGURE 4: Patients experiencing viral breakthrough or meeting stopping rules in TMC435 dose groups combined, compared with placebo control group.



Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PR, PegIFN/RBV; TMC, TMC435

IL28B Genotype

- In TMC435 treatment groups, no major differences in mean change in HCV RNA were observed between different IL28B genotypes (Figure 5).
- In the placebo control group, HCV RNA change from baseline was greater for patients with IL28B CC genotype compared with patients with CT and TT genotypes (Figure 5)

Adverse Events

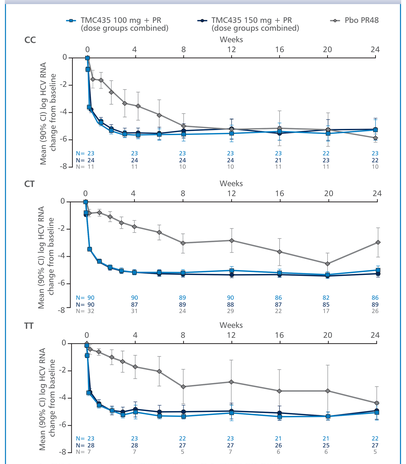
- Median treatment exposure was higher for TMC435 patients compared with placebo (30 weeks for TMC435 compared to 26 weeks in placebo control group; Table 2), due to higher attrition in the placebo control group which was mainly related to lack or loss of virologic response. This bias should be kept in mind when assessing safety comparisons.
- Overall incidence of AEs was similar across treatment groups (Figure 2, Table 2), except for occurrence of influenza-like illness and pruritus, which were more commonly reported in TMC435 patients.
- The majority of these AEs were grade 1 or 2 in severity.
- Serious AEs were reported in 5.8% of patients treated with TMC435 and in 1.5% of subjects in the placebo control group. No differences were observed between the TMC435 dose groups.
- AEs leading to discontinuation of TMC435/placebo were reported in 5.6% of the TMC435 treated patients and in 1.5% of the placebo control patients.
- Decreases in hemoglobin, red blood cell, white blood cell, and platelet count were observed in all treatment groups, including control. Mild and reversible increases in bilirubin (total, direct and indirect) were observed in TMC435 dose groups with no major differences between 100 mg and 150 mg (data not shown).

TABLE 2. Treatment exposure and adverse events occurring during treatment phase.

	TMC12/PR48 100 mg N=16	TMC24/PR48 100 mg N=16	TMC48/PR48 100 mg N=17	TMC12/PR48 150 mg N=17	TMC24/PR48 150 mg N=17	TMC48/PR48 150 mg N=17	All TMC435 N=100	Pbo24/PR48 N=716
Treatment exposure, median (weeks)	30.45	29.71	30.00	30.07	30.21	29.86	30.00	26.14
Relapsers	30.86	30.64	30.86	30.79	30.86	30.50	30.75	29.86
Partial responders	30.43	29.00	30.71	31.43	31.21	30.29	30.51	24.71
Null responders	28.21	27.86	28.43	28.00	28.86	27.00	28.06	10.93
Five most common adverse events (regardless of severity or causality), %								
Headache	27.3	24.6	33.3	40.9	36.8	36.9	33.3	33.3
Fatigue	42.4	40.0	48.5	36.4	41.2	38.5	41.2	42.4
Influenza-like illness	34.8	36.9	31.8	24.2	25.0	21.5	29.0	19.7
Pruritus	28.8	30.8	27.3	28.8	32.4	30.8	29.8	13.6
Adverse events of interest (regardless of severity or causality), %								
Rash (any type)[†]	13.6	7.7	7.6	13.6	16.2	21.5	13.4	13.6
Anaemia[‡]	21.2	16.9	16.7	7.6	22.1	21.5	17.7	15.2
Serious adverse events	3.0	7.7	3.0	9.1	7.4	4.6	5.8	1.5

[†]Combines all types of reported rash; [‡]reported as an adverse event by study investigator if laboratory abnormalities considered clinically relevant; TMC12PR48, TMC435 for 12 weeks in addition to PegIFN/RBV for 48 Weeks; TMC24PR48, TMC435 for 24 weeks in addition to PegIFN/RBV for 48 Weeks; TMC48PR48, TMC435 for 48 weeks in addition to PegIFN/RBV for 48 Weeks; Pbo24/PR48, Placebo for 24 Weeks in addition to PegIFN/RBV for 48 Weeks

FIGURE 5: Change in HCV RNA (mean and 95% CI) over time, by IL28B genotype: Null responders, partial responders and relapsers combined.



Pbo PR48, Placebo in addition to PegIFN/RBV for 48 Weeks; PR, PegIFN/RBV; TMC, TMC435

CONCLUSIONS

- **In this Week 24 interim analysis, treatment-experienced patients who previously failed PegIFN/RBV achieved significantly greater on-treatment virologic response rates following treatment with a TMC435-containing regimen, compared with placebo/PegIFN/RBV control.**
- **In TMC435 treatment groups, no major differences were observed in virologic response between different IL28B genotypes.**
- **Safety and tolerability were generally similar between TMC435-containing regimen and placebo/PegIFN/RBV control group.**

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