PHENOTYPIC CHARACTERIZATION AND VIROLOGIC RESPONSE IN HCV GENOTYPES 2 TO 6 (STUDY TMC435-C202)

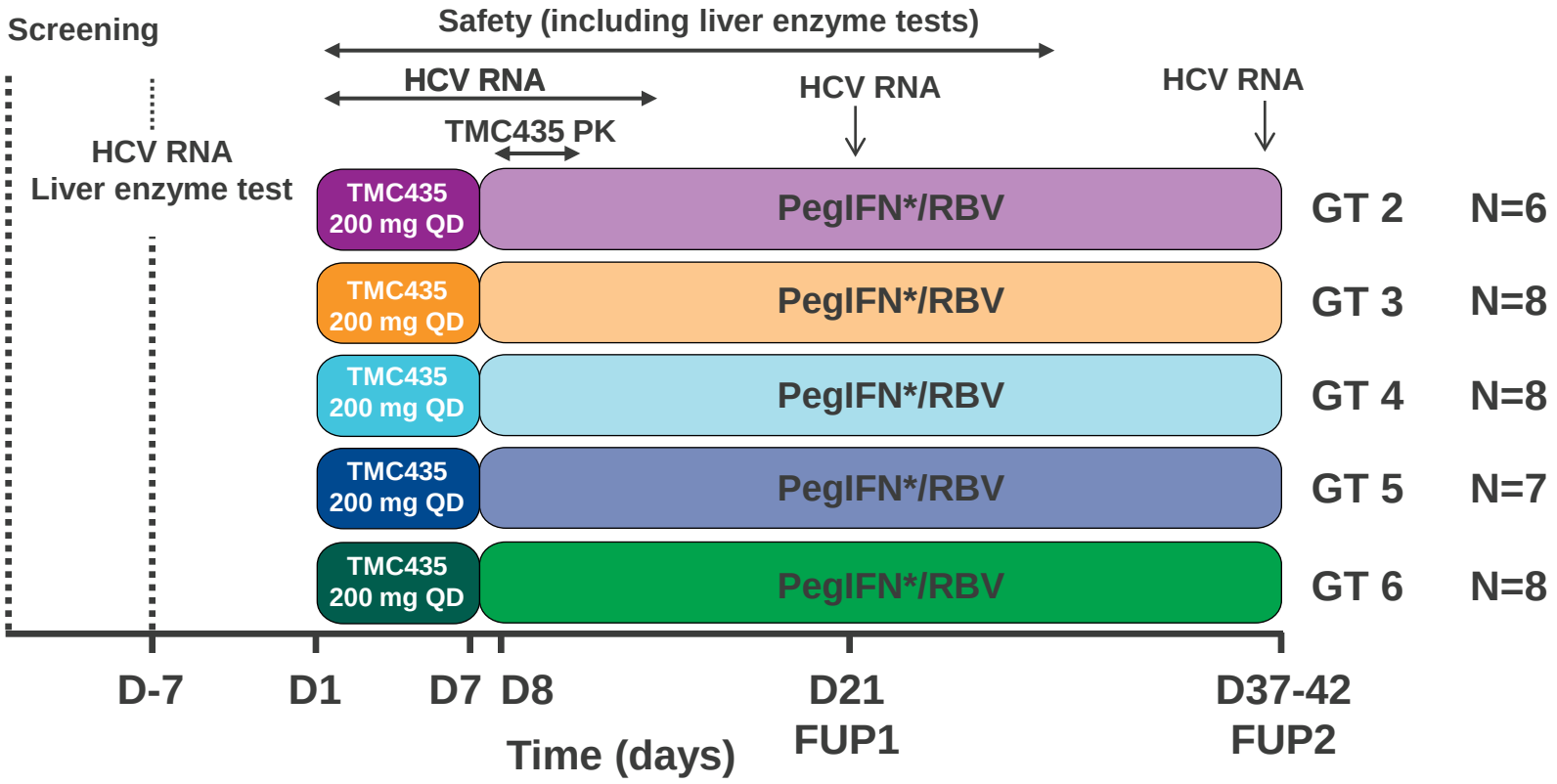
O Lenz,[1] L Vijgen,[1] C Moreno,[2] JM Berke,[1] MD Cummings,[1]
B Fevery,[1] M Peeters,[1] V Sekar,[3] G De Smedt,[1] G Picchio[3]

[1]Jannsen Infectious Disease BVBA, Turnhout, Belgium;
[2]Department of Gastroenterology and Hepatopancreatology, Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Belgium;
[3]Tibotec Inc., Titusville, NJ, USA

DRAG meeting, Amsterdam, The Netherlands

23 April 2013

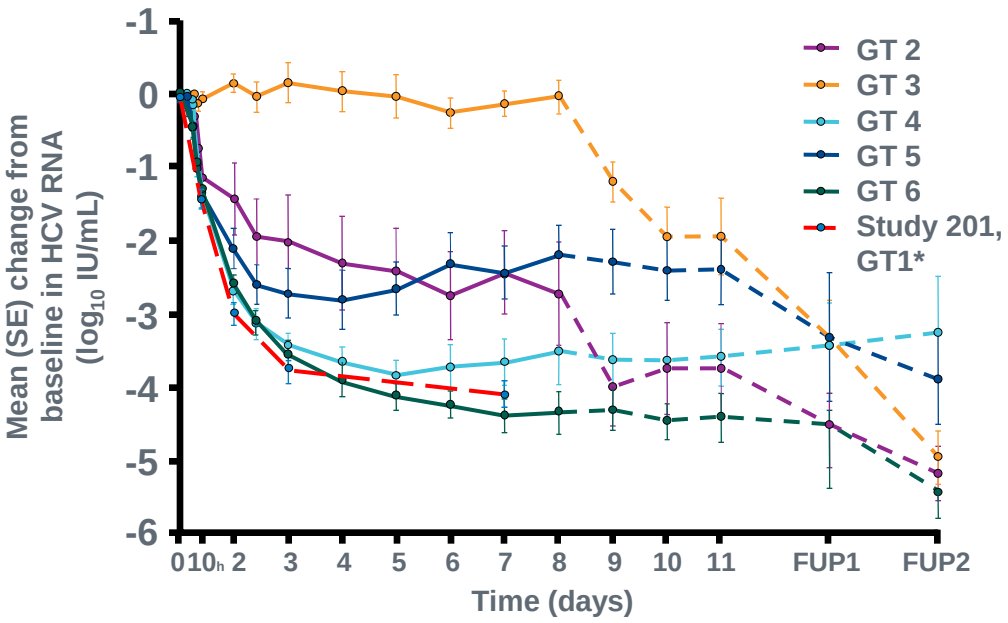
Design of study C202 (Phase IIa)



Treatment-naïve patients infected with HCV GT 2, 3, 4, 5, and 6 were enrolled in Belgium, Germany, and Thailand

*Patients could start treatment with either PegIFNa-2a or PegIFNa-2b in combination with RBV
D, day; FUP, follow-up; GT, genotype; PegIFN, pegylated interferon; PK, pharmacokinetics; QD, once daily; RBV, ribavirin; RNA, ribonucleic acid

Mean change in HCV RNA from baseline observed in study C202



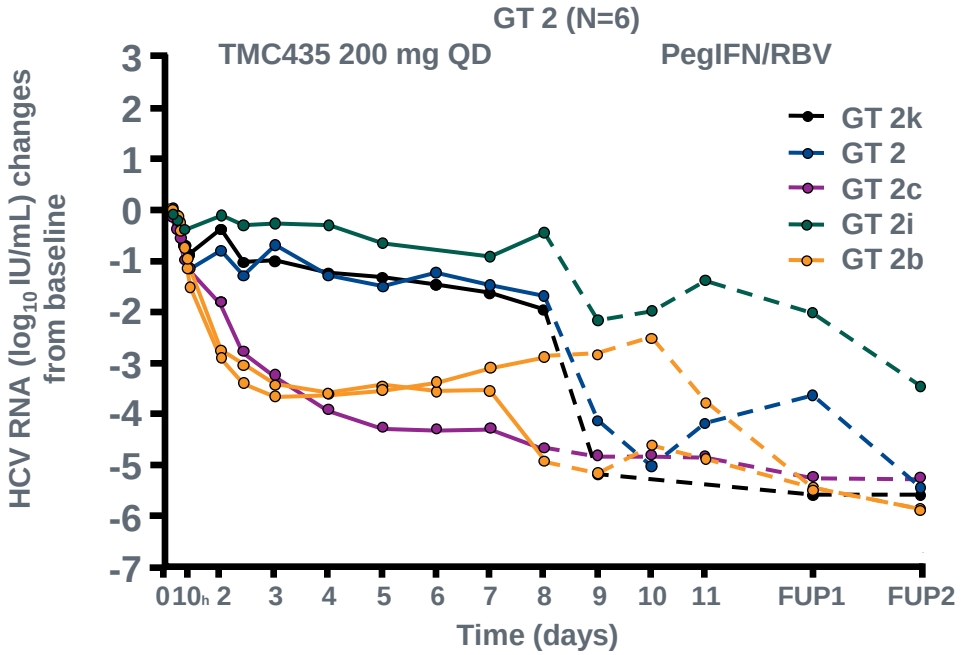
GT	Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
2 (N=6)	-2.02 (0.63)	-2.73 (0.71)
3 (N=8)	-0.16 (0.26)	-0.04 (0.23)
4 (N=8)	-3.43 (0.17)	-3.52 (0.43)
5 (N=7)	-2.71 (0.34)	-2.19 (0.39)
6 (N=8)	-3.57 (0.20)	-4.35 (0.29)

Antiviral activity was observed with TMC435 in GT 2, 4, 5, and 6

*Data from study C201 TMC435 200mg monotherapy against HCV GT1 included for comparison.
FUP, follow-up; GT, genotype; HCV, hepatitis C virus; RNA, ribonucleic acid; SE, standard error

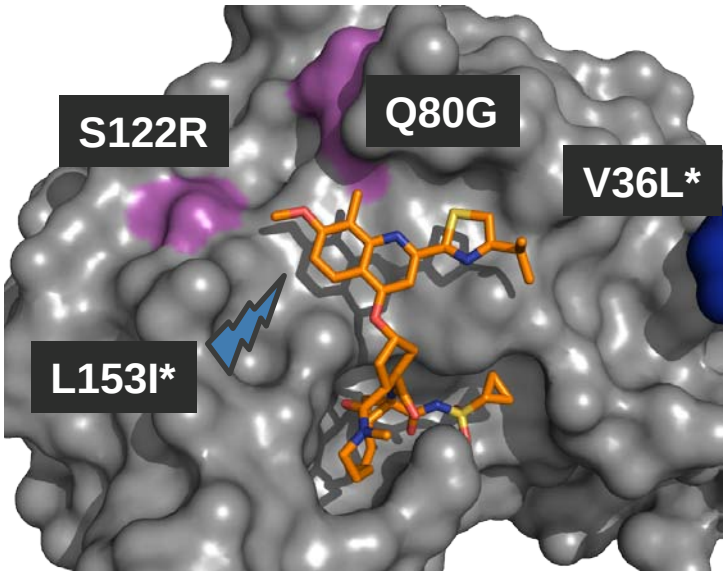
TMC435-C202: Genotype 2

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-2.02 (0.63)	-2.73 (0.71)

Polymorphisms* observed at baseline



* V36 and L153 are buried and thus do not contribute directly to the protein surface

* Polymorphisms are defined as changes from reference (H77). Only polymorphisms at NS3 positions 36, 43, 54, 55, 80, 138, 155, 156, 168, and 170 are shown

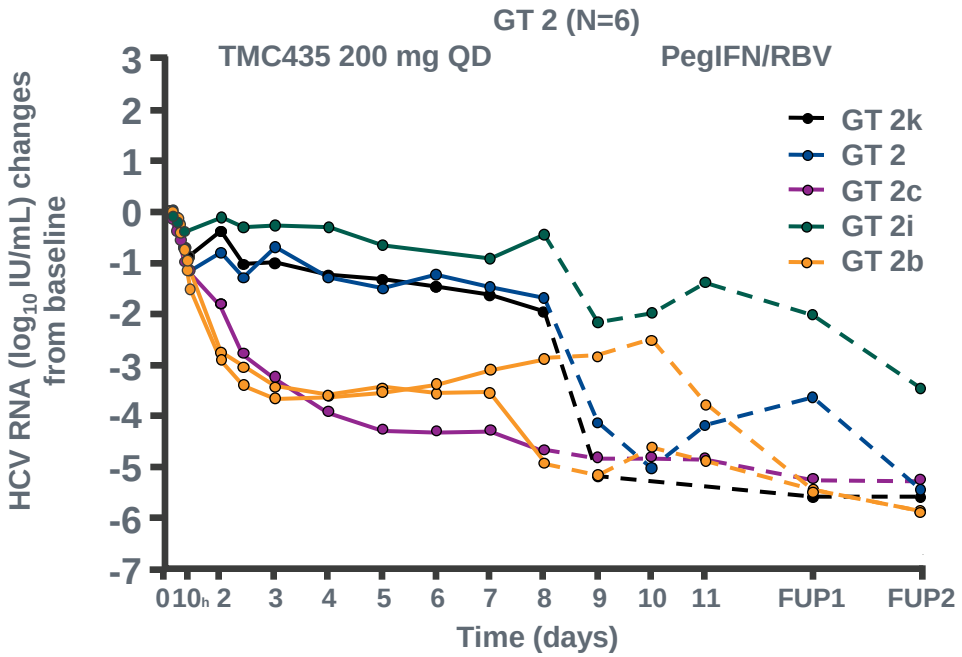
Potent antiviral activity in 3/6 GT 2-infected patients

- GT 2b and 2c: change in HCV RNA from baseline at Day 3: -3.19 to -3.61 (log_{10} IU/mL)
- GT 2, 2k, and 2i: change in HCV RNA from baseline at Day 3: -0.26 to -0.99 (log_{10} IU/mL)

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid

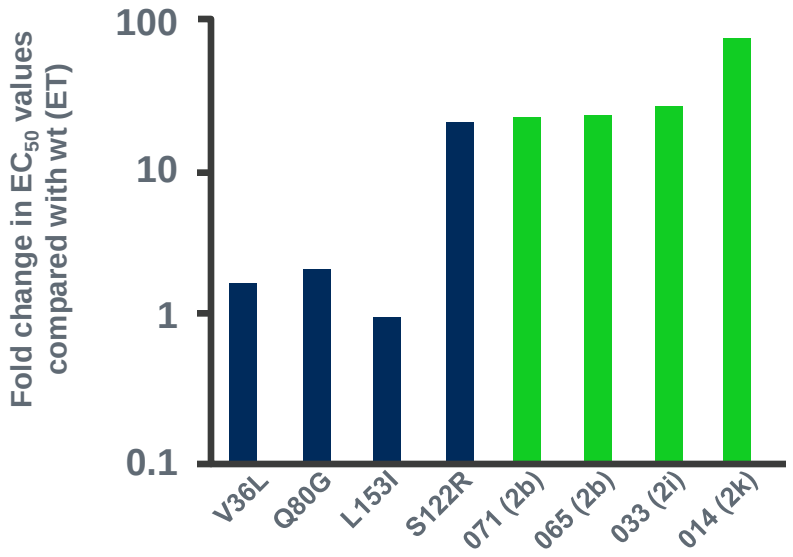
TMC435-C202: Genotype 2

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-2.02 (0.63)	-2.73 (0.71)

In vitro susceptibility to TMC435 of baseline isolates or single polymorphisms



*Fold change in EC_{50} values to TMC435 were assessed in a transient assay as SDM in GT 1b replicon backbone (blue bars) or in a chimeric replicon with NS3prot derived from patient isolate cloned into a JFH-1 (GT 2a) backbone (green bars)

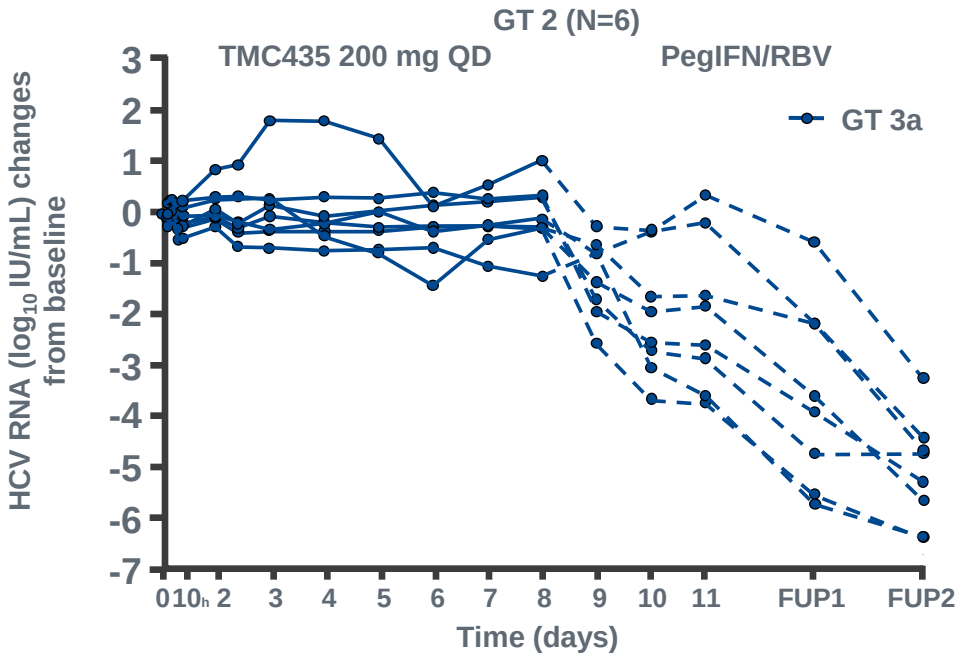
Potent antiviral activity in 3/6 GT 2-infected patients

- GT 2b and 2c: change in HCV RNA from baseline at Day 3: -3.19 to -3.61 (log_{10} IU/mL)
- GT 2, 2k, and 2i: change in HCV RNA from baseline at Day 3: -0.26 to -0.99 (log_{10} IU/mL)

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SDM, site directed mutant; wt, wild type

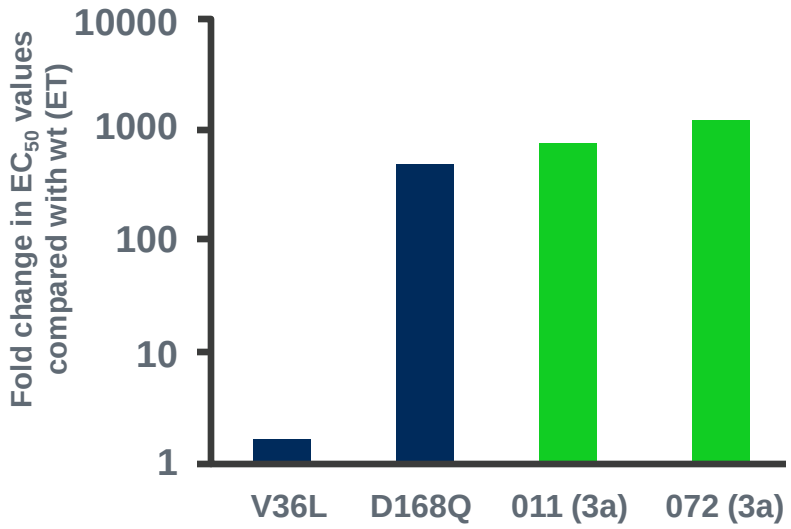
TMC435-C202: Genotype 3

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-0.16 (0.26)	--0.04 (0.23)

In vitro susceptibility to TMC435 of baseline isolates or single polymorphisms



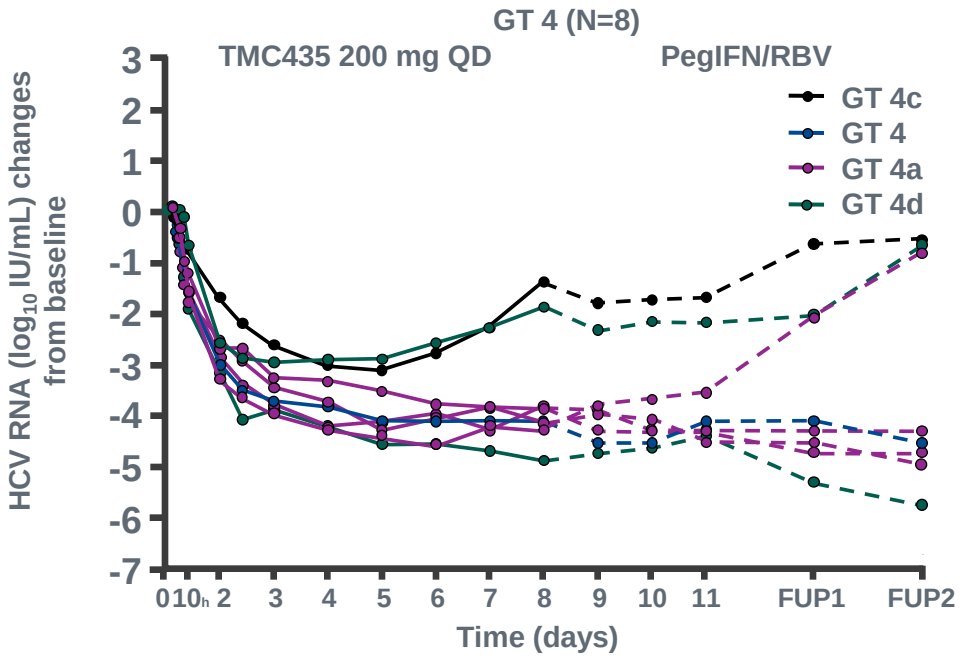
Fold change in EC_{50} values to TMC435 were assessed in a transient assay as SDM in GT 1b replicon backbone (blue bars) or in a chimeric replicon with NS3prot derived from patient isolate cloned into a GT 1b backbone (green bars)

No antiviral activity was observed with TMC435 in GT 3-infected patients

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SDM, site directed mutant; wt, wild type

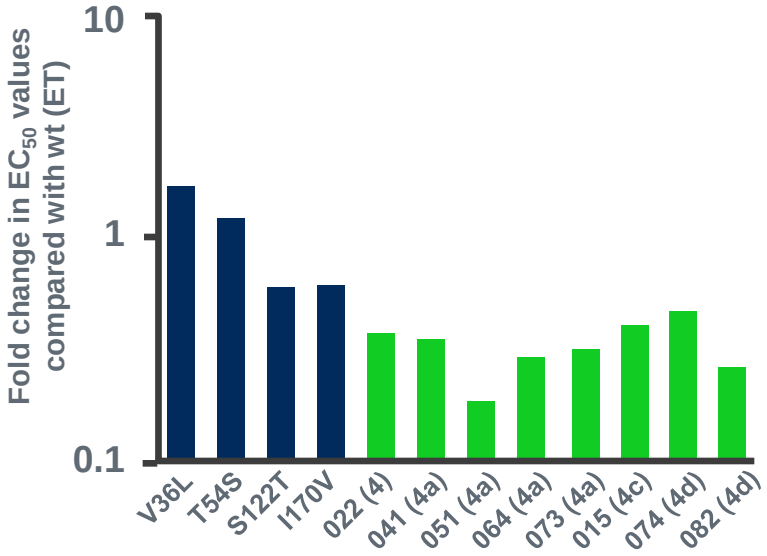
TMC435-C202: Genotype 4

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-3.43 (0.17)	-3.52 (0.43)

In vitro susceptibility to TMC435 of baseline isolates or single polymorphisms



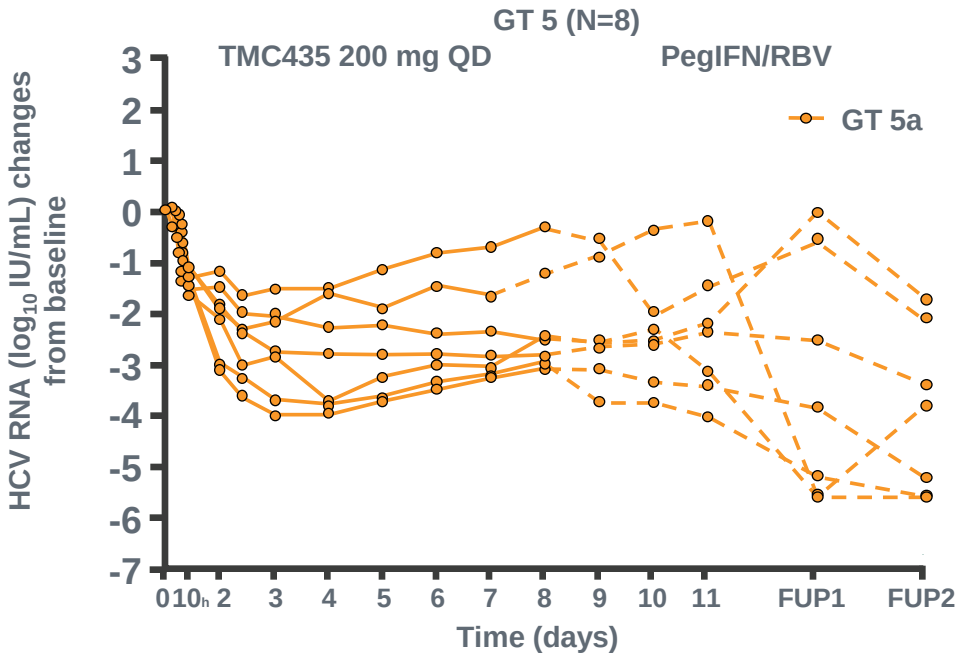
Fold change in EC_{50} values to TMC435 were assessed in a transient assay as SDM in GT 1b replicon backbone (blue bars) or in a chimeric replicon with NS3prot derived from patient isolate cloned into a GT 1b backbone (green bars)

Potent antiviral activity with TMC435 in GT 4-infected patients with 2/8 patients achieving HCV RNA <25IU/mL at Day 8

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SDM, site directed mutant; wt, wild type

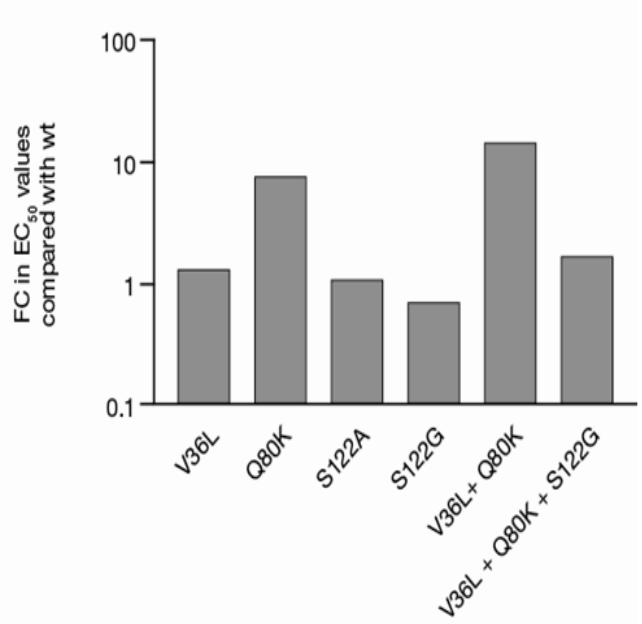
TMC435-C202: Genotype 5

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-2.71 (0.34)	-2.19 (0.39)

In vitro susceptibility to TMC435 of baseline polymorphisms



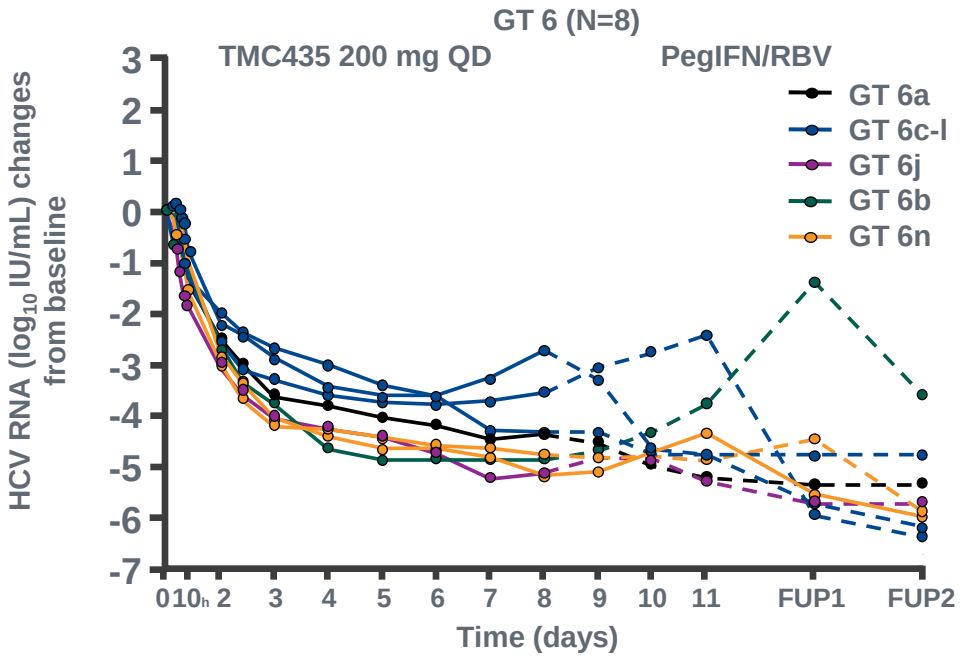
Fold change in EC_{50} values to TMC435 were assessed in a transient assay as SDM in GT 1b replicon backbone

Potent antiviral activity with TMC435 in GT 5-infected patients

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SDM, site directed mutant; wt, wild type

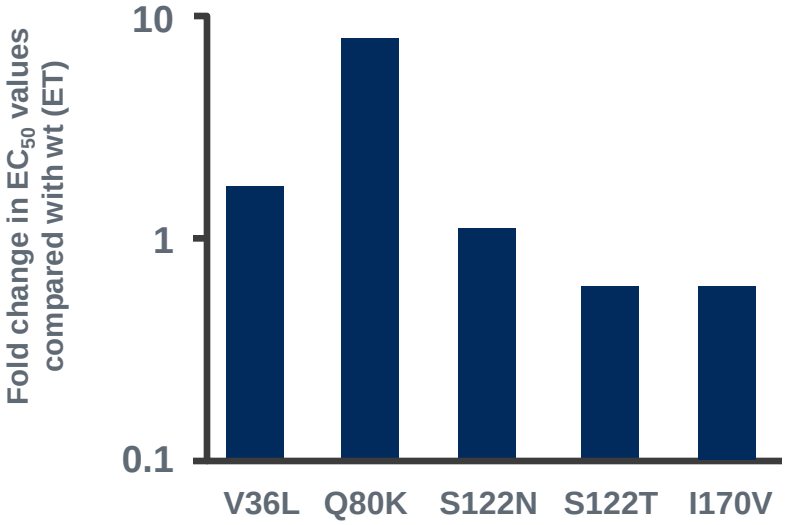
TMC435-C202: Genotype 6

Individual change in HCV RNA



Mean (SE) change in HCV RNA Day 3 (log_{10} IU/mL)	Mean (SE) change in HCV RNA Day 8 (log_{10} IU/mL)
-3.57 (0.20)	-4.35 (0.29)

In vitro susceptibility to TMC435 of baseline polymorphisms

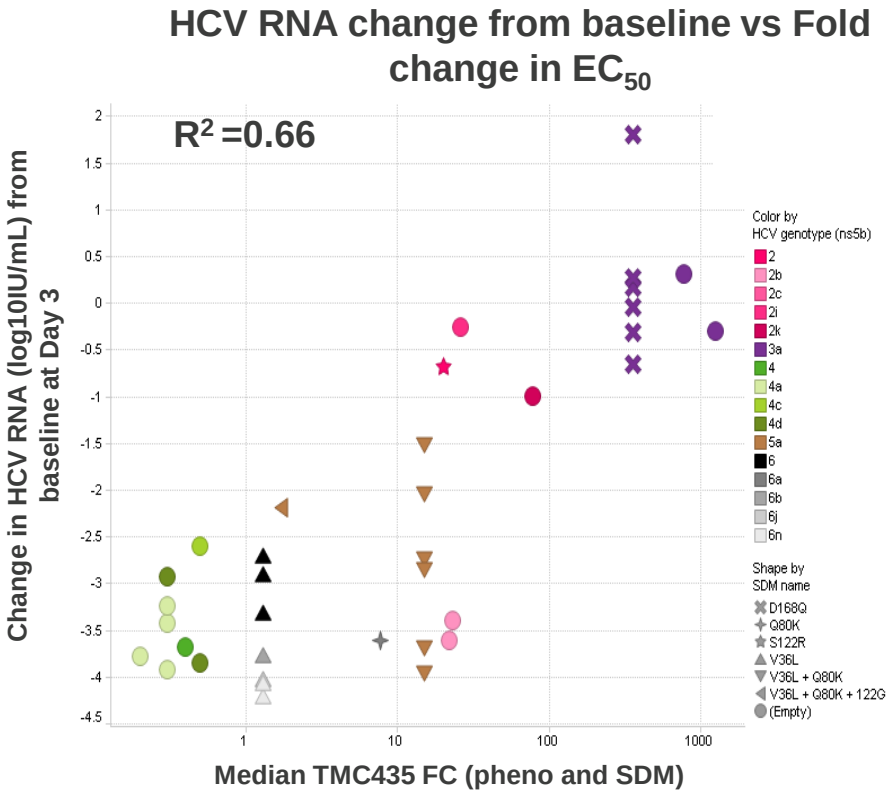


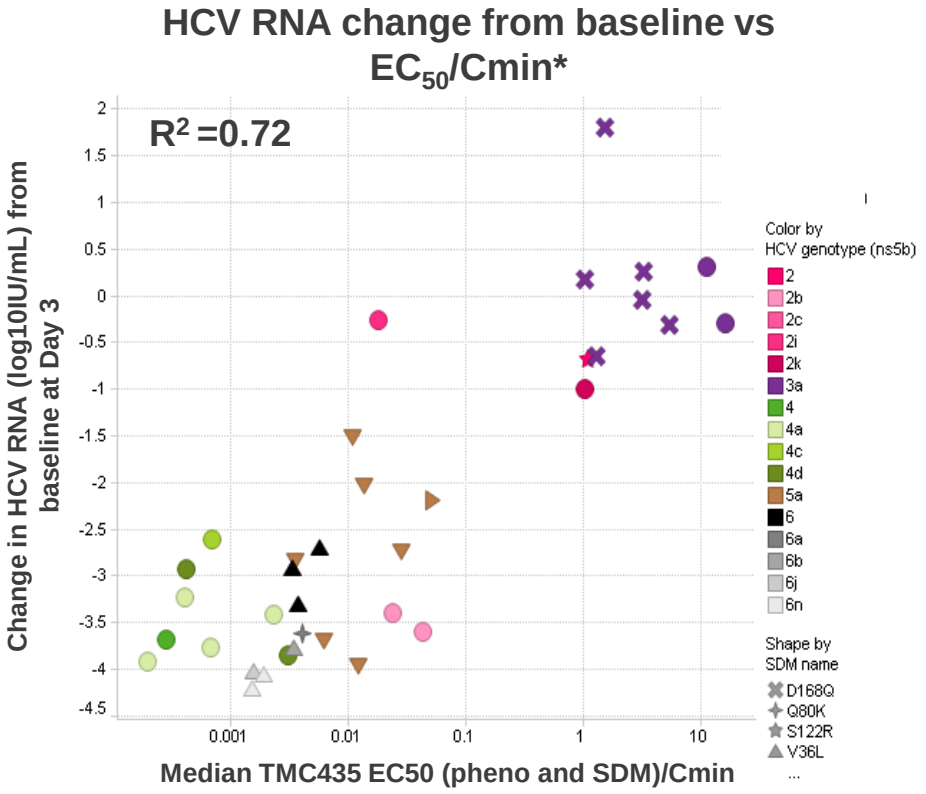
Fold change in EC_{50} values to TMC435 were assessed in a transient assay as SDM in GT 1b replicon backbone

Potent antiviral activity with TMC435 in GT 6-infected patients with 2/8 patients achieving HCV RNA <25IU/mL at Day 8

FUP, follow-up; GT, genotype; HCV, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SDM, site directed mutant;

C202: correlation between individual change in HCV RNA from baseline to day 3 versus *in vitro* baseline susceptibility





Fold change in EC_{50} values to TMC435 were assessed in a transient assay using a chimeric replicon with NS3prot derived from patient isolates, cloned into a GT 1b or JFH-1 backbone (filled circles) or SDM in a genotype 1b backbone (shape by SDM). *Cmin determined at steady state at Day 7.

Baseline susceptibility correlates with change in HCV RNA from baseline at Day 3

Summary

- TMC435 200 mg QD showed most potent antiviral activity in GT 4-, and 6-infected patients, followed by GT 5 and GT 2 (3/6 with response). No antiviral activity in GT 3.
- Good Correlation between HCV RNA changes from baseline and in vitro susceptibility (chimeric replicon assay and/or SDM) for GT 4 and GT6 (fully susceptible) as well as GT 3 (fully resistance).
- Correlation improved by including Cmin plasma exposure for isolates with low/intermediate level of resistance (GT2 and GT5)
- Change from baseline at Day 8 (efficacy) can be affected by emergence of resistant variants.

Acknowledgment

- The patients and their families
- The Investigators
- Colleagues from Janssen who contributed to this work