# Pharmacokinetics of simeprevir (TMC435) in volunteers with severe renal impairment

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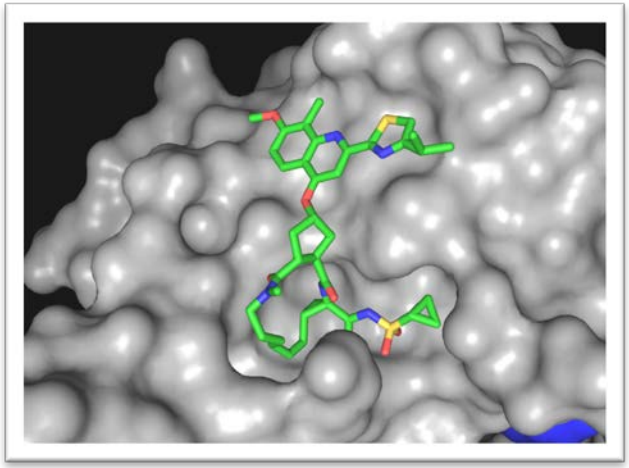
# Simeprevir (SMV, TMC435)



- Potent, oral, once-daily, investigational, HCV NS3/4A protease inhibitor currently in Phase III clinical development for the treatment of HCV genotypes 1 and 4
- Results from the QUEST-1, QUEST-2 and PROMISE Phase III international trials in genotype 1, naïve patients showed SVR12 rates of 80%, 81%, and 79% respectively[1–3]
- Readily absorbed when formulated as an oral solution or a capsule

SMV, simeprevir
SVR12, sustained virologic response 12 weeks after end of treatment

[1]Manns M et al. Oral presentation at EASL 2013
[2]Jacobson I et al. Poster presented at EASL 2013
[3]Lawitz E et al. Oral presentation at DDW 2013

# Rationale and objectives

- Renal clearance plays an insignificant role in the elimination of SMV and its metabolites
  - On average, <1% of the administered oral dose is excreted in urine[1]
  - SMV is metabolized by liver CYP3A4
- Although renal clearance of SMV is low, renal impairment can affect:[2,3]
  - Pathways of hepatic and intestinal metabolism
  - Transport of some compounds, potentially impacting their plasma concentration
- Primary objective: to assess the steady-state PK of SMV in subjects with severe renal impairment and compare with PK in matched subjects with normal renal function

PK, pharmacokinetics

*[1]TMC435 Investigator's Brochure, Edition 6, October 2011*
*[2]Dreisbach AW et al. Expert Opin Drug Metab Toxicol 2008;4:1065-74*
*[3]Nolin TD et al. Clin Pharmacol Ther 2008;83:898-903*

# Study subjects

- Male or female aged 18–70 years with severe renal impairment (N=8) and matched healthy subjects (N=8)
  - Renal impairment defined as eGFR ≤29 mL/min/1.73m$^2$ (MDRD equation)
  - Normal renal function defined as eGFR ≥80 mL/min/1.73m$^2$ (MDRD)
  - Subjects matched for sex, race, age (±10 years) and body mass index (BMI, ±20%)
- Other inclusion criteria included:
  - Patients with severe renal impairment not on dialysis and not expected to start dialysis in the next 3 months
- Exclusion criteria included HCV infection, use of disallowed medication in renal impaired subjects and use of any medication other than paracetamol or ibuprofen in healthy subjects

eGFR, estimated glomerular filtration rate
MDRD, Modification of Diet in Renal Disease

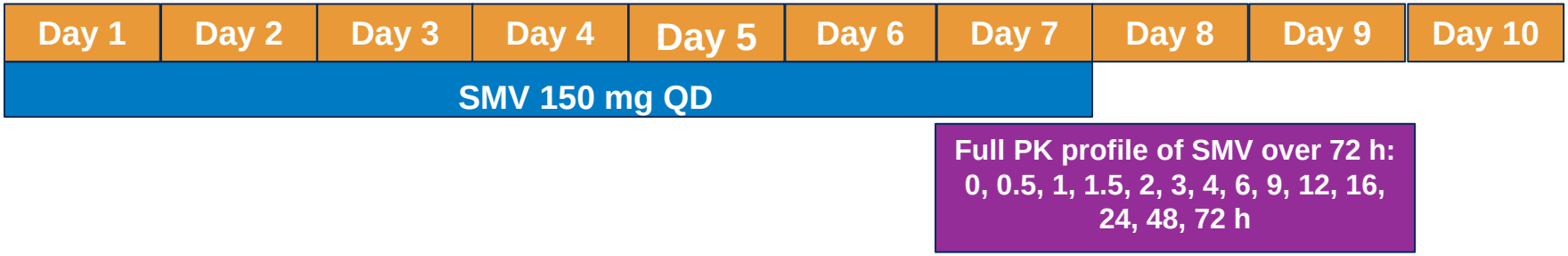
# Study design

- Phase I, open-label study (NCT01381835)


- Full PK profiles of SMV up to 72 hours post-dose were determined on Day 7
- Unbound SMV plasma concentrations were also determined pre-dose and 4 hours post-dose on Day 7
- Safety and tolerability were monitored throughout the study
- PK data from renal impaired and healthy subjects were compared using LS mean ratios

FU, follow-up; QD, once daily; LS, least squares

# Dosage and administration of SMV




- All subjects received one capsule of SMV150 mg QD in the morning under fed conditions
  - On Day 7 (day of full PK profiling), subjects fasted overnight for ≥10 hours before a standardised breakfast was served
- Venous blood samples were collected for determination of SMV plasma concentrations

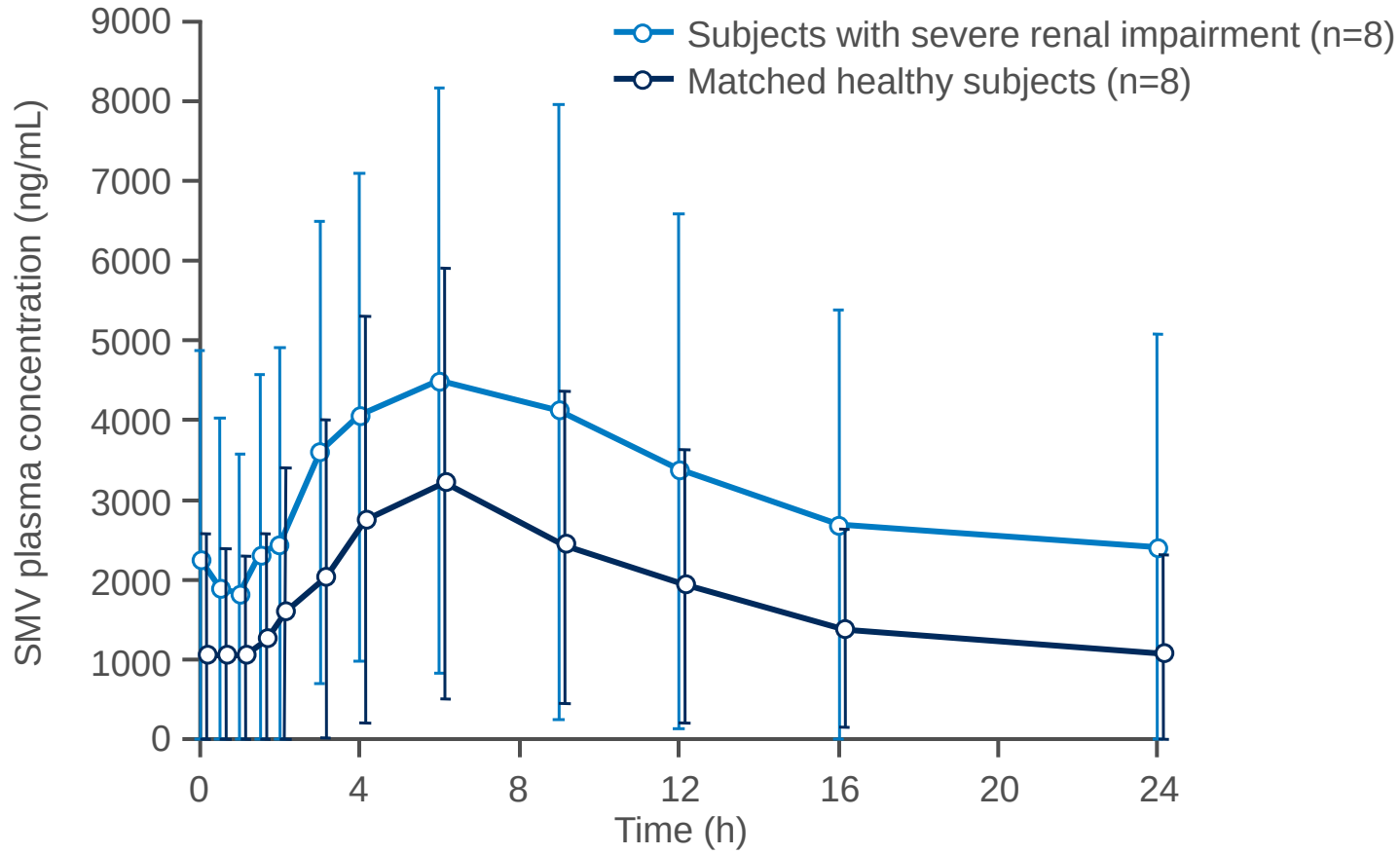
# Subject demographics and baseline characteristics

| Parameter | Renal impaired (N=8) | Healthy controls (N=8) |
|---|---|---|
| **eGFR, mL/min/1.73m$^2$ (mean [SD])** | **19.7 (6.52)** | **96.0 (9.23)** |
| Age, years (median [range]) | 55.0 (36, 67) | 57.0 (37, 61) |
| BMI, kg/m$^2$ (mean [SD]) | 27.5 (2.57) | 25.9 (2.52) |
| Male, n (%) | 7 (87.5) | 7 (87.5) |
| White race, n (%) | 8 (100.0) | 8 (100.0) |

SD, standard deviation

# Plasma concentration–time profiles of SMV

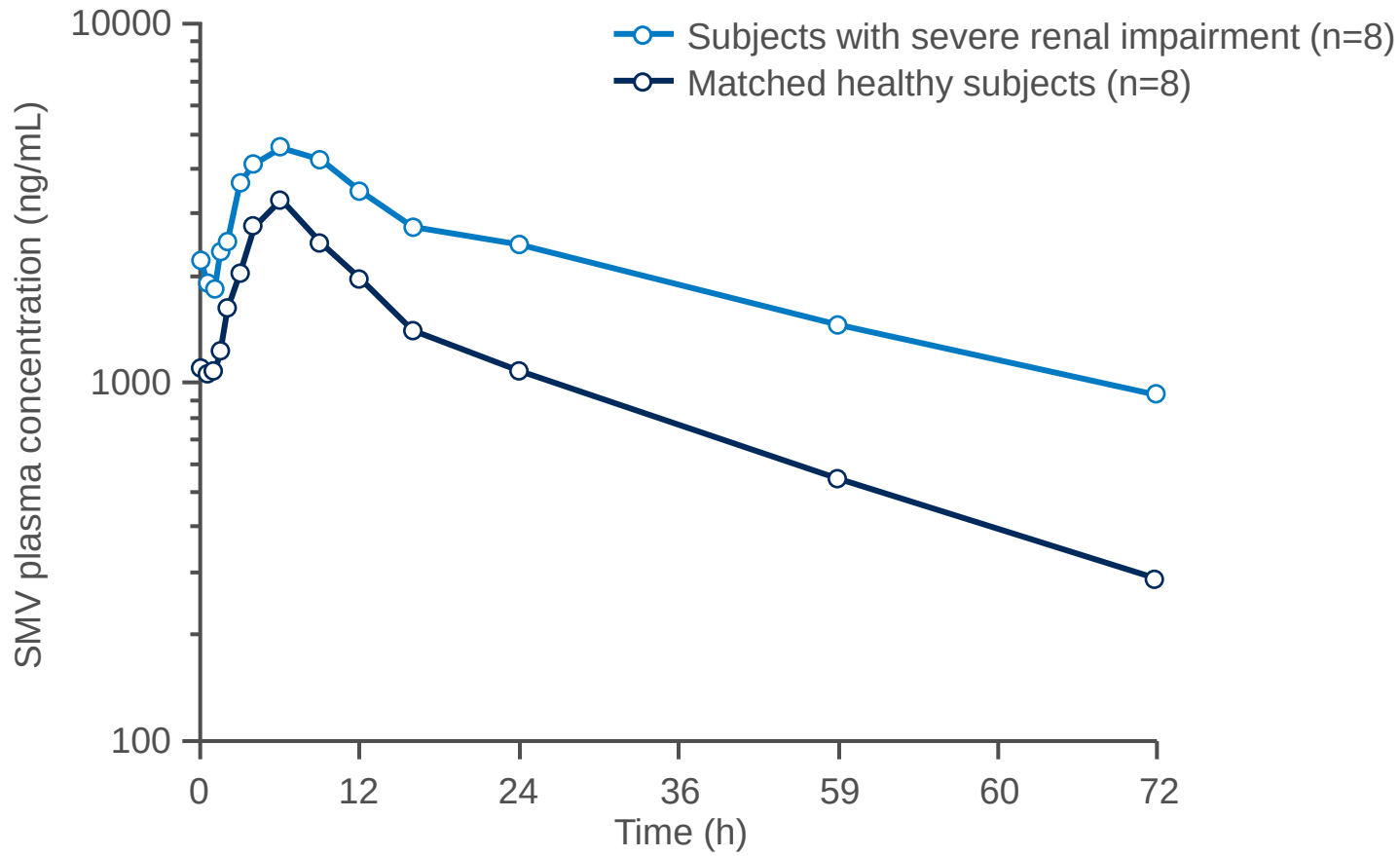
Linear mean plasma concentration–time profiles of SMV comparing severely renal impaired and matched healthy subjects




Bars represent SD

# Plasma concentration–time profiles of SMV

Semi-logarithmic mean plasma concentration–time profiles of SMV comparing severely renal impaired and matched healthy subjects



# Statistical evaluation of SMV PK

| Parameter | LS means[a] | | LS means ratio | 90% CI |
|---|---|---|---|---|
| | Renal impaired (test) | Healthy controls (reference) | | |
| $C_{min}$, ng/mL | 985.5 | 577.5 | 1.71 | 0.65, 4.50 |
| $C_{max}$, ng/mL | 3459 | 2588 | 1.34 | 0.66, 2.72 |
| $AUC_{24h}$, ng.h/mL | 51710 | 32010 | 1.62 | 0.73, 3.59 |
| | Median[a] | | Treatment difference median | 90% CI |
| $t_{max}$, h | 6.0 | 6.0 | 0.0 | 0.0, 2.0 |

- For subjects with severe renal impairment, SMV $C_{min}$, $C_{max}$ and $AUC_{24h}$ were about 71%, 34% and 62% higher, respectively, compared with matched healthy controls
  - For $t_{max}$, no relevant differences were observed between the groups

$AUC_{24h}$, area under the plasma-time curve; CI, confidence interval; $C_{max}$, maximum plasma concentration; $C_{min}$, minimum plasma concentration; $t_{max}$, time to reach $C_{max}$

[a]N: 8 for reference (healthy controls) and N: 8 for test (renal impaired)

# Plasma concentration of SMV

- Steady-state conditions were generally achieved prior to full PK blood sampling on Day 7 for most subjects
- After SMV150 mg QD, mean plasma concentrations were higher in subjects with severe renal impairment compared with matched healthy subjects
  - No major differences were observed in the shape of the mean plasma concentration–time curves for SMV
- In subjects with severe renal impairment, the decline in mean SMV plasma concentration was slower than in matched healthy subjects
  - Mean half-life was 24.0 hours in subjects with severe renal impairment compared with 16.7 hours in matched healthy subjects
- Mean fraction of SMV unbound to protein ($f_u$) in plasma pre- and 4 hours post-dose was <0.0001 for subjects in both groups

# Incidence of adverse events

| Incidence of AE, n (%) | Renal impaired (N=8) | Healthy controls (N=8) |
|---|---|---|
| **Any AE** | **4 (50.0)** | **1 (12.5)** |
| **Hyperbilirubinemia** | **1 (12.5)** | **1 (12.5)** |
| **Investigations** | **1 (12.5)** | **0** |
| Blood ALP ↑ | 1 (12.5) | 0 |
| **Myalgia** | **1 (12.5)** | **0** |
| **Rhabdomyolysis** | **1 (12.5)** | **0** |
| **Hypertension** | **1 (12.5)** | **0** |

AE, adverse event; ALP, alkaline phosphatase

# Adverse events: summary

- The majority of AEs were grade 1 or 2
  - No subject permanently discontinued SMV prematurely due to AEs
  - One (12.5%) renal impaired subject had an SAE (grade 3 rhabdomyolysis)
  - There were no skin events of interest reported
- All AEs were considered not or doubtfully related to SMV
  - Exception: rhabdomyolysis and myalgia both considered probably related to SMV
    - Both AEs occurred in the same renal impaired subject
    - This subject was receiving concomitant high-dose fenofibrate

# Conclusions

- SMV exposure was higher in subjects with severe renal impairment versus matched healthy subjects with normal renal function
  - Steady-state conditions were generally achieved prior to full PK blood sampling on Day 7 for most subjects
- For subjects with severe renal impairment, $C_{min}$, $C_{max}$, and $AUC_{24h}$ of SMV were about 71%, 34% and 62% higher, respectively, versus values in matched healthy subjects
- Severe renal impairment had no effect on SMV plasma protein binding
  - Mean $f_u$ values of SMV in plasma pre-dose and 4 hours post-dose were ~0.0001 for subjects with severe renal impairment and matched healthy subjects
- SMV was generally safe and well tolerated in subjects with severe renal impairment and in those with normal renal function
- SMV dose adjustment is not required in subjects with renal impairment

# Acknowledgements


- The volunteers and their families
- The Janssen study team
- Medical writing support was provided by Complete Medical Communications, and was funded by Janssen