A novel microdose approach to assess bioavailability, intestinal absorption, gut metabolism, and hepatic clearance of simeprevir in healthy volunteers

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Presenter’s disclosure information

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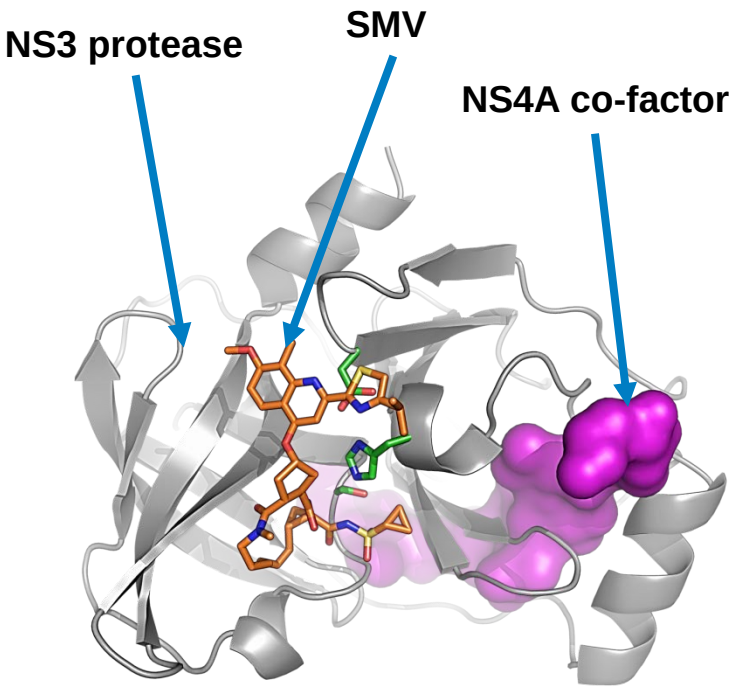
Simeprevir (SMV/TMC435)



- Once-daily capsule, HCV NS3/4A protease inhibitor
- Approved in Japan, Canada, the USA, Russia and Europe
- Antiviral activity in patients infected with HCV GT 1, 2, 4, 5, and 6
- Phase III trials of SMV+PR in HCV GT 1- and GT 4-infected treatment-naïves and relapsers showed SVR12 rates ~80%[1–4]
- In a Phase II trial (COSMOS) of SMV + sofosbuvir ± ribavirin in HCV GT 1-infected treatment-naïves and prior null responders, the overall SVR12 rate was 92.2%[5,6]
- Safe and well tolerated (~3800 patients treated in clinical trials to date)
- In development as part of IFN-free combinations

GT, genotype; IFN, interferon; PR, peginterferon-α-2a/-2b + ribavirin; SVR12, sustained virologic response 12 weeks after end of treatment

1. Jacobson I *et al*. Lancet In press; 2. Manns M *et al*. Lancet In press; 3. Forns X *et al*. Gastroenterology Mar 3 [Epub ahead of print]; 4. Moreno C *et al*. HepDART 2013; 5. Lawitz E *et al*. EASL 2014; 6. Sukowski MS *et al.* EASL 2014.

Initial Conventional Mass Balance Study
TMC435-TiDP16-C103

Design

- Study in healthy male volunteers (N=6)
- Single oral dose of 200 mg ^{14}C-SMV (50 µCi)
- Unchanged SMV was determined in plasma and blood
- Total radioactivity and metabolic profiles were determined in plasma, urine, and feces

Results that were used in the design of C118

- Blood / plasma ratio of SMV = 0.69
- LC-MS/MS response factor of metabolites in feces

LC-MS, liquid chromatography–mass spectrometry

Objectives
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- A Phase I, open-label, sequential, single-dose study in healthy volunteers (N = 6, all completed)
- Primary objective
  - To evaluate the absolute bioavailability (F_{abs}) and pharmacokinetics (PK) of SMV after administration of a single oral dose of 50 mg or 150 mg, followed by a single iv dose of 100 µg [^{3}H]-SMV

Note:150 mg is the therapeutic dose, 50 mg was added to investigate mechanism of non-linear PK

- Secondary objectives
  - To evaluate the proportion of the iv dose excreted in urine and feces
  - Safety and tolerability

Treatment
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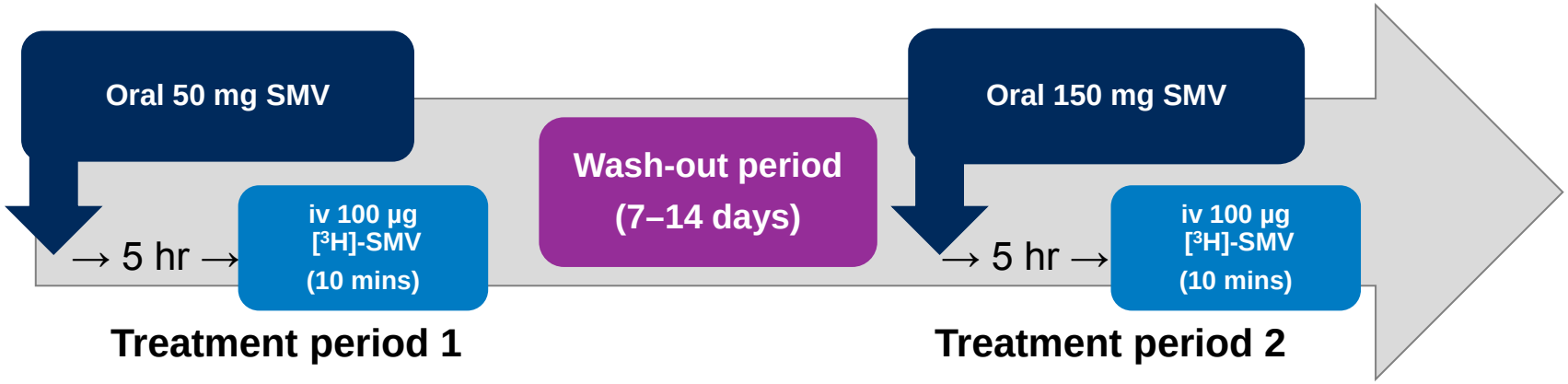
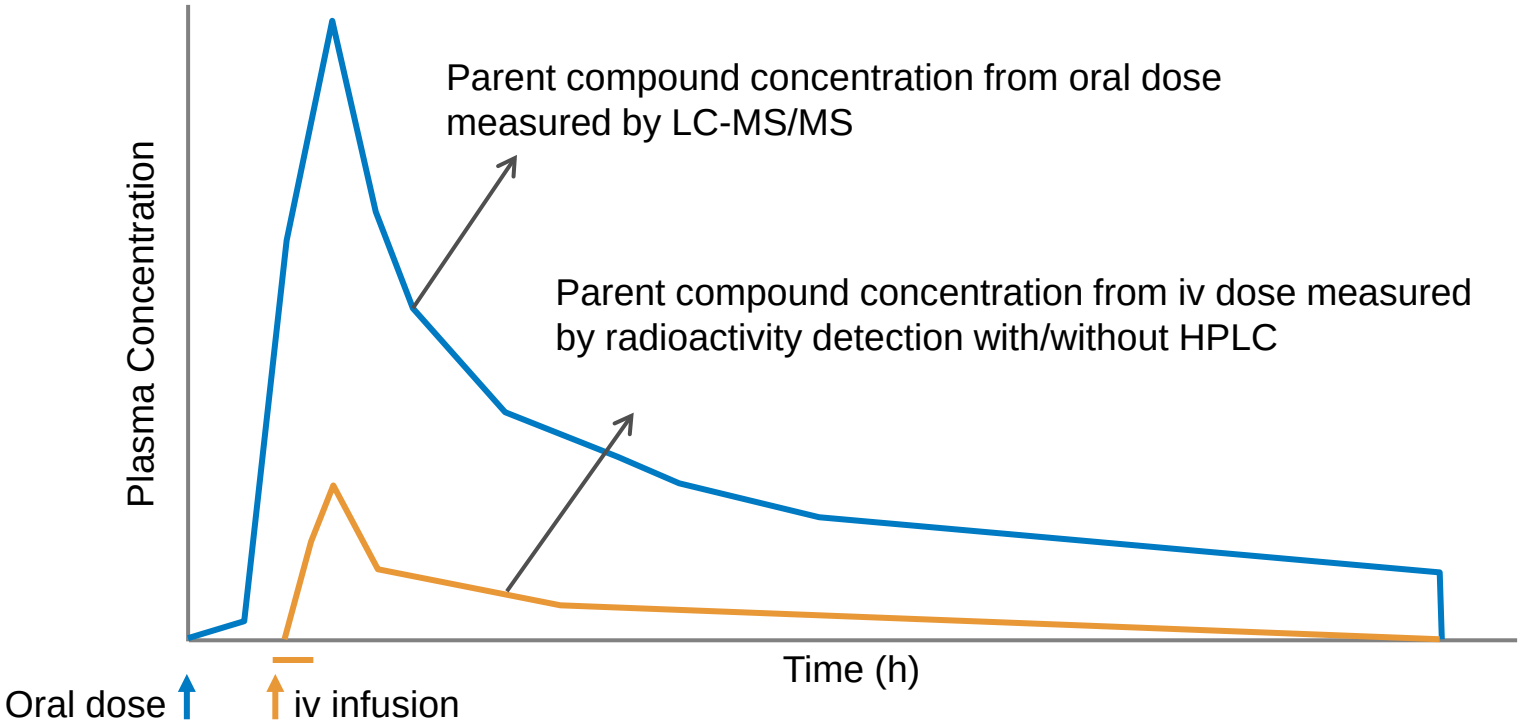
- Oral dose of SMV followed by an iv dose of [^{3}H]-SMV
  - 10 min iv infusion at t_{max} of oral dose (5 hr)
  - Two dosing periods
  - Plasma, urine, and feces collected



- SMV and [^{3}H]-SMV plasma PK profiles, and total plasma radioactivity were determined for both treatments 0–72 hours after oral SMV administration
- Urine per 24-hour interval and feces were collected for at least 96 hours after oral SMV administration

Concept of iv micro-radiotracer design

Simultaneous generation of oral and iv PK profiles



Plasma PK parameters
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Parameters	SMV 50 mg oral + 100 µg iv (Treatment period 1)	SMV 150 mg oral + 100 µg iv (Treatment period 2)
iv dose, mean ± SD (t_{max}: median [range])		
C_{max}, ng/mL	12.07 ± 2.21	12.64 ± 2.78
AUC_{∞}, ng.h/mL	17.1 ± 4.58	23.3 ± 8.28
$t_{1/2term,}$ h	10.8 ± 1.64	11.5 ± 2.11
CL, L/h	6.23 ± 1.77	4.75 ± 1.56
V_d, L	94.4 ± 15.4	75.3 ± 15.9
Oral dose, mean ± SD (t_{max}: median [range])		
C_{max}, ng/mL	262 ± 60.5	1503 ± 550
t_{max}, h	4.99 (2.50–5.00)	5.00 (4.99–6.00)
AUC_{∞}, ng.h/mL	3976 ± 1257	21676 ± 7805
$t_{1/2term,}$ h	11.6 ± 1.75	12.0 ± 1.39
$F_{abs,}$ %	45.98 ± 2.56	62.12 ± 5.65

Cumulative excretion in urine and feces
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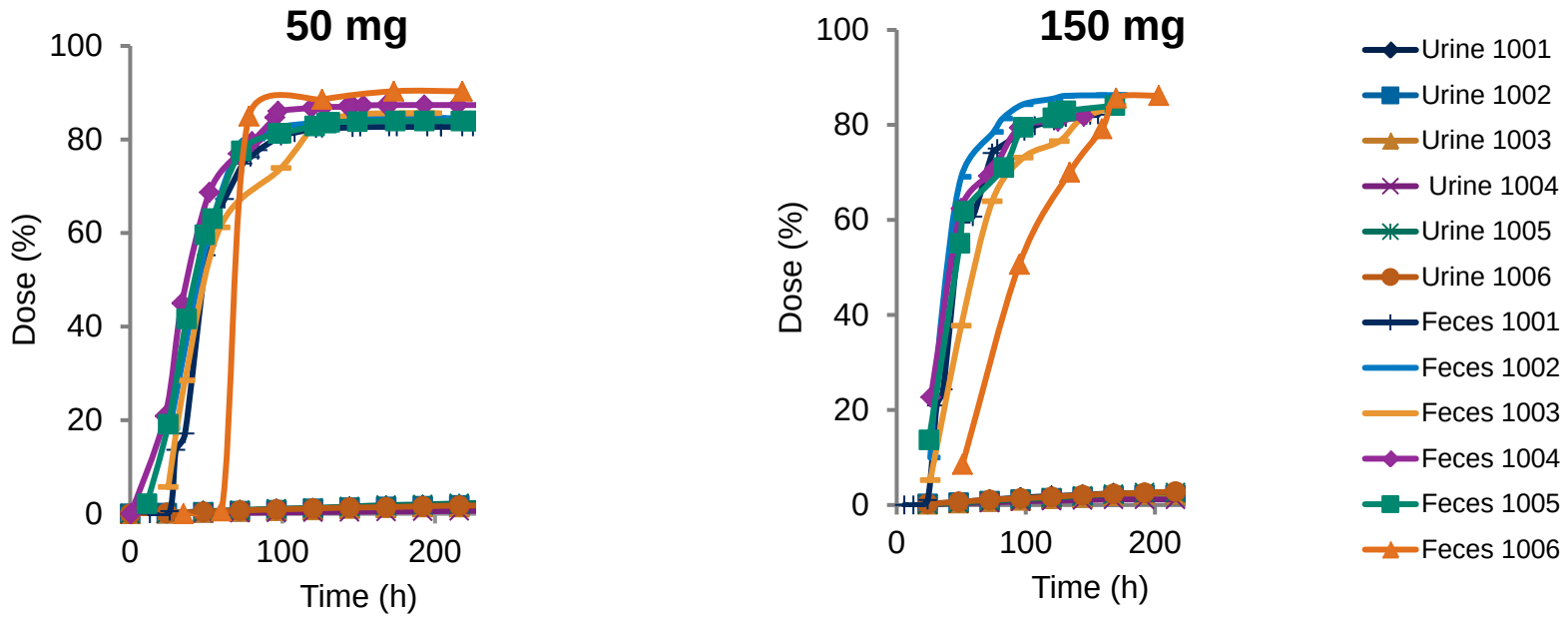
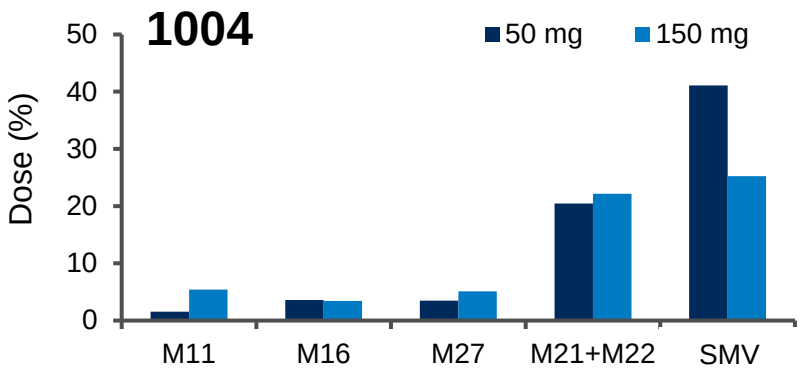
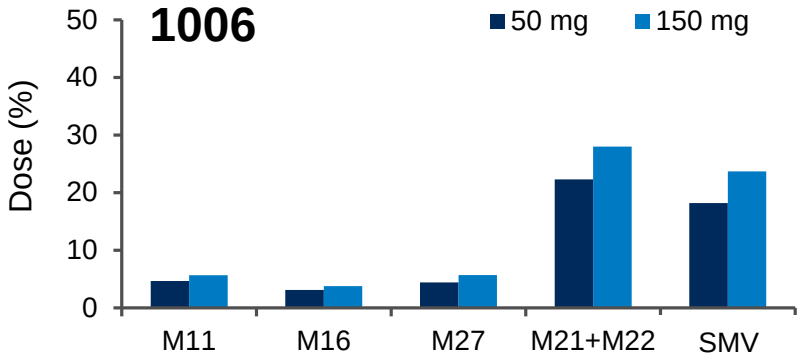


Total recovery , % (mean ± SD)	SMV 50 mg oral + 100 µg iv (Treatment period 1)	SMV 150 mg oral + 100 µg iv (Treatment period 2)
Urine	1.85 ± 0.68	2.22 ± 0.59
Feces	85.68 ± 2.80	84.10 ± 1.91
Urine + feces	87.53 ± 2.48	86.32 ± 2.28

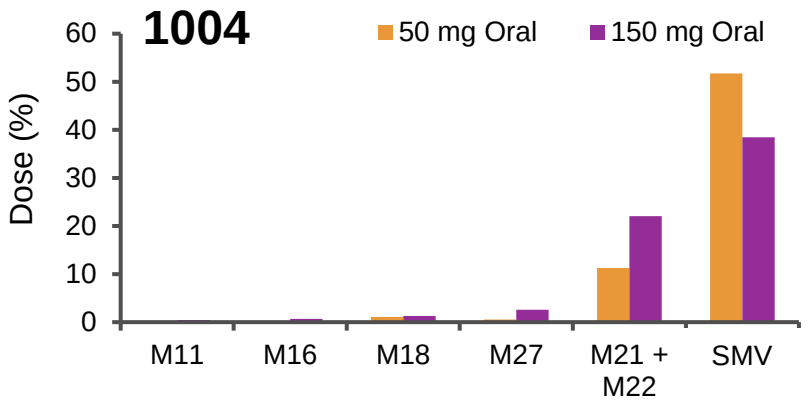
Metabolite profiling in feces could distinguish between oral and intravenous doses

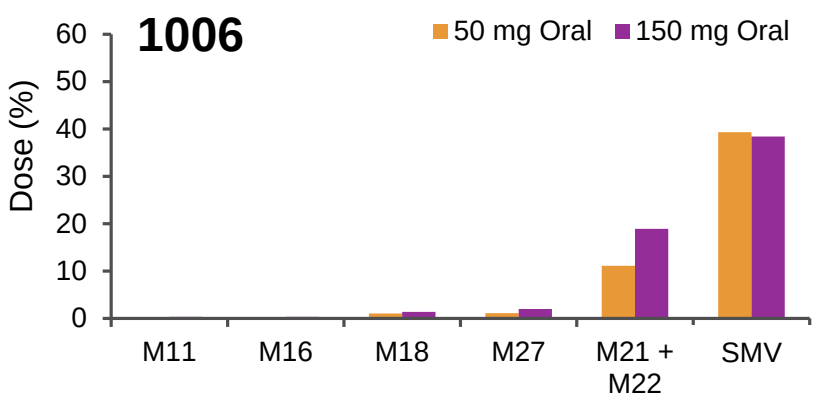
Radiochromatograms for metabolism after iv dose





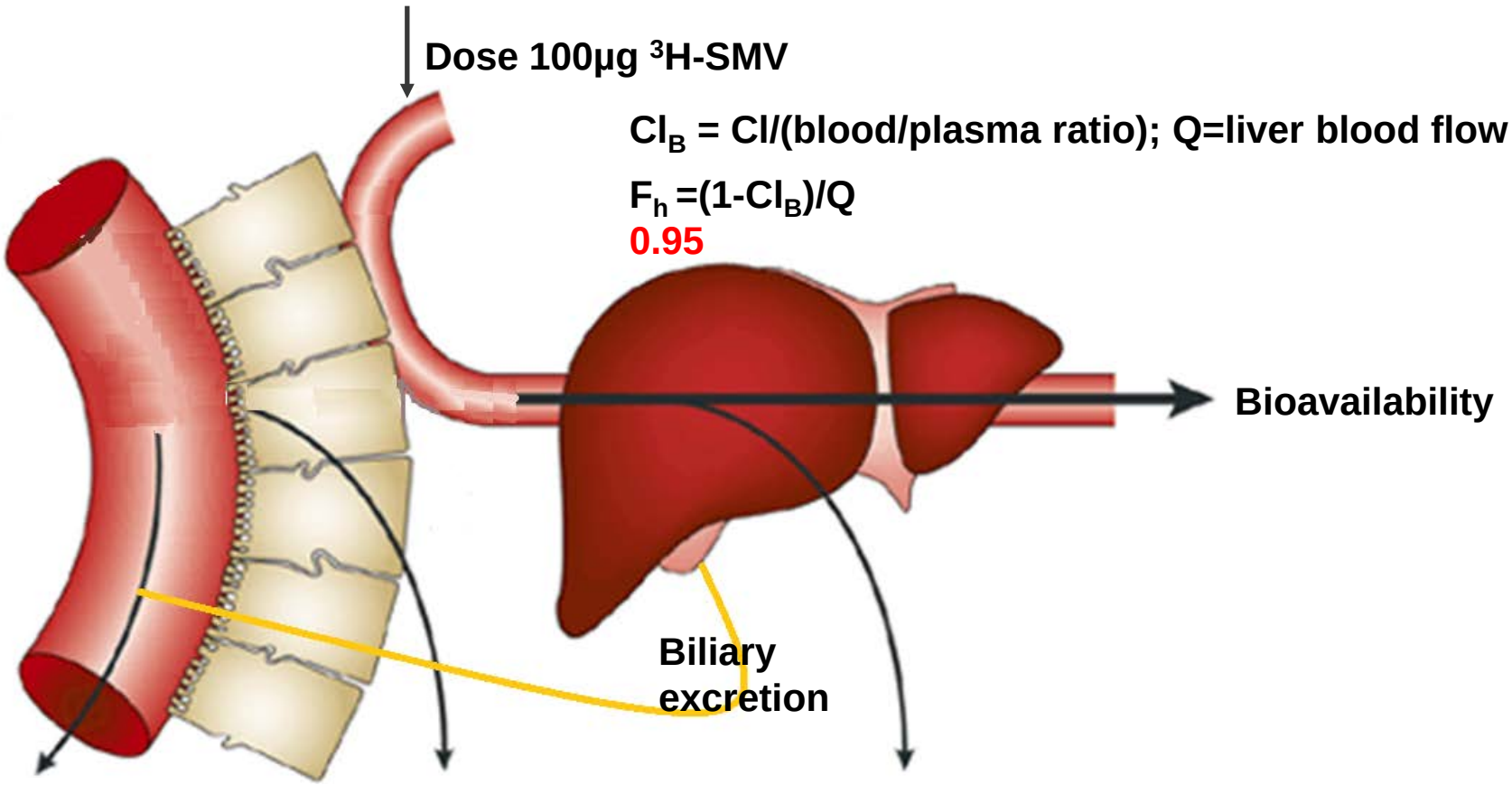
LC-MS/MS for metabolism after oral dose



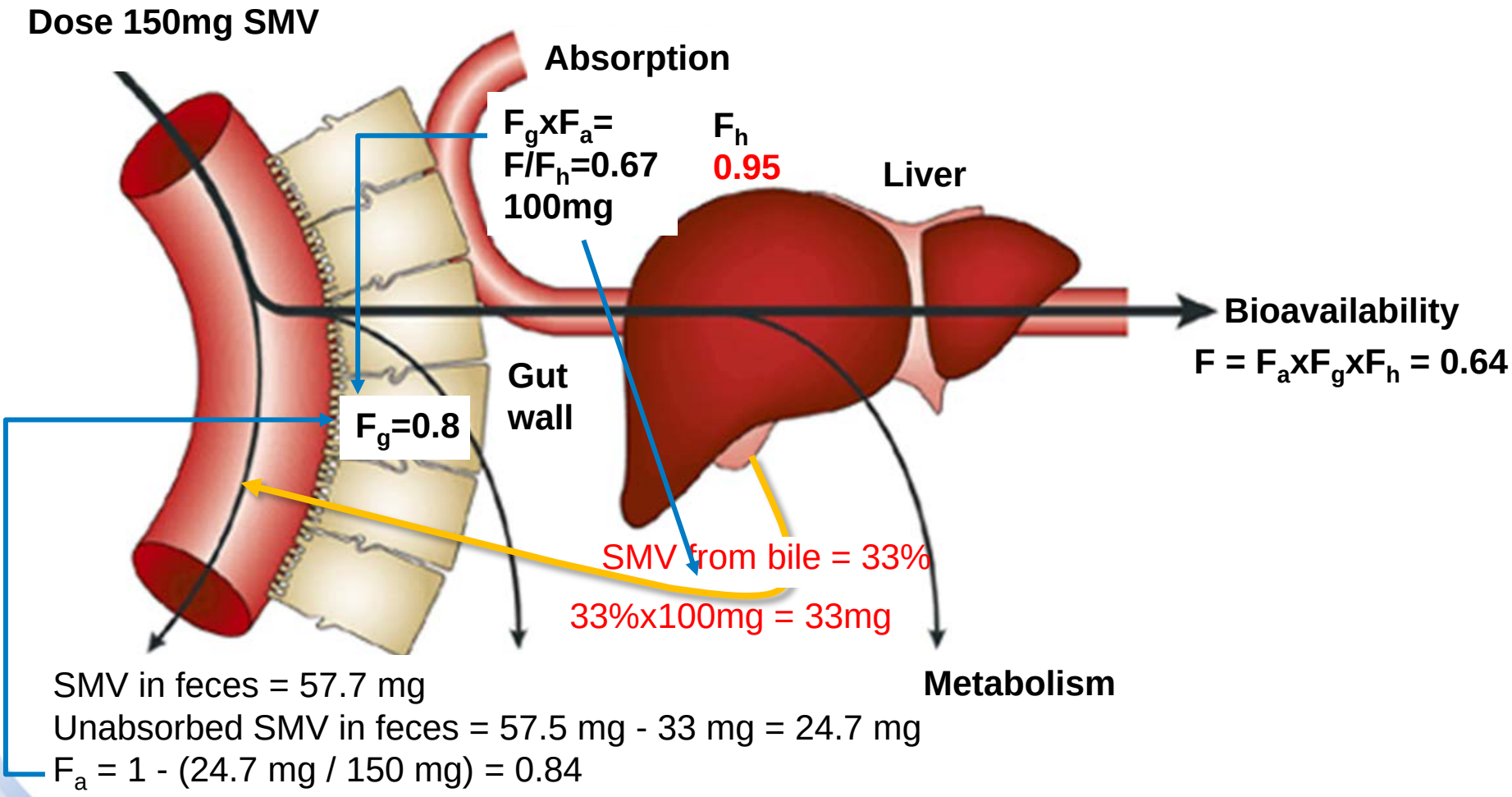


1004, 1006 = patient number

Intravenous dose: 100 µg ^{3}H-SMV



Oral dose: unlabelled SMV 150mg



Parameters influencing bioavailability
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	Absolute bioavailability (F_{abs})	Fraction absorbed (F_a)	Fraction escaping liver extraction (F_h)	Fraction escaping gut-wall elimination (F_g)
50 mg oral +100 µg iv (Treatment period 1)	46.0 ± 2.6	0.75 ± 0.07	0.90 ± 0.03	0.69 ± 0.07
150 mg oral +100 µg iv (Treatment period 2)	62.1 ± 5.6 ↑	0.83 ± 0.06 ↑	0.92 ± 0.03	0.81 ± 0.03 ↑

Effect on
⇨saturation of intestinal efflux by P-gp
⇨saturation of 3A4 in intestine
⇨ saturation of uptake in hepatocytes

Conclusions

- The absolute bioavailability of orally administered SMV was dose-dependent; 46% at 50 mg and 62% at 150 mg
- Intestinal absorption, metabolism, and hepatic uptake were saturable, with a greater fraction absorbed and lower fraction metabolized at the higher dose
- Both treatments were generally well tolerated in healthy male volunteers

Acknowledgements

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- The authors would like to thank the volunteers
- Medical writing support was provided by Martin Goulding on behalf of Complete Medical Communications, funded by Janssen