Goals of optimal HCV DAA

1. **Potency** to suppress HCV replication
2. **Safety** profile to dose long enough to clear HCV in the liver
3. **No clinically relevant resistance**

- Nucleotide analogs accomplish these critical objectives with the potential to treat all potential patient populations
  - All HCV genotypes
  - No dependence on a second agent - IFN or another DAA - to "cover" resistant variants
  - Potential for one pill, once a day
  - Minimal drug interactions

Considerations in Individuals with Bleeding Disorders

- Drug Interactions:
  - recombinant clotting factors
  - aminocaproic acid
  - DDAVP
  - HIV therapy in co-infected individuals
- Liver biopsy for inclusion into trials
- Increased likelihood of advanced fibrosis/cirrhosis

PSI-7977 DMPK Program
Consistent Metabolism Across Species Confirms Low Risk of Drug Interaction

Study	Status	Results
Rat ADME	**Complete**	• **Extent of absorption >70%** • **Total recovery >95% with >70% in urine** • **PSI-6206 is major metabolite, PSI-7977 not detected**
Rat QWBA	**Complete**	• **Highest radioactivity in alimentary canal, lymphatic system, and excretory system** • **Lowest in CNS, bone, eye lens, and white adipose** • **No evidence of binding with melanin**
Dog ADME	**Complete**	• **Total recovery >96% with >80% in urine** • **PSI-6206 is major metabolite, PSI-7977 detected in plasma/urine**
PGP substrate /inhibition	**Complete**	• **PSI-7977 & PSI-352707 are substrates, not inhibitors** • **PSI-6206 is neither substrate or inhibitor**
Human hepatocyte induction	**Complete**	• **Little or no induction in CYP1A2 or CYP3A4/5 activity or CYP1A2 mRNA expression levels** • **Slight increases in CYP2B6 activity and CYP2B6/3A4 mRNA levels**

US Epidemiology: 5 to 7 Million Individuals Living with HCV

Population	Reported prevalence range	Estimated number in US population	Estimated range of HCV cases
Homeless	22.2–52.5%	643 067 (14)	142 761–337 610
Incarcerated	23.1–41.2%	1 613 656 (96)	372 754–664 826
Veterans	5.4–10.7%	22 915 943 (97)	1 237 461–2 452 006
Active military duty	0.48%	1 417 747 (98)	6805
Healthcare workers	0.9–3.6%	7 200 950 (99)	64 809–259 234
Nursing home residents	4.5%	1 413 540 (85)	63 609
Chronic haemodialysis	7.8%	263 820 (80)	20 578
Haemophiliacs with transfusions before 1992	76.3–100%	17 000 (92)	12 971–17 000
		Unaccounted number of HCV positive NHANES*	1 921 748–3 821 668
		Total	3 270 000 5 191 748–7 091 668

"Our most conservative estimates suggest that there are at least 5.2 million persons living with HCV in USA today, approximately 1.9 million of whom were unaccounted for in the NHANES survey."

S Saab, et al *Liver International* 2011

PSI-7977 Clinical Pharmacology

- Clinical Pharmacology Objectives:
  - Support potential for accelerated NDA with required Clinical Pharmacology Data
  - Rapidly generate sufficient data to support enrollment of relevant patient populations with HCV
    - Renal impairment
    - Hepatic insufficiency
    - Methadone
    - QT
    - Population PK for age>65, ethnic/racial groups, expanded BMI

PSI-7977 Development Program: Addressing Special populations

1. **Adequate representation of females & minorities**
2. **HIV/HCV co-infected** – drug interaction study protocol finalized with PSI-7977 tenofovir/emtricitabine; results will support clinical trial in HCV/HIV co-infected
3. **Liver Transplant**
4. **Bleeding disorders** – not excluded from current trials
5. **Current and Historical Substance Abuse**
6. **Pediatrics**
7. **Decompensated Liver Disease** – Hepatic Impairment in HCV+ CP B complete; CP C enrolling. Intent to include these subjects in Ph3 studies

Additional cohorts in HCV GT1 added to IFN-free ELECTRON Trial