Idenix PHARMACEUTICALS

Samatasvir (IDX719), a Potent Pan-Genotypic NS5A Inhibitor, for the Treatment of Hepatitis C Virus (HCV) Infection

Douglas Mayers, MD

December 11, 2013

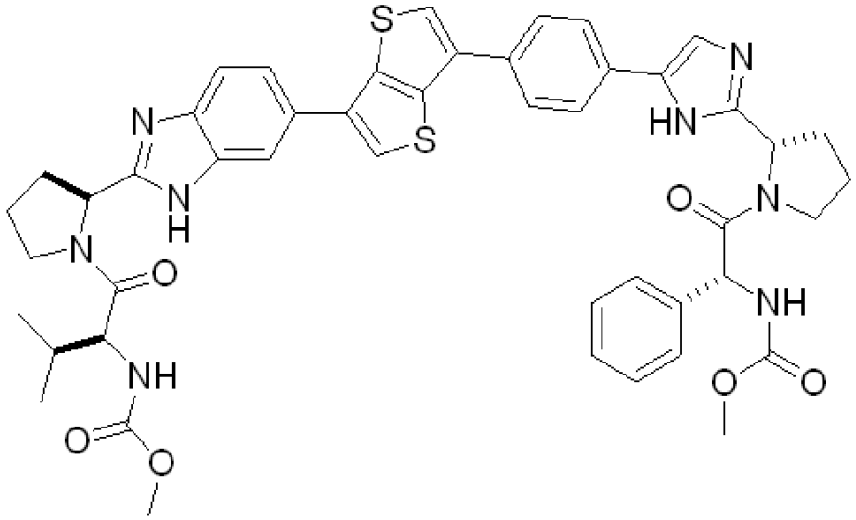
Idenix: Advancing All-Oral, Pan-Genotypic Combination HCV Regimens

- Samatasvir (IDX719) – phase II NS5A inhibitor
  - Favorable safety and potent pan-genotypic activity of samatasvir demonstrated in HCV-infected patients
  - Ongoing all-oral phase II 2-DAA HELIX-1 trial in combination with Janssen's simeprevir
  - Ongoing all-oral phase II 3-DAA HELIX-2 trial with Janssen's simeprevir and ritonavir-boosted non-nucleoside inhibitor (TMC647055)
  - All-oral phase II combination study of samatasvir and nucleotide in 2014
- IDX21437 – phase I/II nucleotide prodrug inhibitor candidate
  - Single-dose escalation in Healthy Volunteers and HCV-infected subjects is ongoing
- Multiple, earlier-stage nucleotide prodrug candidates

Idenix PHARMACEUTICALS

Samatasvir: Best-in-Class Profile Among HCV NS5A Inhibitors

- Strong preclinical profile
- Granted FDA fast track designation
- 3-Day proof-of-concept phase I/II clinical trial in 64 GT1-4 HCV-infected patients demonstrated safety and pan-genotypic activity
- Two 12-week phase II all-oral DAA combination HELIX clinical trials in collaboration with Janssen Pharmaceuticals, Inc.



Idenix PHARMACEUTICALS

Samatasvir: NS5A Inhibitor

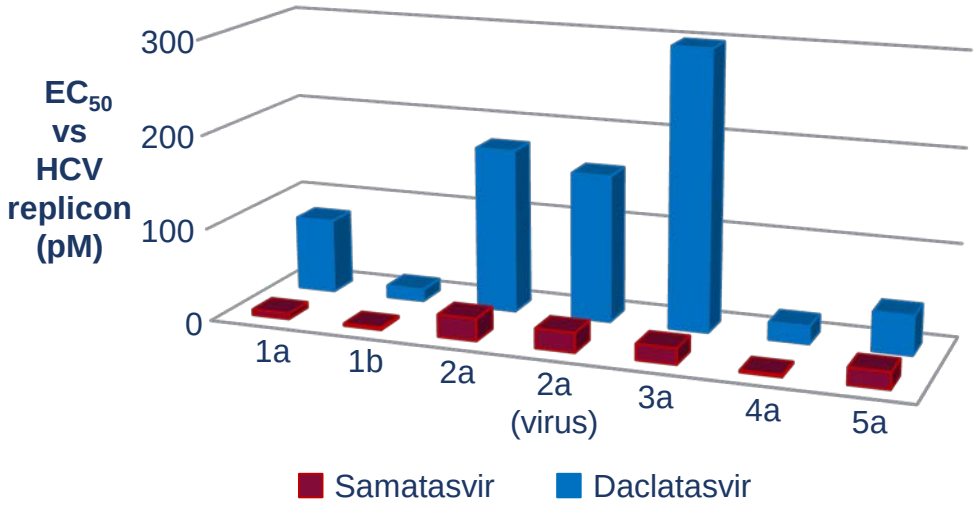
Promising Profile for Combination Therapy

- Clean preclinical safety profile
- Potential for low mg doses and QD dosing in humans
- No *in vitro* interaction with 7 human CYP 450 enzymes at 10 µM (well above physiologic concentrations)
- No significant interaction with human transporters at physiologic concentrations
- Additive antiviral effects with other HCV DAAs
- No *in vitro* DDIs with common HBV and HIV therapeutic agents

Idenix PHARMACEUTICALS

Samatasvir

Strong Preclinical Profile



- Potent activity against genotypes 1a, 1b, 2a, 3a, 4a and 5a with high selectivity indices *in vitro*
  - 2-24 pM activity overall

Idenix PHARMACEUTICALS

Samatasvir Phase I/II Clinical Trial

Potent and Pan-genotypic in 3-Day Proof-of-Concept Study

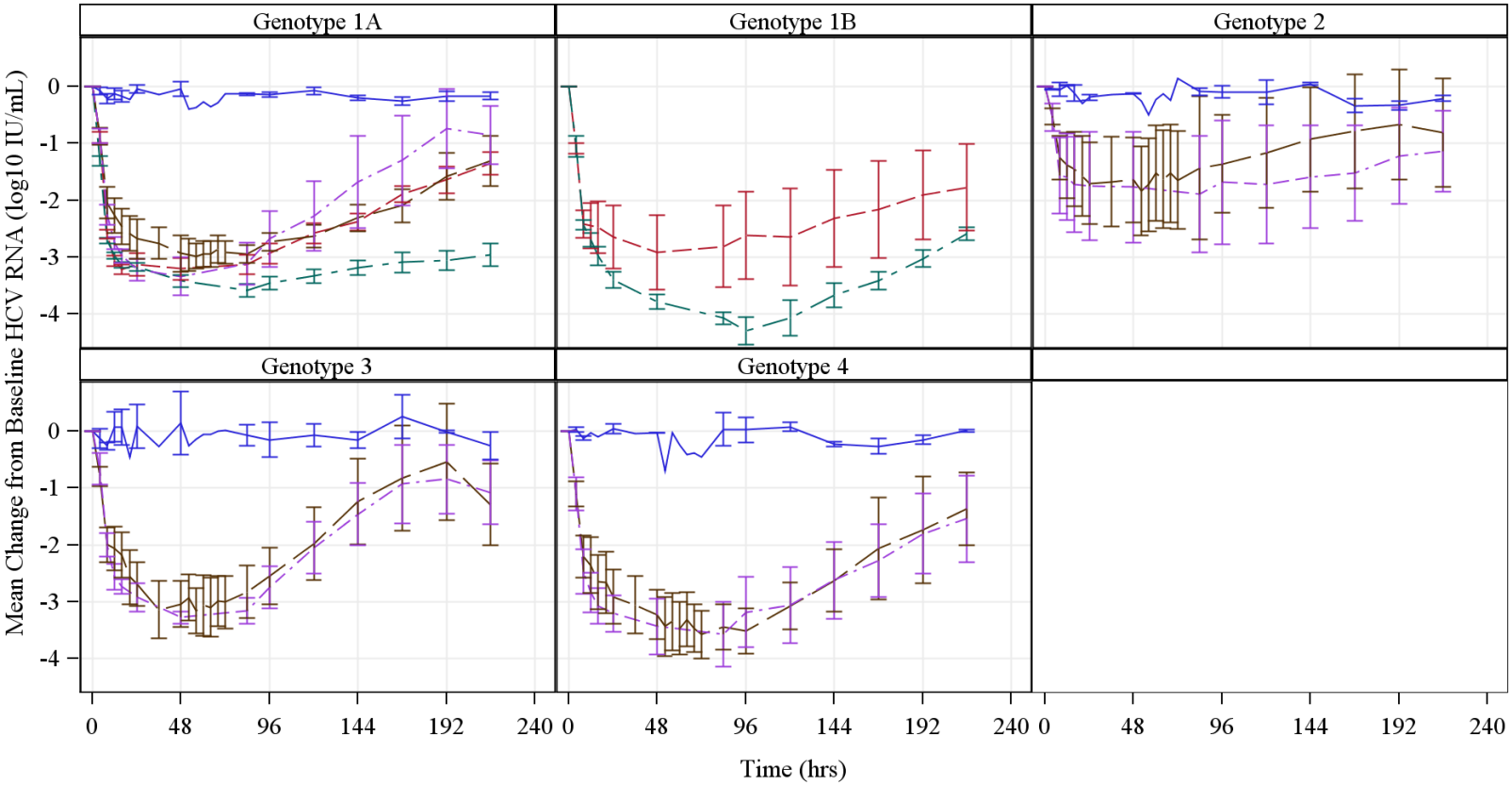
- Three-day proof-of-concept clinical trial in 64 HCV-infected patients
  - GT 1 patients: placebo, 25 mg QD, 50 mg QD, 50 mg BID or 100 mg QD
  - GT 2, 3 or 4 patients: placebo, 50 mg BID or 100 mg QD
- Well-tolerated with no treatment-emergent serious adverse events reported and no safety-related discontinuations
- Potent antiviral activity across genotypes GT1-4 in HCV-infected patients with mean maximal viral load reductions up to ~4.0 $\log_{10}$ IU/mL

Dose	Mean Maximum Viral Load Reduction				
	GT1a n=23	GT1b n=5	GT2 n=8	GT3 n=8	GT4 n=8
25 mg QD	3.3 $\log_{10}$	3.0 $\log_{10}$	--	--	--
50 mg QD	3.6 $\log_{10}$	4.3 $\log_{10}$	--	--	--
50 mg BID	3.2 $\log_{10}$	--	2.0 $\log_{10}$	3.3 $\log_{10}$	3.9 $\log_{10}$
100 mg QD	3.5 $\log_{10}$	--	2.0 $\log_{10}$	3.4 $\log_{10}$	3.6 $\log_{10}$

Idenix PHARMACEUTICALS

Samatasvir Phase I/II Clinical Trial

3-Day Proof-of-Concept Antiviral Activity in GT 1-4 HCV-Infected Patients

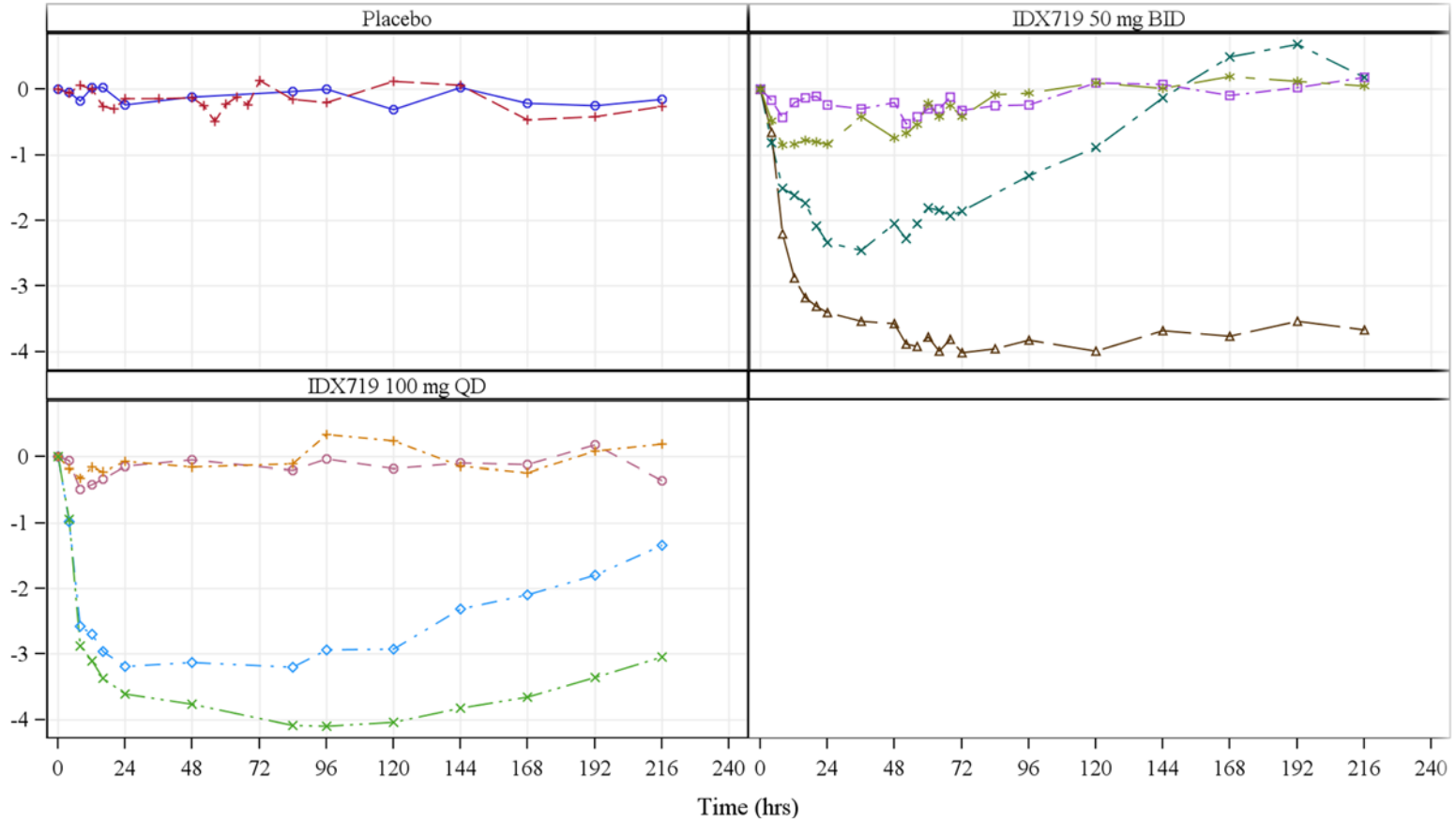


Idenix PHARMACEUTICALS

Samatasvir Phase I/II Clinical Trial

3-Day Proof-of-Concept Antiviral Activity in GT 2 HCV-Infected Patients

Individual antiviral activity in genotype 2 HCV-infected subjects

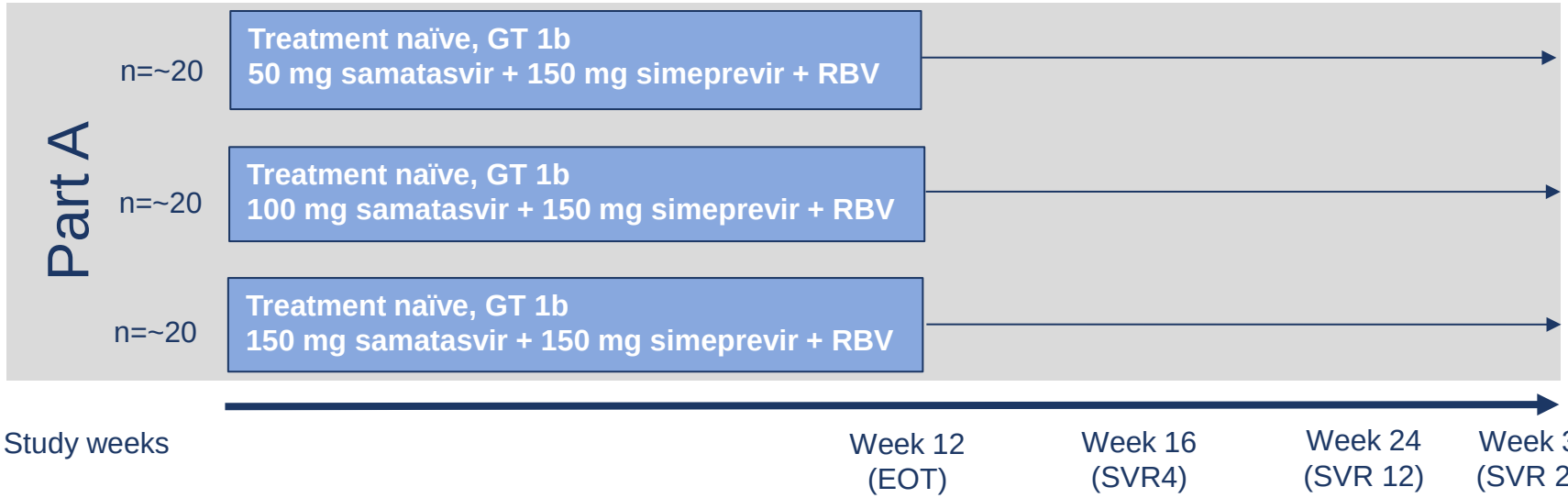


- M31 NS5A Polymorphism was associated with reduced antiviral responses in GT 2 but not GT 4-infected subjects

Idenix PHARMACEUTICALS

HELIX-1 Clinical Trial Design

All-oral 12-week 2-DAA Combination Regimen

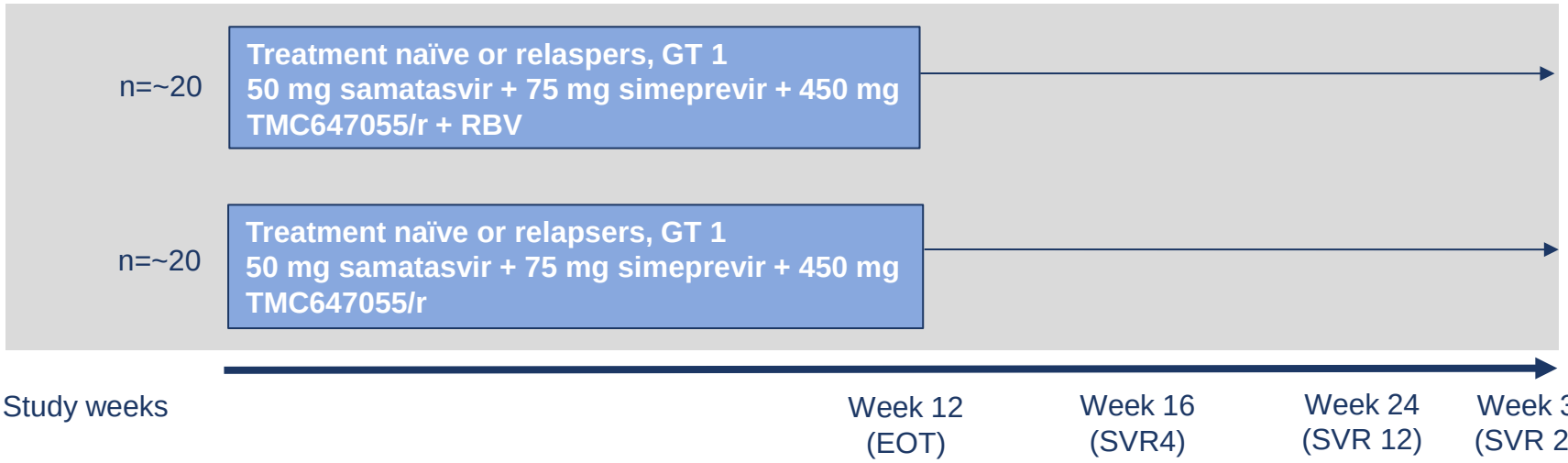


- Part B is currently enrolling exploratory arms designed to evaluate safety and antiviral activity of simeprevir and ribavirin combined with:
  - 25 mg dose of samatasvir in GT 1b-infected patients
  - 100 mg dose of samatasvir in GT 6-infected patients
  - 100 mg dose of samatasvir in additional GT 1b-infected patients
- Objectives: safety and tolerability, efficacy (primary SVR_4 with supportive SVR_{12} and SVR_{24}), pharmacokinetics and pharmacodynamics, emergence of resistance

Idenix PHARMACEUTICALS

HELIX-2 Clinical Trial Design

All-oral 12-week 3-DAA Combination Regimen



- Additional exploratory arms may be added to evaluate safety and antiviral activity
- Objectives: safety and tolerability, efficacy (primary SVR_4 with supportive SVR_{12} and SVR_{24}) , pharmacokinetics and pharmacodynamics, emergence of resistance

Idenix PHARMACEUTICALS

Novel Nucleotide Prodrug Discovery Program

- Identify promising compounds *in vitro* and in mouse and monkey
  - Triphosphate production, kinetics of metabolism, favorable safety, cytotoxicity
  - Levels of TP in the liver after oral administration *in vivo*
- Explored diverse spectrum of nucleotides
  - Purines and pyrimidines, known and novel prodrugs, and 2' Me sugars and some novel sugars
- Strong intellectual property position
  - Covering diverse range of candidate compounds in R&D pipeline
- NUC discovery capability also can be applied to non-HCV therapeutic areas
  - External interest in screening library
  - Restructured Novartis agreement allows flexibility to explore other indications

Idenix PHARMACEUTICALS

IDX21437: Next-Generation Uridine Nucleotide Prodrug

Phase *I/II clinical trial ongoing*

- Single-dose escalation in Healthy Volunteers and HCV-infected subjects ongoing
- Potent, pan-genotypic activity *in vitro;* high liver triphosphate levels generated *in vivo*
  - Potential for high potency at low once-daily doses in the clinic
  - Suitable for fixed-dose combination with samatasvir and other DAAs
- Favorable preclinical safety profile
  - Preclinical toxicology profile to date provides good safety margins for anticipated clinical doses
  - Clean genotoxicity and cardiac safety assessments to date

Idenix PHARMACEUTICALS

IDX21437: Phase I/II Clinical Trial Design

- A phase I/II study assessing single and multiple doses of IDX21437 in healthy volunteers and HCV-infected patients

Single Dose

- Healthy Volunteers IDX21437 monotherapy
- Treatment naïve, GT 1 IDX21437 monotherapy
- Treatment naïve, GT 1, Cirrhotic IDX21437 monotherapy (1 dose)

Multiple Dose (7-day)

- Healthy Volunteers IDX21437 monotherapy (1 dose)
- Treatment naïve, GT 1 IDX21437 monotherapy
- Treatment naïve, GT 2-6 IDX21437 monotherapy
- Treatment naïve, GT 1, Cirrhotic IDX21437 monotherapy (1 dose)

Idenix PHARMACEUTICALS

Summary/Conclusions

- Samatasvir has been safe and well tolerated after single and multiple doses of up to 150 mg in healthy volunteers up to 14 days duration, and in HCV-infected patients up to 12 weeks duration
- Samatasvir proof-of-concept study in HCV GT 1 – 4-infected patients showed potent, pan-genotypic activity with mean maximal viral load reductions up to approximately 4.0 $\log_{10}$ IU/mL
- *In vitro* results for samatasvir were predictive of *in vivo* antiviral activity
- All-oral 12-week phase II combination studies including samatasvir in collaboration with Janssen ongoing
- Initiation of 12-week combination studies of samatasvir and IDX21437 planned in 2014

Acknowledgments

- Idenix Montpellier
  - Medicinal Chemistry team
  - Clinical team
- Idenix Cambridge
  - Clinical team
  - Biology team
  - DMPK team
  - CMC team
- With special thanks to all of our investigators and patients who participated in our clinical trials of samatasvir

Idenix PHARMACEUTICALS