Development update

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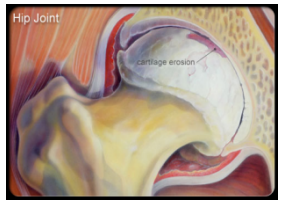
Topics to be discussed

- Osteoarthritis
  - MIV-711 – phase I data
- Simeprevir - today and tomorrow
  - Overview of available and expected clinical data
  - Regulatory status and process
  - Interferon free opportunities

MIV-711 - A cathepsin K inhibitor for osteoarthritis (OA) and other bone related disorders

Mechanism of action

- Cathepsin K degrades collagen in both bone and cartilage
- Pathological processes in both cartilage and bone occur in OA
- Genetic, animal and human data shows that cathepsin K inhibition improves bone quality



Phase I study recently finished

- Placebo controlled, double-blind study in healthy subjects
- Ascending single and multiple (7 - 28 days) once daily dosing
- Included biomarkers for bone and cartilage turnover
- Multiple dose data recently presented*
- Partnering activities initiated aiming for partnership for further clinical development

MIV-711 is a potent and selective cathepsin K inhibitor that is efficacious in preclinical models of osteoarthritis

* American Society for Bone and Mineral Research, Baltimore, 4 -7 Oct 2013

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Once daily MIV-711 demonstrated favorable safety, tolerability, and pharmacokinetics in Phase I

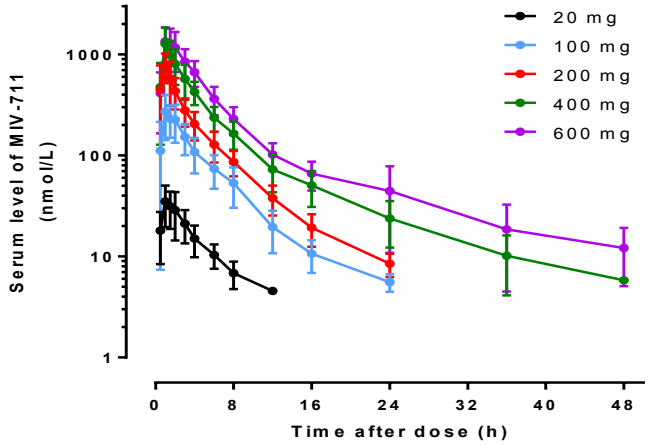
Safety & tolerability:

- MIV-711 was generally well tolerated with no significant changes in haematology, clinical chemistry, vital signs or ECG parameters (50 – 200mg, OD for 7 – 28 days)
- Overall incidence of drug-related adverse events was similar across all dose levels and was comparable to placebo.

Pharmacokinetics:

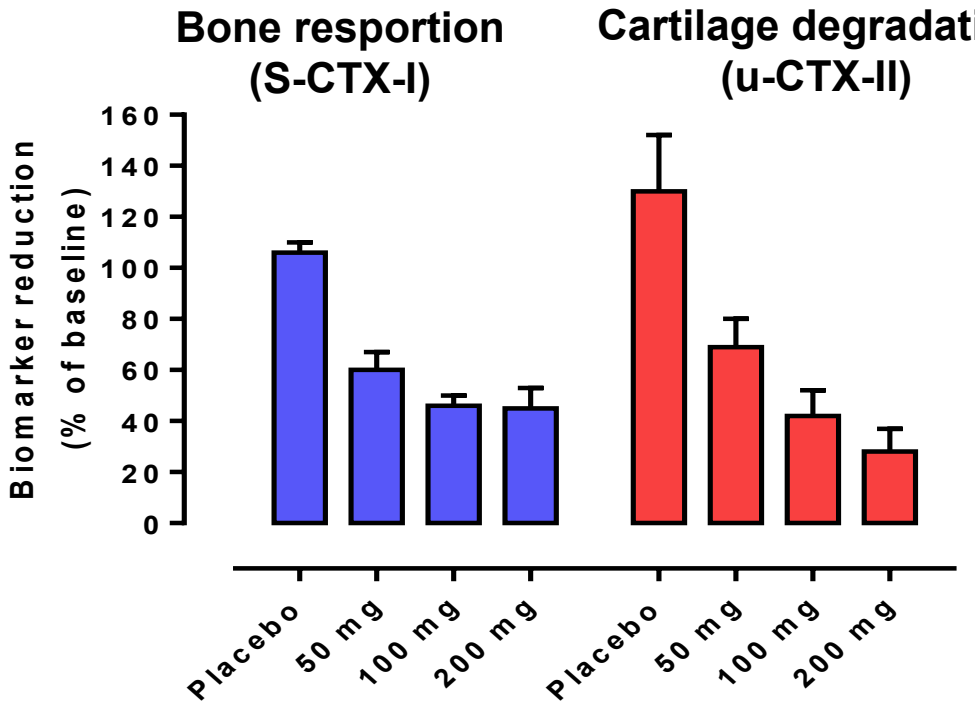
•MIV-711 was rapidly absorbed with an elimination half life of approx. 4 hours

•Mean Cmax values and AUC increased in a slightly more than proportional manner over the 50 to 200 mg OD dose range



Single dose data presented at the ECTS annual meeting Lisbon May, 2013

MIV-711 Phase I: potent effects on cartilage and bone turnover of once daily MIV-711 over 7 days



Mean ± SEM
n = 6-7

MIV-711 showed dose-dependent reduction in markers of both cartilage degradation and bone resorption

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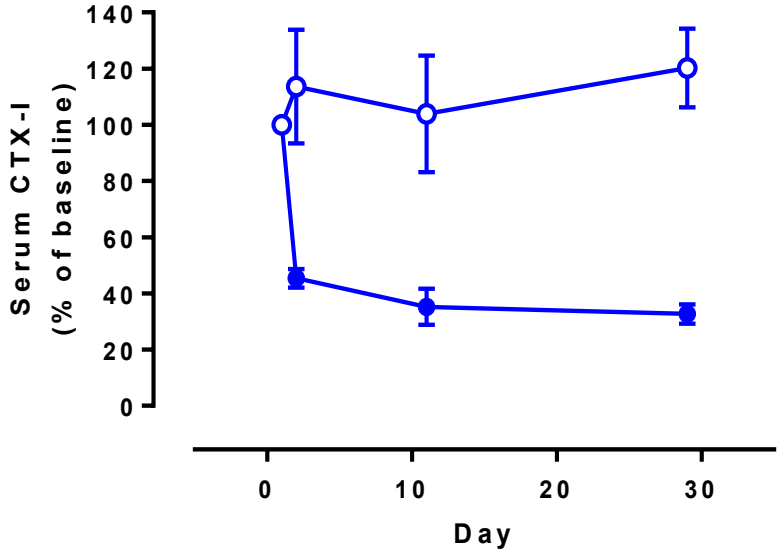
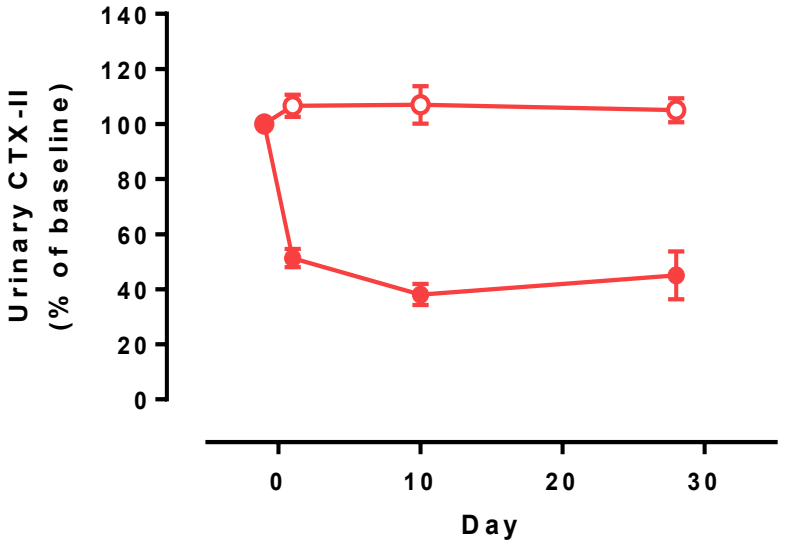
MIV-711 Phase I: reduced cartilage and bone turnover in post-menopausal women (100 mg for 28 days)

Bone resportion (S-CTX-I)



Cartilage degradation (u-CTX-II)



Clinical data support further development of MIV-711 for osteoarthritis and other bone related disorders

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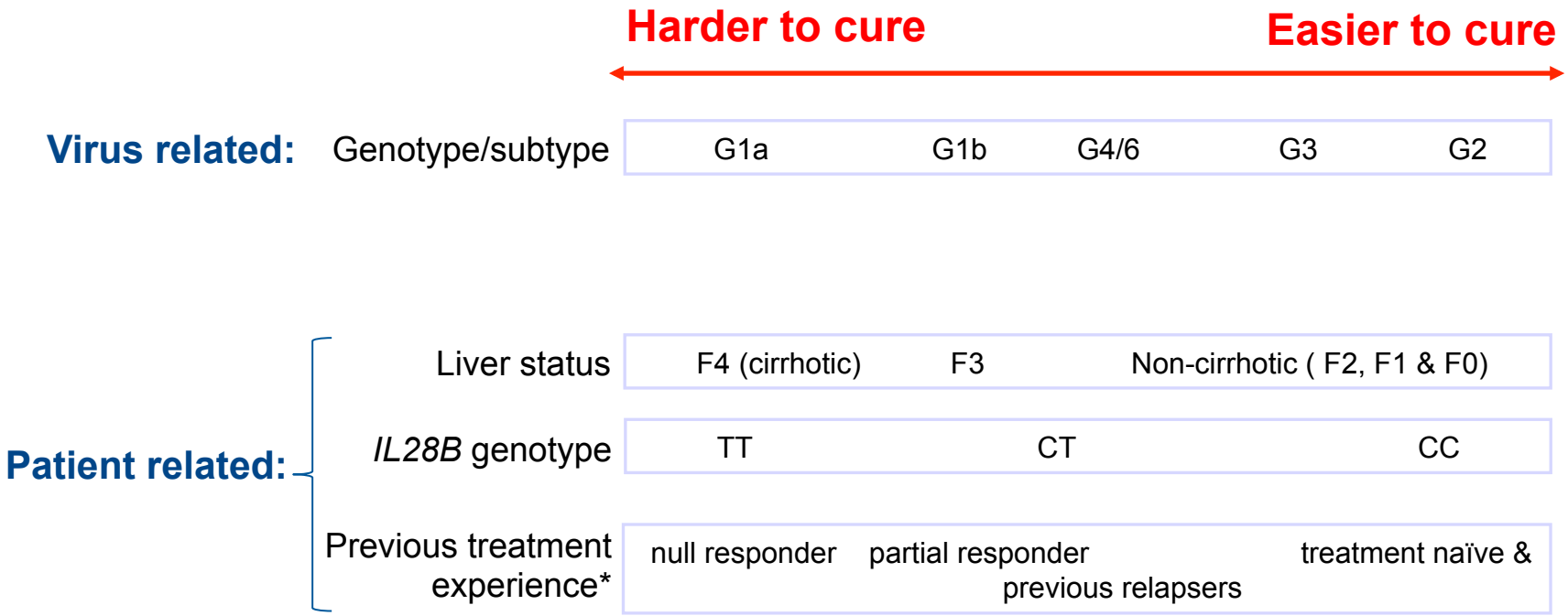
Hepatitis C

A viral infection of the liver which often leads to advanced liver disease and may cause cirrhosis and cancer

Variability in patient response to hepatitis C treatment creates a complex picture for clinicians



Treatment success: measured as Sustained Virological Response 12 weeks after end of treatment (SVR12)

*interferon +/- ribivirin

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Hepatitis C treatment is undergoing a period of rapid transformation

Before mid-2011: IFN/ribavirin for 48 weeks (genotype 1)

- 40 – 50 % cure rates with cumbersome side effects:
  - PegIFN: neuropsychiatric, influenza-like symptoms, bone-marrow suppression
  - Ribavirin: anemia, mutagenic and teratogenic

Mid-2011 to 2013: 1st generation protease inhibitors added on to IFN/ribavirin

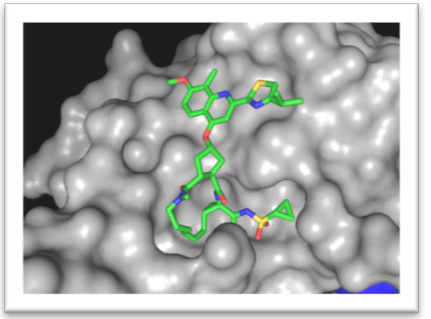
- Increased cure rates to 75 – 79%, shortened treatment to 24-48 weeks, but added safety issues and inconvenient dosing:
  - Telaprevir: rash (sometimes severe), pruritus, nausea, anemia,
  - Boceprevir: anemia

2014 - : Next generation DAAs (incl. simprevir) and IFN-free combinations

- Increased cure rates 80%+, shortened treatment to 12-24-48 weeks
- Departure from IFN-based therapy should drive higher treatment rates, easier patient management, and increased patient satisfaction

Simeprevir

Simeprevir: a next generation HCV protease inhibitor



- Approved in Japan with a broad label
- Under review in US and EU
- Activities underway to expand commercial opportunity of triple regimen
- An important cornerstone in coming IFN free treatment options
    - currently studied in a large number of IFN and ribavirin free combinations

Simeprevir – High cure rates in broad patient populations and a favorable safety profile

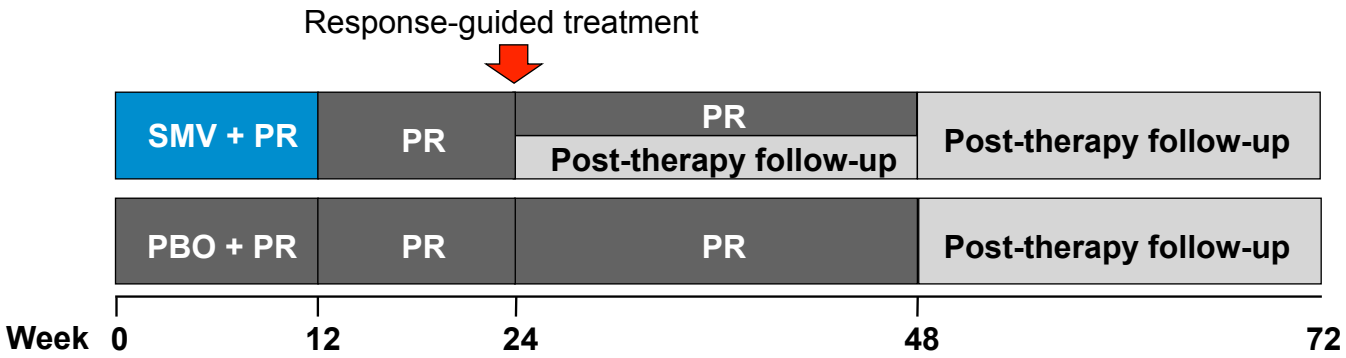
Simeprevir – pivotal phase III studies in genotype 1 HCV infected patients

Global program

- **QUEST 1** treatment-naïve (n=394)
- **QUEST 2** treatment-naïve (n=391)
- **PROMISE** prior relapsers (n=393)

Japan

- **CONCERTO 1-4** treatment naïve & experienced, four studies



SMV: simeprevir; PR: PEG-interferon + ribavirin; PBO: placebo

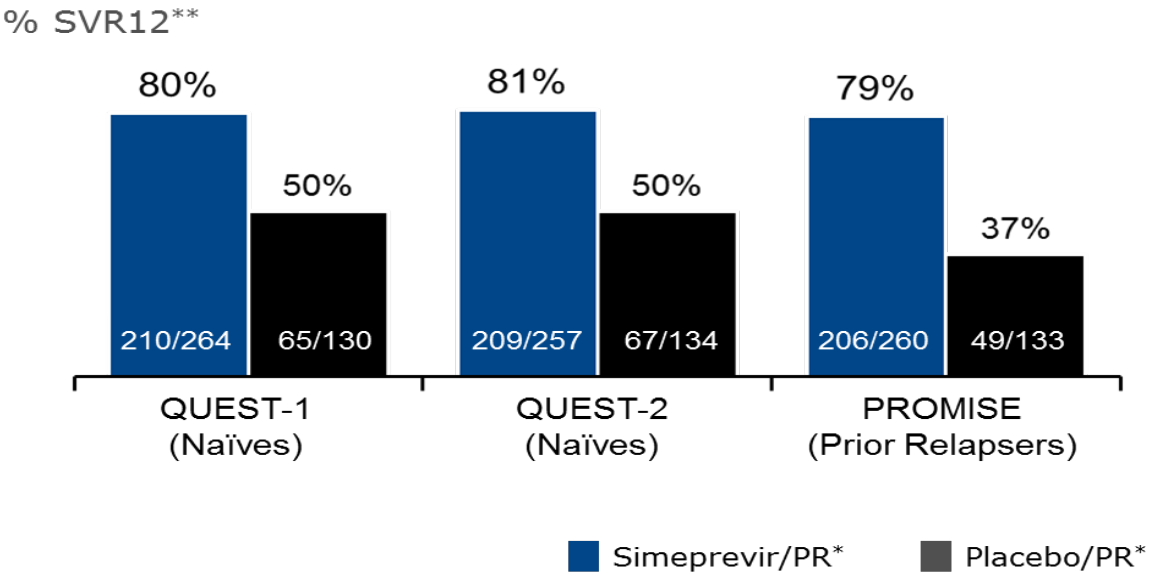
Simeprevir

Global phase III studies - efficacy

Simeprevir - pivotal global phase III studies highlight differentiated profile

Excellent efficacy, safety and tolerability in phase III (150 mg, OD)

- ~80% overall cure rates
- up to 91% could stop all treatment at 24 weeks (83-91% cured)
- comparable adverse event profile to IFN/ribavirin



Simeprevir showed robust overall efficacy in all studies

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**SVR12; Sustained Virologic Response 12 weeks (cure rate)
*PR; Peginterferon/ribavirin

High cure rates even in difficult-to-cure sub-groups of treatment-naive patients (QUEST-1 and-2)

	Cure rate (SVR12) %		Week 4 response (RVR) %	SVR12 in those who achieved RVR %
	SMV + PR	PBO + PR	SMV + PR	SMV + PR
All patients	*80**	*50*	*78*	*90*
METAVIR F4	60*	34	67	75
IL28B TT	61*	21	69	77
HCV GT 1a overall	75*	47	72	87
HCV GT 1a with Q80K	58*	47**	63	79

Early treatment response (undetectable HCV RNA at Week 4) predicts high cure rates

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*p<0.05 for all comparisons SMV vs PBO; ** pooled placebo, includes all GT1a patients
SMV: simeprevir; PR; Peginterferon/ribavirin; RVR: Rapid Virologic Response

High cure rates in difficult-to-cure sub-groups of prior relapsed patients (PROMISE)

	Cure rate (SVR12) %	
	SMV + PR	PBO + PR
All patients	*79**	*37*
METAVIR F4	74*	26
IL28B TT	65*	19
HCV GT 1a overall	70*	28
HCV GT 1a with Q80K	47*	28**

Clinical benefit with simeprevir across different sub-populations of patients who relapsed after previous treatment

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*p<0.001 SMV vs PBO; ** pooled placebo, includes all GT 1a patients
SMV: simeprevir; PR; Peginterferon/ribavirin

Simeprevir

Global phase III studies - safety

Simeprevir triple therapy has comparable AEs and discontinuation rates to IFN/ribavirin

Patients, %	QUEST-1[1]		QUEST-2[2]		PROMISE[3]	
	SMV + PR (N=264)	PBO + PR (N=130)	SMV + PR (N=257)	PBO + PR (N=134)	SMV + PR (N=260)	PBO + PR (N=133)
Grade 3 or 4 AE	23	29	26	24	20	21
Serious AE	3	4	2	2	1	2
AE leading to discontinuation of SMV	3	3	2	1	0	0
Most common AEs[4]						
Fatigue	40	38	35	39	32	42
Headache	31	37	37	34	32	36
Rash (any type)	27	25	24	11	18	14
Pruritus	21	11	19	15	24	16
Pyrexia			30	36		
Influenza-like illness			26	26	30	20
Other AEs of interest						
Increased bilirubin	9	4			6	2
Photosensitivity	3	1	4	1	4	0
Anemia	16	11	14	16	11	6
Neutropenia	19	11			15	16

Overall incidence of adverse events was similar to placebo control

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[1]Jacobson I *et al*. EASL 2013; [2]Manns M *et al*. EASL 2013; [3]Lawitz *et al* DDW 2013;
SMV: simeprevir; PR: PEG-interferon + ribavirin; PBO: placebo
[4] ≥25% in SMV arm in either study

Simeprevir

Phase III program in Japan

Four Simeprevir phase III studies in Japan provide robust data set

Patient population	% SVR12 (n/N)	Study
Treatment naive	**89** (109/123)* **92** (22/24)	Concerto-1 and -4
Prior relapser	**96** (47/49) **100** (29/29)	Concerto-3 and -4
Prior non-responders	**53** (28/53) **39** (10/26)	Concerto-2 and -4

* vs 62% (37/60) in placebo group

Simeprevir has been approved in Japan with a broad label

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Additional phase III studies of simeprevir triple therapy to enhance commercial profile

Regional expansion - China

- A pivotal study of Efficacy, Safety & Tolerability and Pharmacokinetics in treatment naive GT1 HCV patients *(fully enrolled; n=444)*

Patient population expansion

- **HIV/HCV co-infected patients**
  - Interim results: 77% SVR12 (10/13) in naïve/relapser patients (final results at EACS, Brussels, Oct 18th)
- **Genotype 4 HCV infected patients**
  - Interim results to be presented at EACS, Brussels, Oct 18th

Shortened treatment duration

- **12 weeks full stop triple combination study,** open-label, single-arm study in treatment naïve GT1 patients
  - Recruitment ongoing

Simeprevir regulatory status and process

EU

- **Marketing Authorisation Application submitted on April 24th**
  - Adult patients with chronic hepatitis C genotype 1 or 4 with compensated liver disease (including cirrhosis), with or without HIV-1 co-infection, who are treatment naive or who have failed previous interferon therapy

US

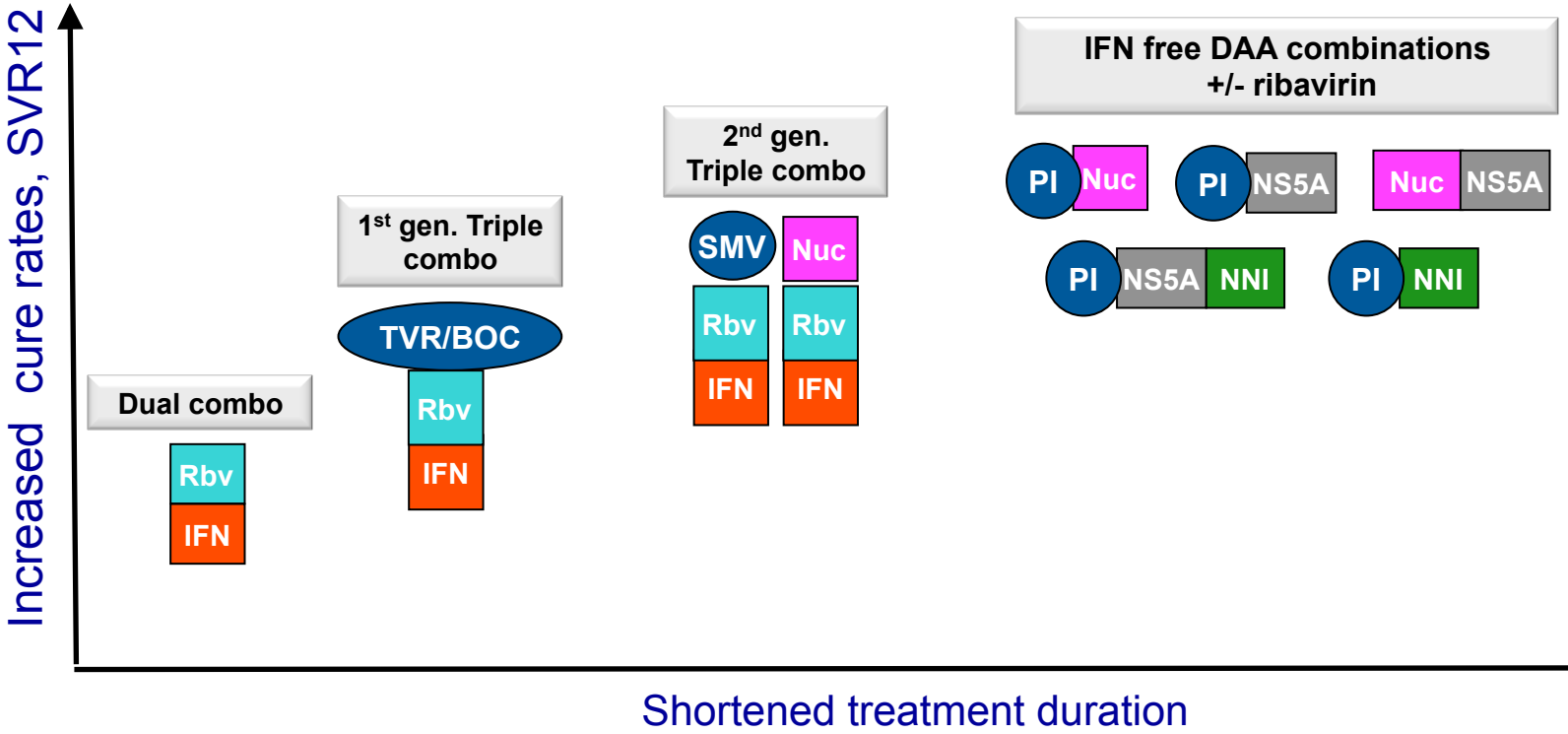
- **New Drug Application (NDA) filed March 28th**
  - In combination with pegylated interferon and ribavirin for the treatment of GT 1 chronic hepatitis C in adult patients

- **FDA Advisory Committee scheduled for October 24th**
  - FDA identify questions where advice from external experts on areas of scientific uncertainty is needed
  - Usually heavy scrutiny of potential safety concerns or gaps in data sets
  - Background material is provided from the FDA and the Sponsor and is made public in advance (usually two days prior to the meeting)
  - The recommendations from the AdCom are not binding

Simeprevir

- A cornerstone in future all oral interferon free treatments

We are in the late stages of the evolution to all oral, interferon-free treatment



Different combinations of direct acting antivirals (DAAs) have shown good efficacy in various patient populations

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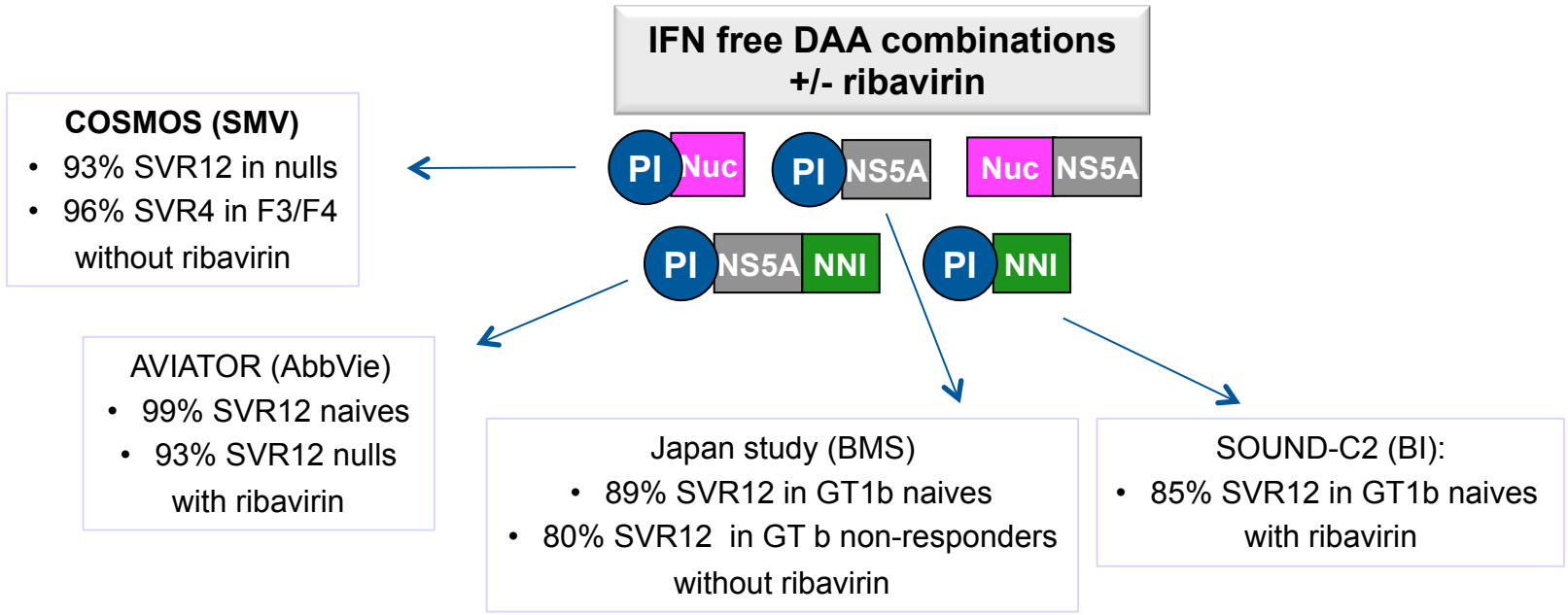
SVR12; Sustained Virologic Response 12 weeks (cure rate)
IFN: Peginterferon; Rbv: ribavirin; Nuc: nucleotide; NS5A; NS5A inhibitor;
NNI: non-nucleotide inhibitor; TVR: telaprevir; BOC: boceprevir

Data driven approach to exploring different interferon free simeprevir combinations (with or w/o ribavirin)

Simeprevir given in combination with:	Investigational compound	Study informtation
Nucleotide	Sofosbuvir	**COSMOS**: Cohort A: nulls ; Cohort B: nulls + naives (F3&4)
	VX-135	DDI finished, Ph II to start H213
NS5A inhibitor	Daclatasvir	Naives and nulls, F0-F4
	Samatasvir	HELIX-1: Phase II on-going (Gt1b and 4)
NS5A inhibitor + NNI	TMC647055 + Samatasvir	HELIX-2 to start, DDI ongoing
	TMC647055 + **GSK2336805**	Phase II, in planning phase
+ NNI	TMC647055	Naives/relapser and nulls

Phase II data of various PI based combinations have shown promising results



PI: Protease inhbitor; Nuc: nucleotide;
NS5A: NS5A inhibitor; NNI: non-nucleotide inhibitor;

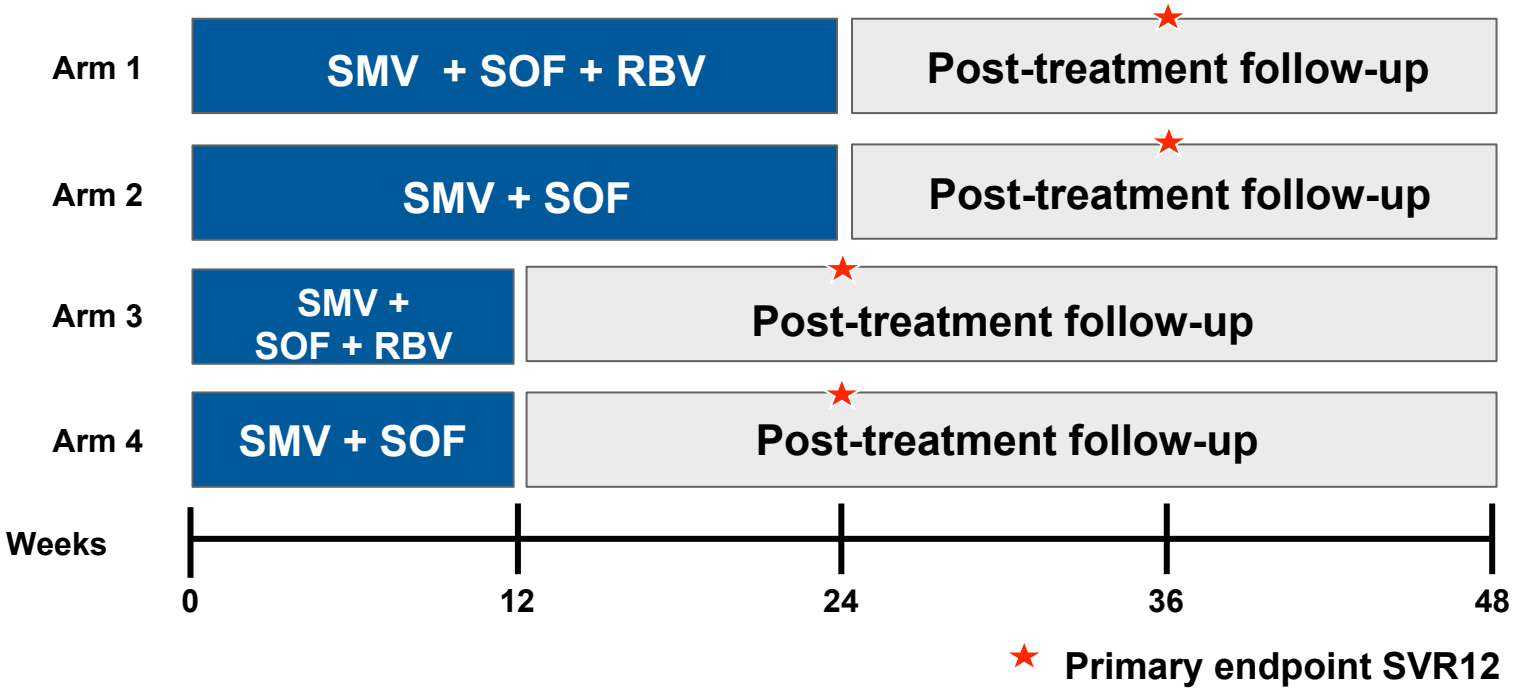
COSMOS Study

(interim analysis)

Once-daily regimen of simeprevir plus sofosbuvir with or without ribavirin in hard to cure HCV patients*

*The **COSMOS** study**: CO**mbination of **SiM**eprevir and s**O**fosbuvir in HCV infected patie**ntS**

COSMOS study was the first in a series of collaborative studies for DAA combinations



- Cohort 1: n=80, nulls, F0-F2
- Cohort 2: n=87, naives and nulls, F3-F4
- SMV 150 mg QD + SOF 400 mg QD with/without RBV

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COSMOS study – interim results show very high cure rates, even without ribavirin

	Cohort 1 Null responders (METAVIR F0-F2)		Cohort 2 Null responder and treatment naïve (METAVIR F3 or F4)	
	SMV / SOF+ RBV (n=27)	SMV / SOF (n=14)	SMV / SOF + RBV (n=27)	SMV / SOF (n=14)
SVR4	26/27 (96%)	13/14 (93%)	26/27* (96%)	14/14** (100%)
SVR12	26/27 (96%)	13/14 (93%)	-	-
SVR12 (GT1a Q80K positive)	8/9 (89%)	5/6 (83%)	-	-

*null responders 14/15 (93%) ** null responders 7/7 (100%)

- ***High efficacy in hardest to cure HCV patients also without ribavirin***
- ***Once-daily simeprevir and sofosbuvir was generally safe and well tolerated***

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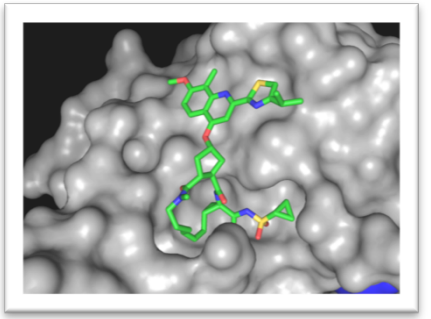
SMV: simeprevir; SOF: sofosbuvir; RBV: ribavirin
Sustained Virological Response 4 or 12 weeks (SVR4 or SVR12) after end of treatment.

Simeprevir: a next generation HCV protease inhibitor



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