Interim Analysis Projections: Sustained Viral Response (SVR) for HCV therapy

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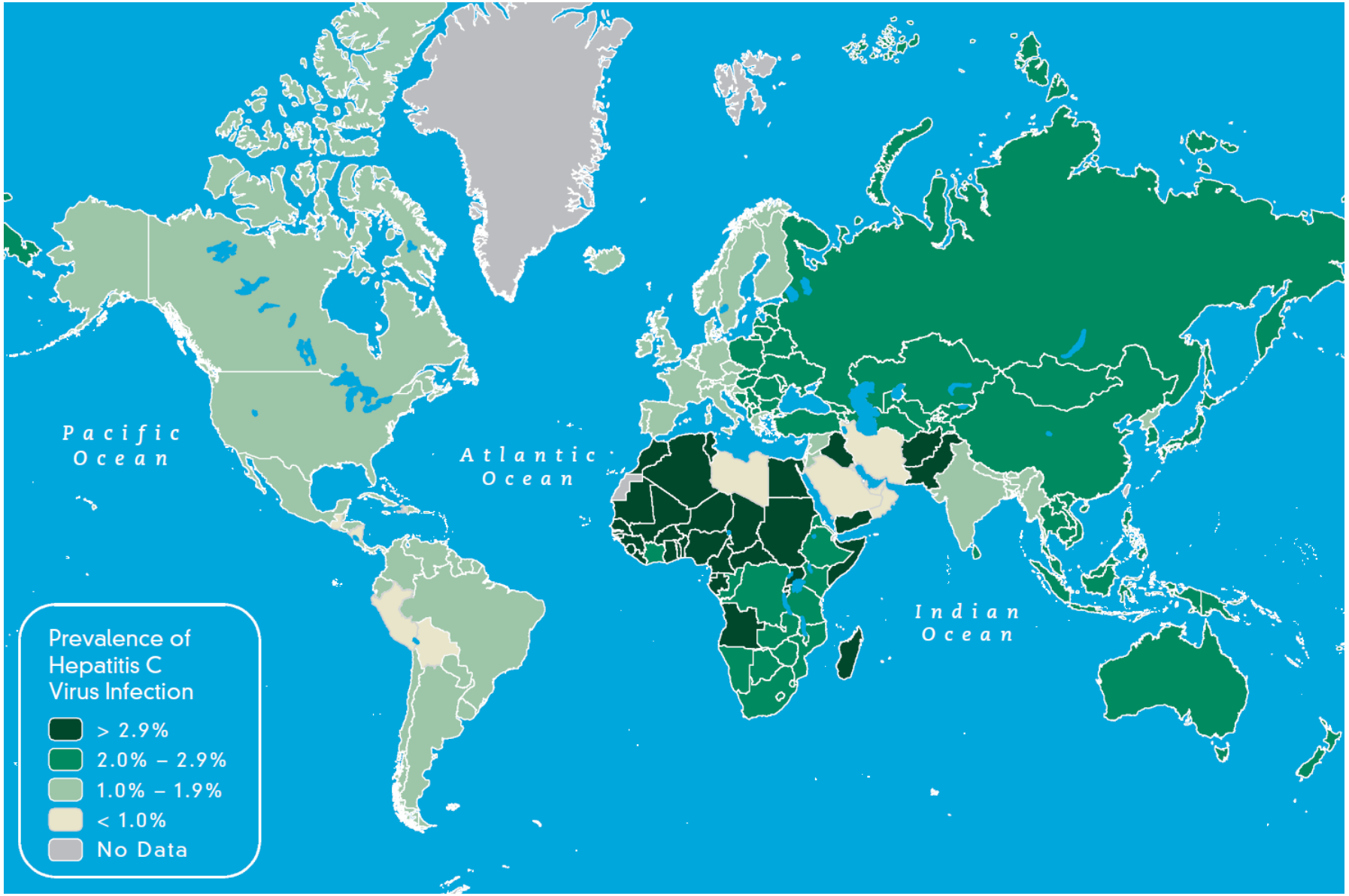
Outline

- Introduce HCV
- Clinical Study / Design factors
- Interim Analysis Modeling
- Comparison of projection results to final analysis

HCV: Hepatitis C Virus ~ 170 million worldwide



HCV consequences

~ 80% develop chronic Hep C infection

Liver Failure/ End stage liver disease: 10-20%

- risk factor, hepatocellular carinoma

HCV Compare / Contrast with HIV

HIV	HCV
Both viruses have RNA genome: • High polymerization errors comp. to DNA • Leads to drug resistance and difficult vaccine development	
Vast array of drug classes / targets	First anti-virals on market 2Q 2011 (Protease inhibitors)
Reservoirs make viral eradication difficult	A cure is possible: Sustained Viral Response: SVR_{24}

HCV Study Design Factors

At the time of the phase 2b design (pre-2011):

- Standard of Care: PEG/INF and RBV
- SVR rate about 40-50% for HCV genotype 1
- Treatment Duration: 48 weeks plus 24 weeks follow-up to achieve SVR

HCV Study : novel Direct-Acting Antiviral (nDAA)

- Non – nucleoside polymerase inhibitor
- Expected to be less potent than Protease Inhibitors but higher resistance threshold
- Expected response vs. SOC: higher SVR and faster viral suppression
- Treatment Duration (early responders): 24 weeks plus 24 weeks follow-up to achieve SVR

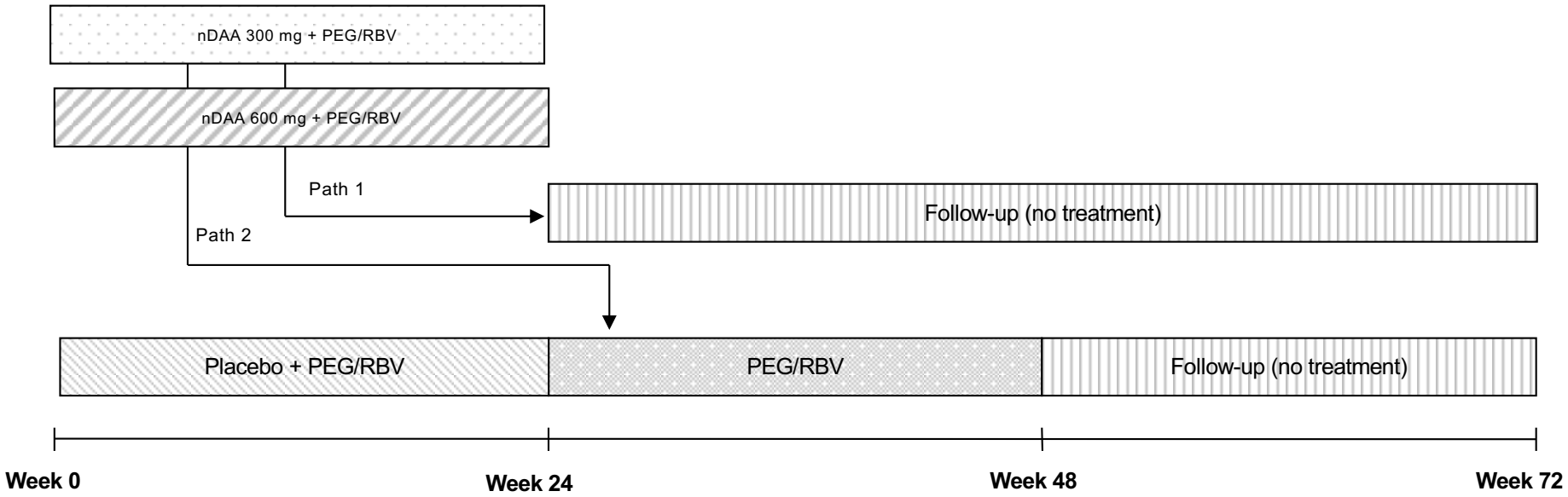
Design / Modeling Question

What is the earliest opportunity to predict the outcome of Phase 2b study to allow for Phase 3 decision / preparations?

Favorable factors:

- Less time on treatment required for nDAA
- Vast experience / data available for SOC

Study Design: Phase 2b study



Strategy

- Conduct and analyze interim data with 100% subjects completed Week 24
- Favorable factors:
  - ~50% nDAA Path 1 subjects have SVR_{12}
  - All nDAA dosing complete
- Challenges:
  - No SVR for nDAA Path 2 subjects or SOC

Interim Analysis Modeling

Methodology

Interim Model for SVR, Standard of Care (PEG IFN / RBV)

- Observed on-treatment response to Week 24
- Literature data indicates:
  - Time to undetectable viral load predicts SVR
  - Other factors conditionally not significant

Methodology: Write equation for P(SVR) as function of on-treatment response + historical data

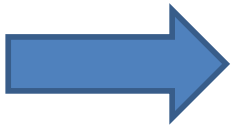
Model

$P(\text{SVR, treatment group } k)$

$$= \sum_i P(S_{i,k})\, P(\text{SVR} \mid S_{i,k})$$

Where

$S_{i,k}$ represents i^{th} response pattern



time to undetectable viral load

Model Terms for SOC

	HCV RNA undetectable at Week:			Parameters	
Response Pattern for SOC	**4**	**12**	**24**	$P(S_{i,SOC})$	$P(SVR \mid S_{i,SOC})$
$S_{1,SOC}$	✓	✓	✓	$P(S_{1,SOC})$	$P(SVR \mid S_{1,SOC})$
$S_{2,SOC}$	x	✓	✓	$P(S_{2,SOC})$	$P(SVR \mid S_{2,SOC})$
$S_{3,SOC}$	x	x	✓	$P(S_{3,SOC})$	$P(SVR \mid S_{3,SOC})$
$S_{4,SOC}$	**Other possible response patterns**			$P(S_{4,SOC})$	$P(SVR \mid S_{4,SOC})=0$

Interim Model for SVR, Standard of Care (PEG/ RBV)

$P(SVR_{SOC} \mid \text{Time to undetectable VL}) =$

$P(\text{Week 4}) * P(SVR_{SOC} \mid \text{Week 4})$

$+ \quad P(\text{Week 12}) * P(SVR_{SOC} \mid \text{Week 12})$

$+ \quad P(\text{Week 24}) * P(SVR_{SOC} \mid \text{Week 24})$

Available Information, Standard of Care (PEG/ RBV)

Study / Location	P(Wk 4)	P(SVR| Wk 4)	P(Wk 12)	P(SVR| Wk 12)	P(Wk 24)	P(SVR| Wk 24)
Ferenci 2005 International	33/298 = 0.11	30/33 = 0.91	113/298 = 0.38	79/113 = 0.70	51/298 = 0.17	23/51 = 0.45
Jensen 2006 International	55/271 = 0.20	50/55 = 0.91				
IDEAL 2009 US	83/1035 = 0.08	62/83 = 0.75	355/1035 = 0.34	250/355 = 0.70	203/1035 = 0.20	72/203 = 0.36
PROVE-2 EU	11/82 = 0.13					
PROVE-1 US	8/75 = 0.11					
Berg 2006 (RBV 800 mg)	86/455 = 0.19	43/51 = 0.84			99/455 = 0.22	17 /47 = 0.36
Sanchez-Tapias 2006 (RBV 800 mg)	80/371 = 0.22					

Interim Model for SVR

Undetectable HCV Viral Load

Week 4	Week 12	Week 24	P(Week X)	P(SVR | Wk X)
Yes	Yes	Yes	14%	83%
No	Yes	Yes	35%	70%
No	No	Yes	20%	37%

Applying naïve pooling gives P(SVR) = 44% for SOC

Model Terms for nDAA

	HCV RNA undetectable at Week:			Parameters	
Response Pattern for nDAA	**4**	**12**	**24**	$P(S_{i,\ nDAA})$	$P(SVR \mid S_{i,\ nDAA})$
$S_{1,nDAA}$	✓	✓	✓	$P(S_{1,\ nDAA})$	$P(SVR \mid S_{1,\ nDAA})$
$S_{2,\ nDAA}$	x	✓	✓	$P(S_{2,\ nDAA})$	$P(SVR \mid S_{2,\ nDAA})$
$S_{3,\ nDAA}$	**Other possible response patterns**			$P(S_{3,\ nDAA})$	$P(SVR \mid S_{3,\ nDAA})=0$

Interim Model for SVR, nDAA

$P(SVR_{nDAA} \mid \text{Time to undetectable VL}) =$

$P(\text{Week 4}) * P(SVR_{nDAA} \mid \text{Week 4})$

$+ \quad P(\text{Week 12}) * P(SVR_{nDAA} \mid \text{Week 12})$

Estimation:

- $P(SVR_{nDAA} \mid \text{Week 4})$ using SVR_{12}, Path 1
- $P(SVR_{nDAA} \mid \text{Week 12})$ using $P(SVR_{SOC} \mid \text{Week 12})$
  - Considered conservative

Interim Model for SVR

Modeling and Estimation

- Set in Bayesian framework to estimate variability

- Use multinomial and binomial distributions with Gibbs sampling to determine posterior distribution of $P(SVR_{nDAA})$, $P(SVR_{SOC})$ and difference (i.e. the treatment effect)

Model Projection Results

Interim Data used in model

Time to first undetectable VL

Treatment Group	Week 4	P(SVR|Wk4)	Week 12	Week 24
300 mg nDAA (N=94)	48 (51%)	24/34 = 71%	23 (24%)	*
600 mg nDAA (N=96)	48 (50%)	26/39 = 67%	25 (26%)	*
IFN/RBV (N=96)	25 (26%)		37 (39%)	12 (13%)

SVR Projections Based on Interim Data

Model Projections					
	nDAA 300 mg	**nDAA 600 mg**	**SOC**	**nDAA 300 mg vs. SOC**	**nDAA 600 mg vs. SOC**
Estimate (%)	53	52	54	-1	-2
95% posterior interval (%)	(41,63)	(40,62)	(40,64)	(-13,13)	(-14,11)
Final Results, Phase 2b Study					
Estimate (%)	42	40	46	-4	-6
95% CI (%)	(32,52)	(30,50)	(36,56)	(-19,11)	(-21,9)

Successful Prediction of Unsuccessful Drug

- Projections available one year before the final study results based on all subjects
- Projection analysis led to identical qualitative conclusions regarding the study outcome as final data

Examining Assumptions: SOC

		Interim	Final
Undetectable at Week	$P(S_{i,soc})$	$P(SVR \mid S_{i,soc})$	$P(SVR \mid S_{i,soc})$
4	26%	83%	68%
12	39%	70%	68%
24	13%	37%	17%

Examining Assumptions: nDAA

- Estimating $P(SVR_{nDAA} \mid \text{Week 4})$ using SVR12, Path 1

  300 mg nDAA group: good
  71 % (interim) vs. 67% (final)

  600 mg nDAA group: OK
  67 % (interim) vs. 60% (final)

- Estimating $P(SVR_{nDAA} \mid \text{Week 12})$ using $P(SVR_{SOC} \mid \text{Week 12})$

70% (historical) vs. 33% (nDAA 300 mg) and 48% (nDAA 600 mg) : BAD

More correct logic: Subjects slower to respond with more drugs actually tougher to treat and achieve viral suppression