Sustained Viral Response (SVR) Rates in Genotype 1 Treatment-naïve Patients with Chronic Hepatitis C (CHC) Infection Treated with Vaniprevir (MK-7009), a NS3/4a Protease Inhibitor, in Combination with Pegylated Interferon Alfa-2a and Ribavirin for 28 Days

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- I have financial relationships within the last 12 months relevant to my presentation with:

  Astra/Arrows, Boehringer Ingelheim, BMS, Gilead, GlaxoSmithKline, Merck, Novartis, Roche, Schering-Plough, Tibotec and Vertex

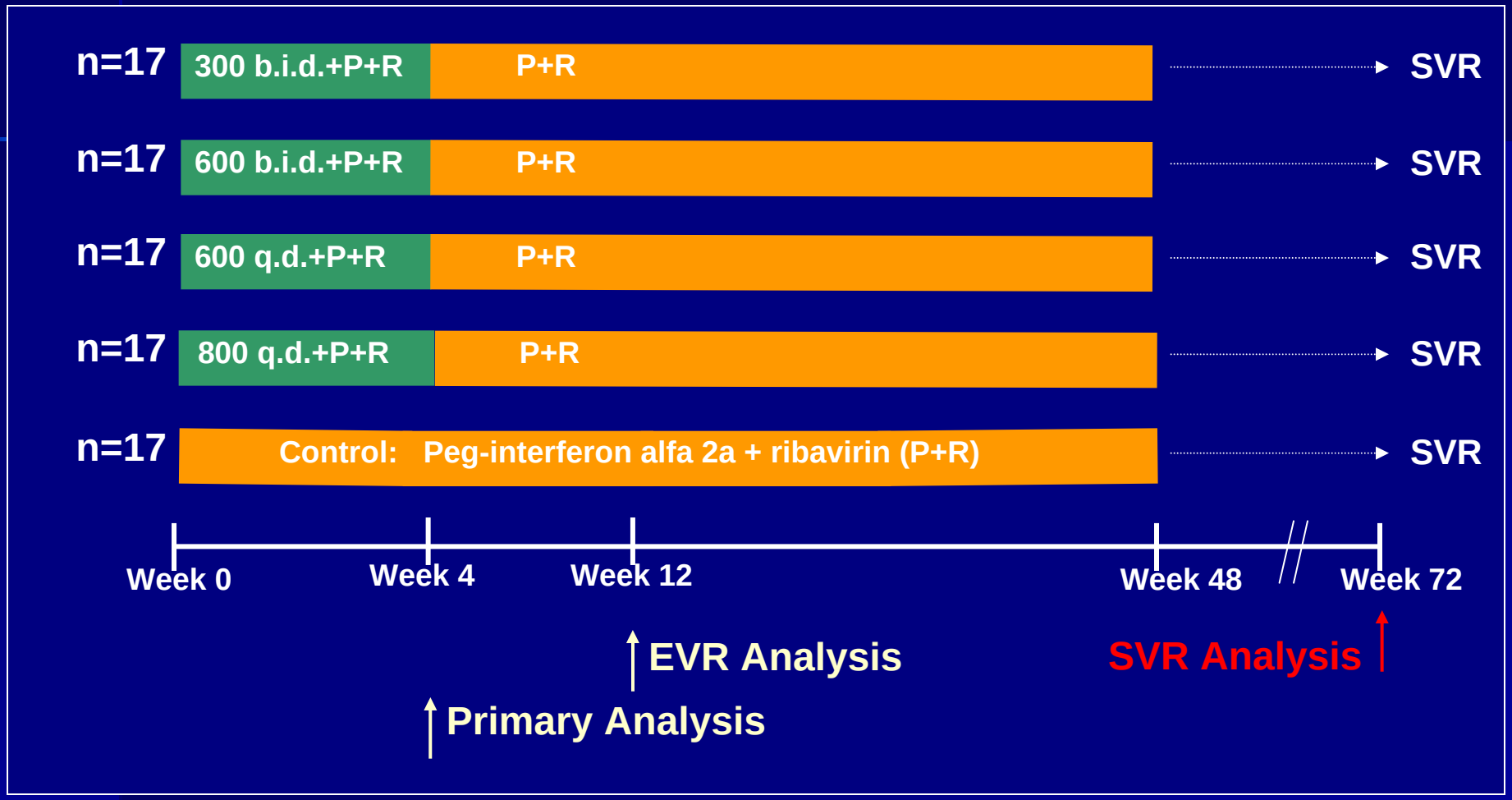
AND

My presentation does include discussion of investigational use of vaniprevir (MK-7009)

MK-7009 007: Phase IIA Study

- **Objective:**
  - Evaluate safety, tolerability and antiviral efficacy of 4 week course of MK-7009 in combination with pegylated interferon 2a and ribavirin (peg-IFN/RBV)
- **Population**
  - Treatment naïve, non-cirrhotic, HCV genotype 1 patients
  - Baseline HCV RNA $\geq 4 \times 10^5$ IU/mL
- **Overall Design**
  - randomized, placebo-controlled, double-blind, dose-ranging
  - MK-7009 was administered for 28 days with peg-IFN/RBV in 1 of 5 regimens: placebo, 300 mg bid, 600 mg bid, 600 mg qd, or 800 mg qd

Study Design



Primary hypothesis: RVR rates for at least 1 MK-7009-treated group superior to control

Selected Methods

- Safety assessments
  - Serious adverse events (SAEs) collected throughout; non-serious AEs were prompted for through day 42 only
  - laboratory and ECG assessments
- HCV RNA assessment: Roche Cobas TaqMAN 2.0
  - Limit of quantitation (LOQ): 25 IU/mL
  - Limit of detection (LOD): 10 IU/mL
- IL-28β genotype analysis: Gentris assay

Baseline Patient Characteristics

Parameter	MK-7009 300 mg bid + P+ R	MK-7009 600 mg bid + P+ R	MK-7009 600 mg qd + P+ R	MK-7009 800 mg qd + P+ R	Placebo + P+ R	Total
	(N=18)	(N=20)	(N=18)	(N=19)	(N=19)	(N=94)
Female %	22	45	61	38	42	42
Median Age	46 y	44 y	51 y	44 y	46 y	45 y
Age Range	27 to 65 y	22 to 58 y	34 to 64 y	21 to 65 y	32 to 65 y	21 to 65 y
Race: Asian %	6	5	11	11	11	9
Black %	11	15	11	5	11	11
Multi-Racial %	-	-	-	-	11	2
Pacific Islander%	6	-	6	-	5	3
White %	78	80	72	84	63	76
HCV Genotype (GT) 1a %	33	40	39	42	42	39
HCV GT 1b %	50	45	44	37	47	44
HCV GT1 nontypeable %	17	15	17	21	11	16

HCV RNA Responses at Week 4 (RVR) and Week 12 (cEVR)

MK-7009 Dose group	RVR (Full Analysis Set)	% RVR	P value (vs. pbo)	cEVR (Full Analysis Set)	% cEVR
300 mg bid	12/18	**67**	<0.001	14/18	**78**
600 mg bid	16/20	**80**	<0.001	17/20	**85**
600 mg qd	12/17	**71**	<0.001	14/18	**78**
800 mg qd	16/19	**84**	<0.001	14/19	**74**
placebo	1/19	**5**	n/a	9/19	**47**

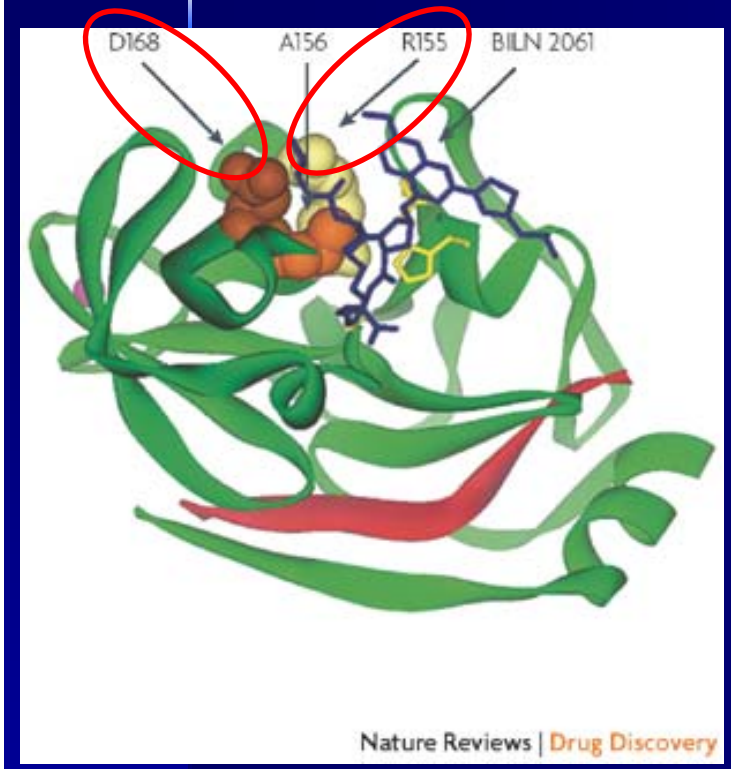
- **All of the MK-7009 dose groups had superior RVR to control (p< 0. 001), satisfying the primary efficacy hypothesis.**
- **The proportion of subjects with undetectable virus generally increased during the peg-IFN/RBV phase from week 4 (67-84%) to week 12 (74-85%)**

HCV RNA Responses at Week 4 (RVR) and 72 (SVR)

MK-7009 Dose group	RVR (Full Analysis Set)	% RVR	SVR (Full Analysis Set)	% SVR
300 mg bid	12/18	**67**	11/18	**61**
600 mg bid	16/20	**80**	16/20	**80**
600 mg qd	12/17	**71**	14/18	**78**
800 mg qd	16/19	**84**	16/19	**84**
placebo	1/19	**5**	12/19	**63**

- **SVR for QD and high BID doses of MK7009 numerically higher than placebo**
  - **Placebo SVR rate higher than expected/historical rate**

Viral Resistance Summary



- Population sequencing of NS3/4A gene was performed on subjects with HCV RNA >1000 IU/ml through day 42 of the study.
  - Clonal sequencing of the NS3 region was performed on subjects with HCV RNA >1000IU/ml through week 24 of the study
- Variants detected at positions 155 and 168
  - Consistent with published resistance variants for other NS3/4A protease inhibitors

Figure from Manns et al., 2007 *Nat Rev Drug Disc.*

Safety Overview

- No serious adverse events (SAEs) and no discontinuations due to an adverse event were observed during the first 42 days; no MK-7009-related SAEs throughout the study.
- The most common adverse events reported were headache, nausea, vomiting, fatigue, and influenza-like illness.
  - The incidence of vomiting with MK-7009 600 mg BID was higher than placebo.
  - Vomiting was mild-moderate in severity, and did not lead to discontinuation of MK-7009.
- No increase in rash adverse events over placebo were observed.
- No changes from baseline ECG were observed.
- Changes in laboratory values were as expected for peg-IFN/RBV.
  - No significant elevations in bilirubin associated with MK-7009.

Conclusions

- Addition of vaniprevir for 28 days to peg-IFN/RBV led to significantly increased RVR for all doses and numerically greater SVR rates for the majority of vaniprevir dose groups.
- Vaniprevir is well-tolerated when given in combination with peg-IFN/RBV.
  - No dose-limiting toxicity observed

A Phase IIB study of vaniprevir + peg-IFN/RBV in treatment-experienced subjects is ongoing

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