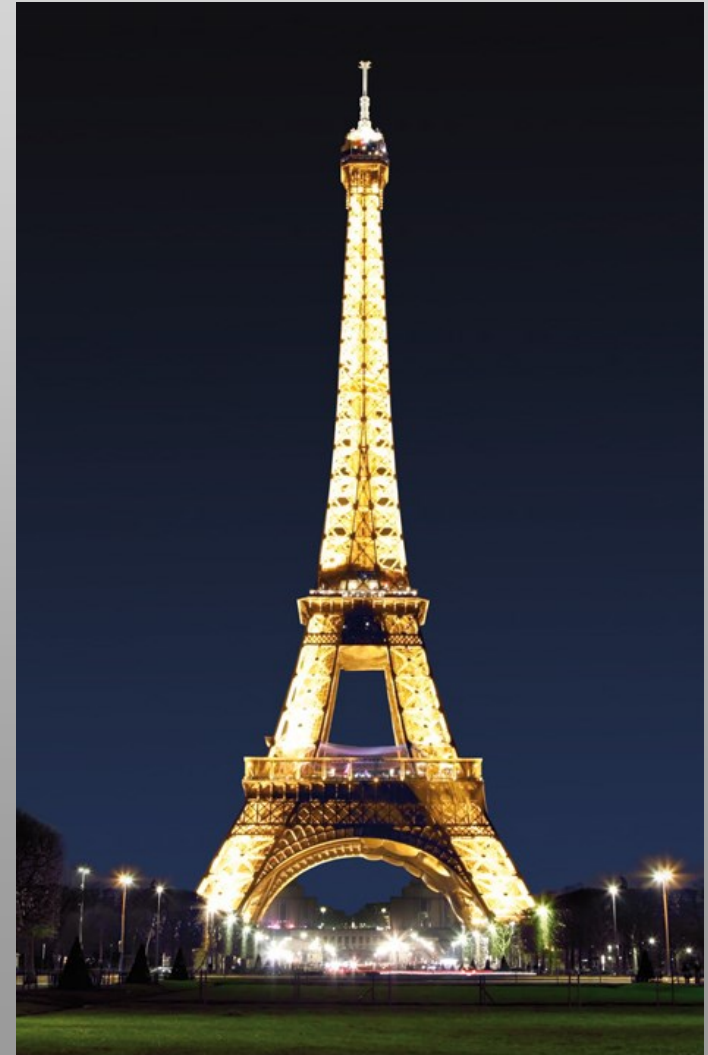


# HCV therapeutic new strategies IFN free regimens?

## Paris Hepatitis Conference

14 January 2013

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Service d' Hépatologie  
INSERM U773, CRB3  
University Paris Diderot,  
Hôpital Beaujon, Clichy



# IFN free regimens

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- **Introduction (background)**

- Direct acting antivirals (DAAs)
- IFN-free ongoing trials
- Conclusion

# Where are we : The present

## Advantages of Triple therapy: PI + PEG-IFN + RBV

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- Increased Efficacy in G1 patients ( $\Delta > 25\%$ )
  - G1 naive patients
  - G1 relapsers
- Shorten duration ( $\approx 50\%$ )
- Predictors of non response
  - Cirrhosis
  - Subtype 1a
  - IL28B

# Where we are : The present

## Limitations of Triple therapy

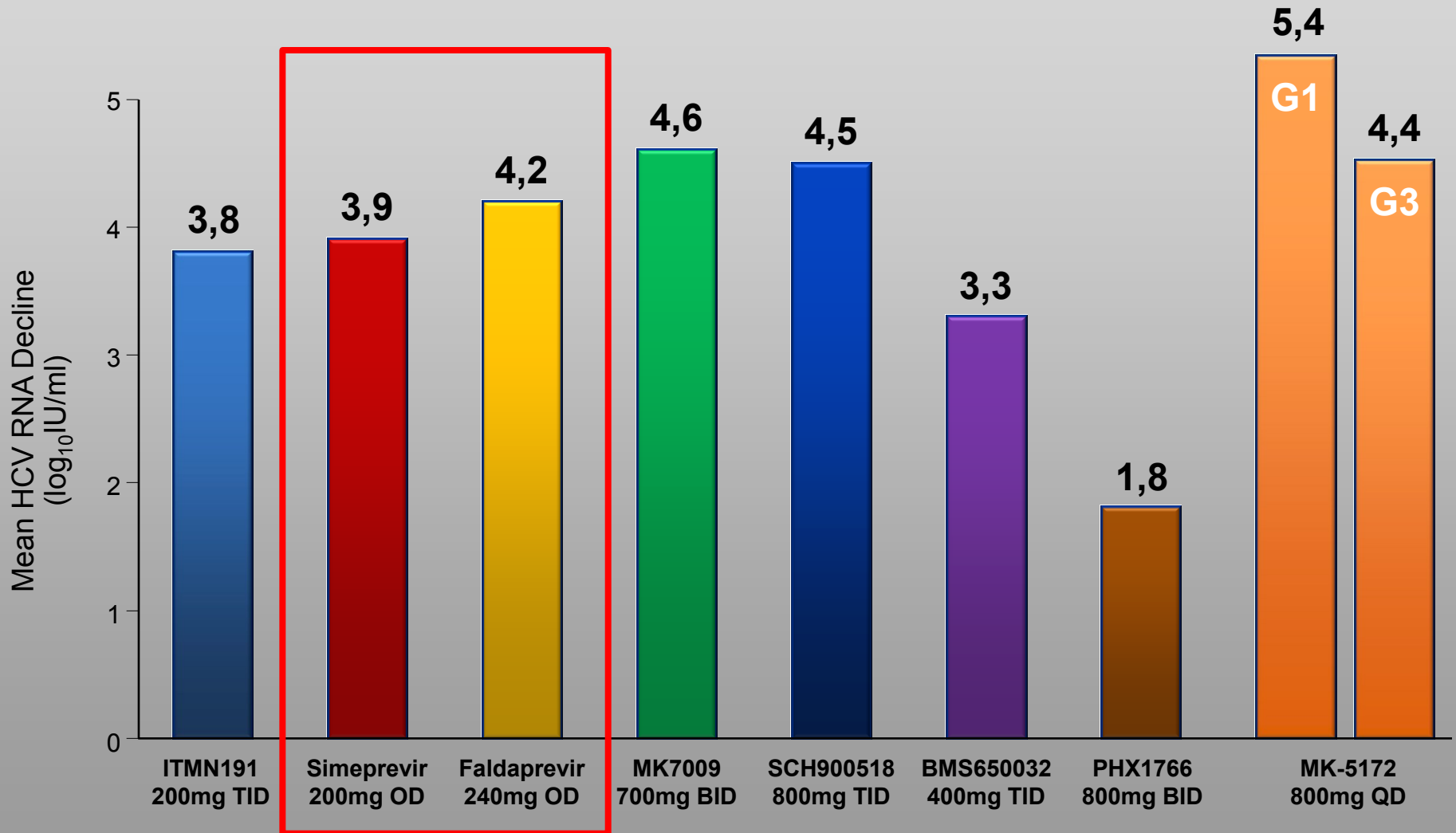
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- Efficacy approved only in G1 patients
- Low SVR in difficult to treat patients
  - Cirrhosis
  - Previous null responders
- Side Effects
- Costs



## New Generation DAAs

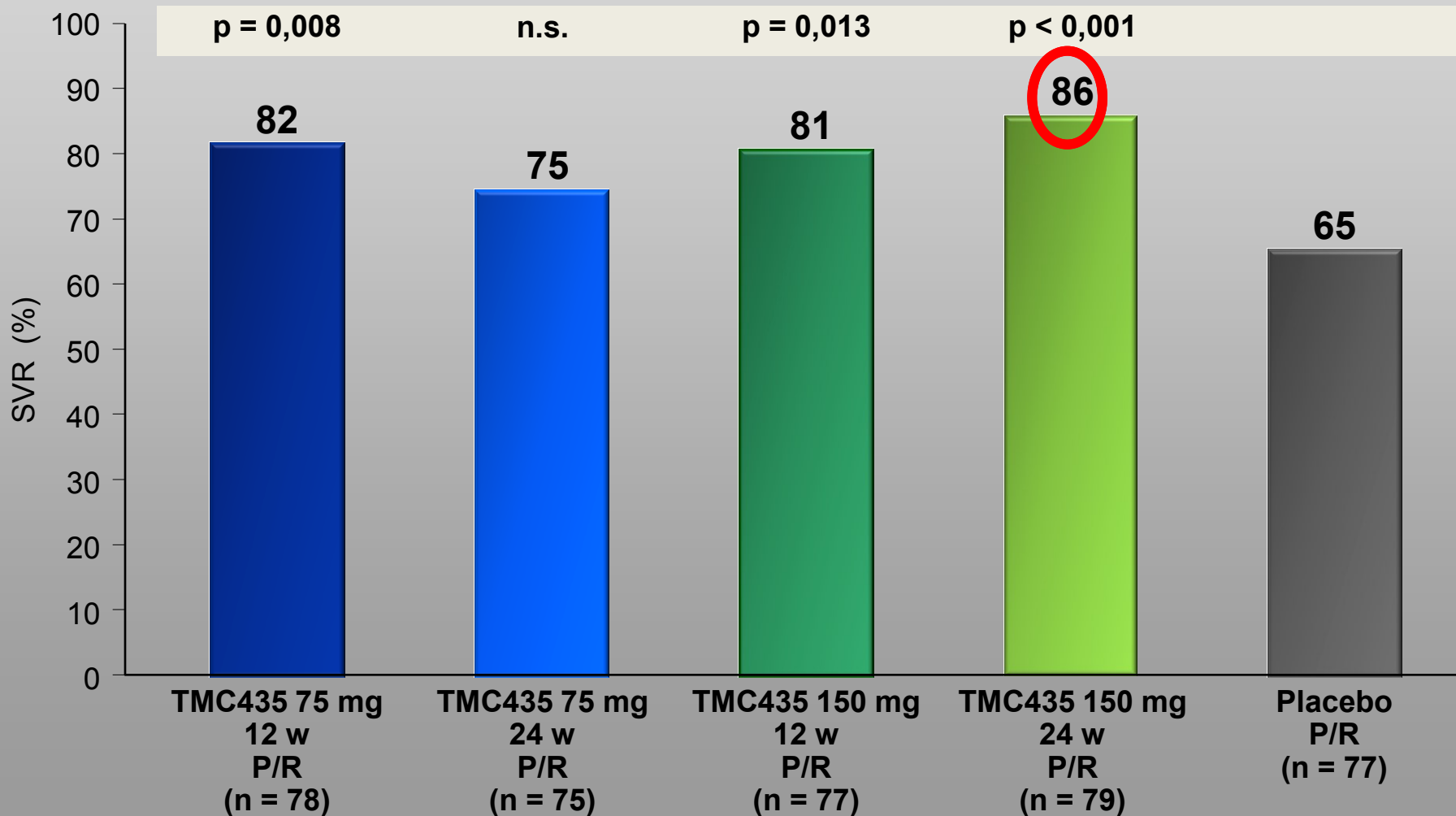
# Protease inhibitors in development



# Simeprevir (TMC435)

(Janssen)

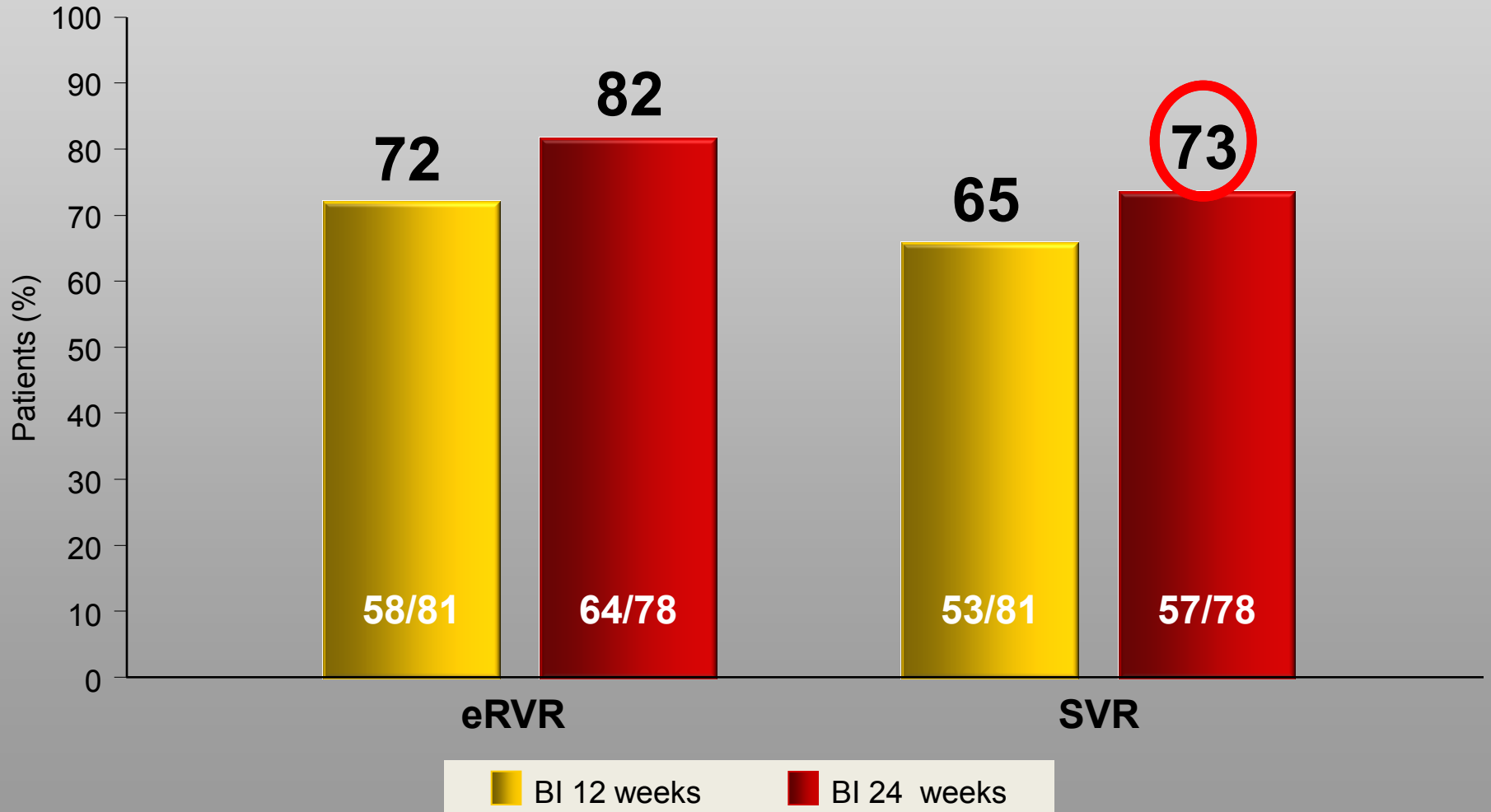
## G1 naive



# Faldaprevir (BI201335)

(Boehringer-Ingelheim)

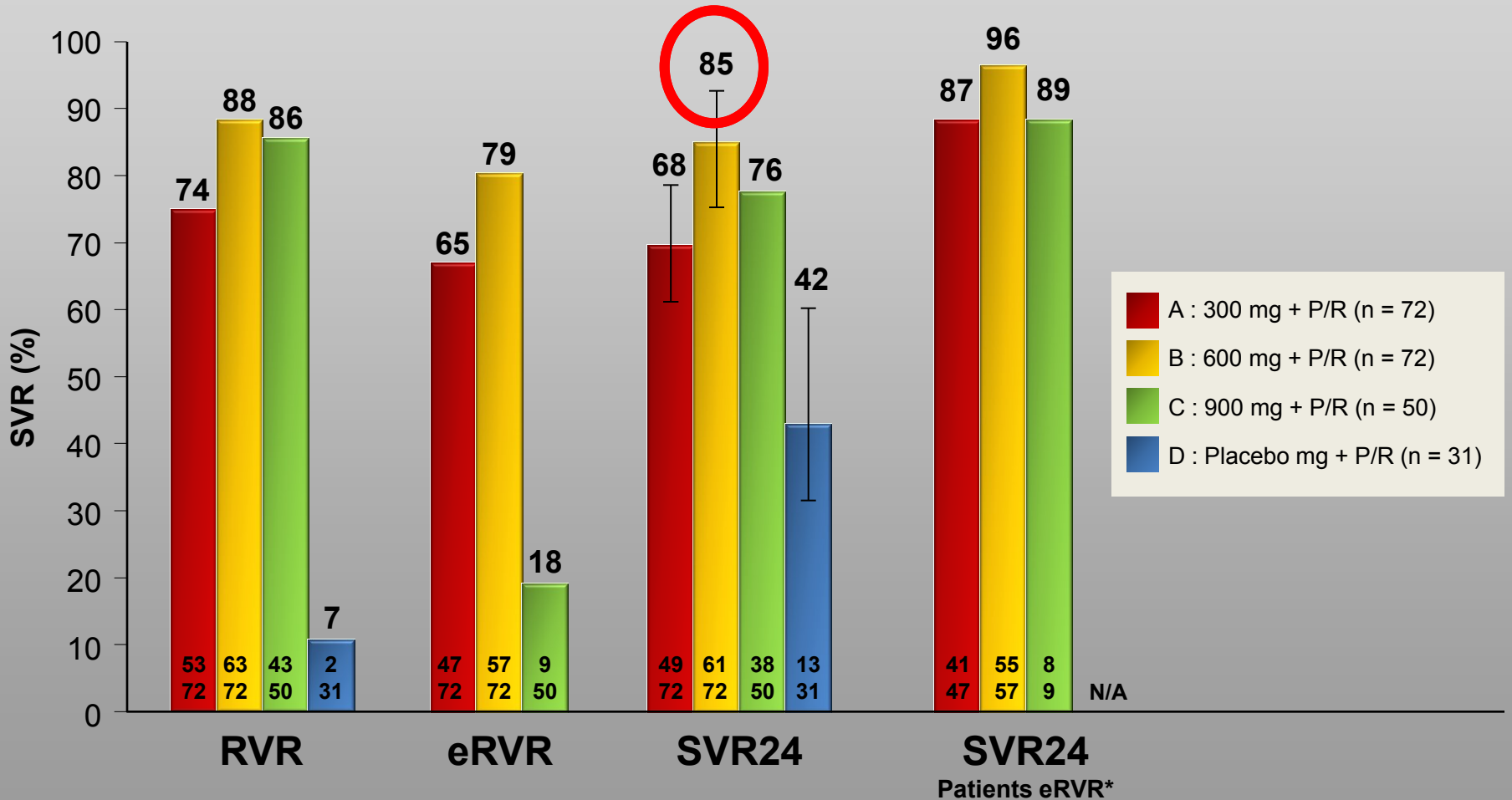
## G1 naive



# Danoprevir (DNO, RG7227)

(Roche)

## G1 naive



\*Patients RVRe : patients with HCV RNA undetectable from W4 to W20

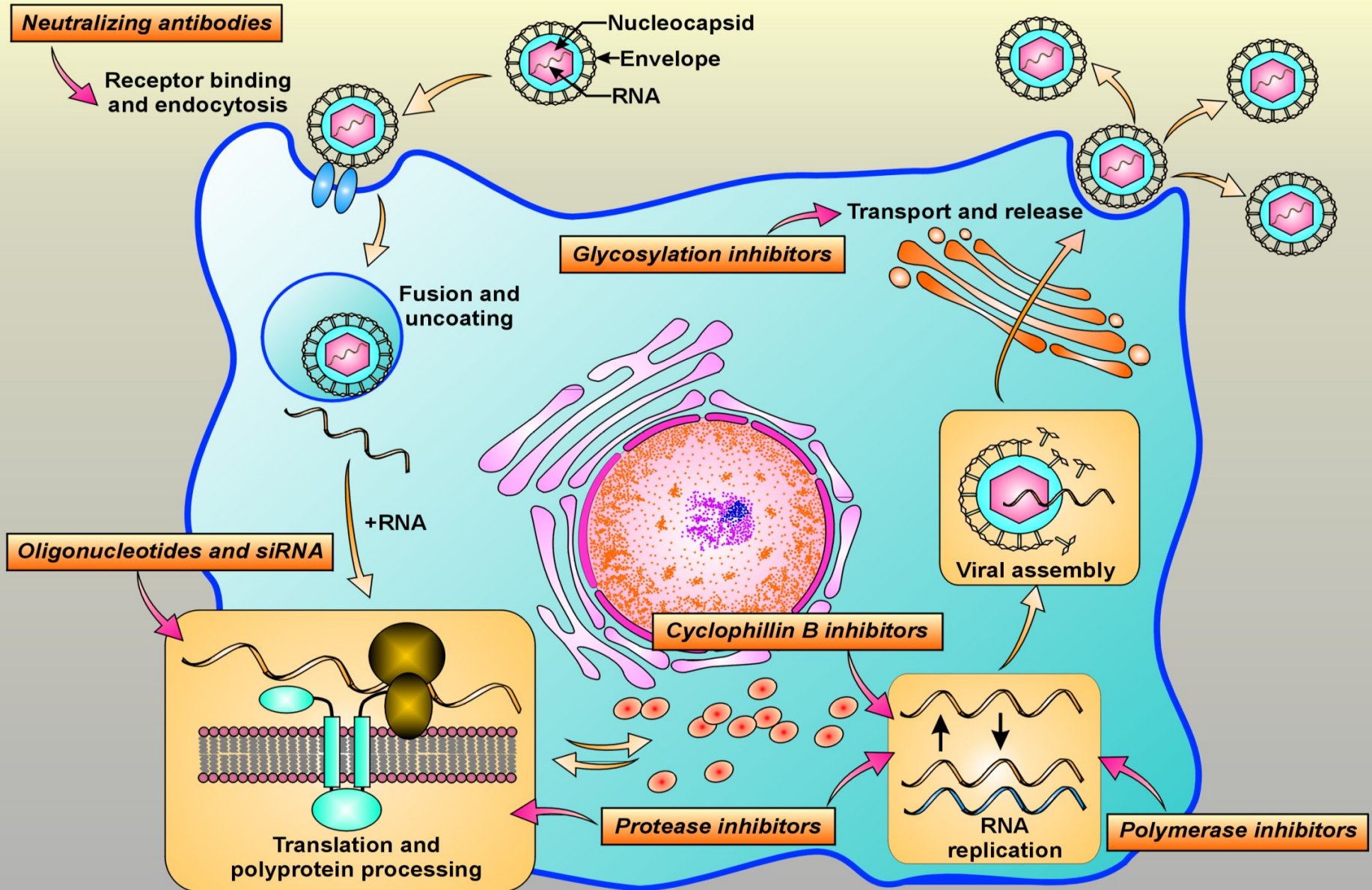


# IFN free regimens

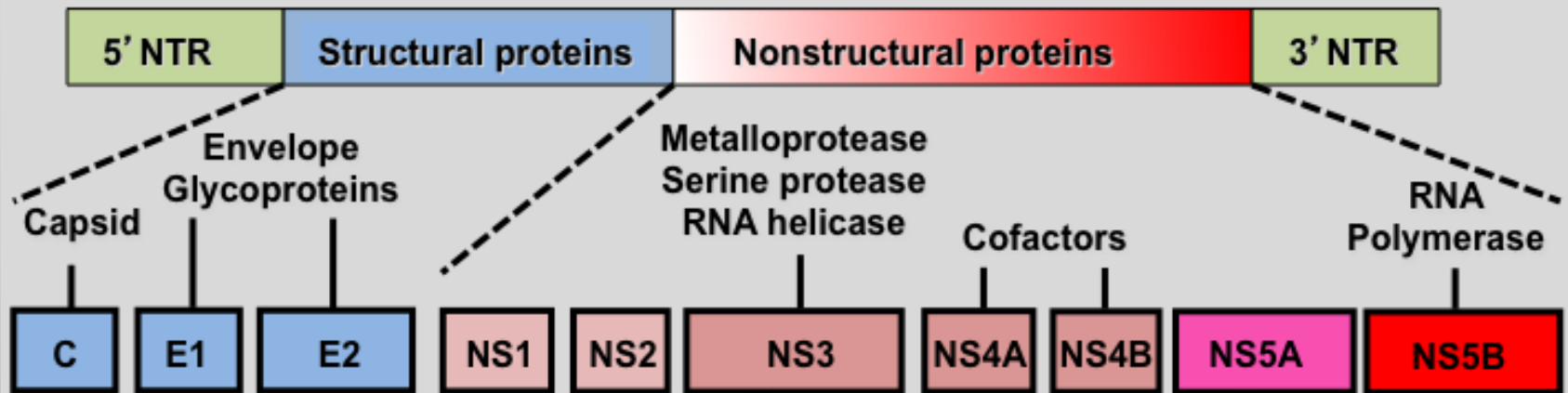
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- Introduction (background)
- **Direct acting antivirals (DAAs)**
- IFN-free ongoing trials
- Conclusion

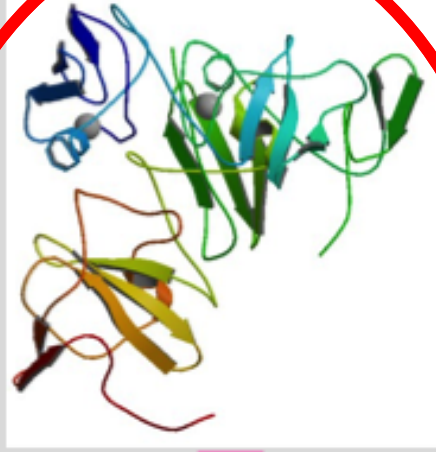
# Viral cycle and drug targets



# Direct-acting antivirals



**NS3/4A  
Protease  
Inhibitors**

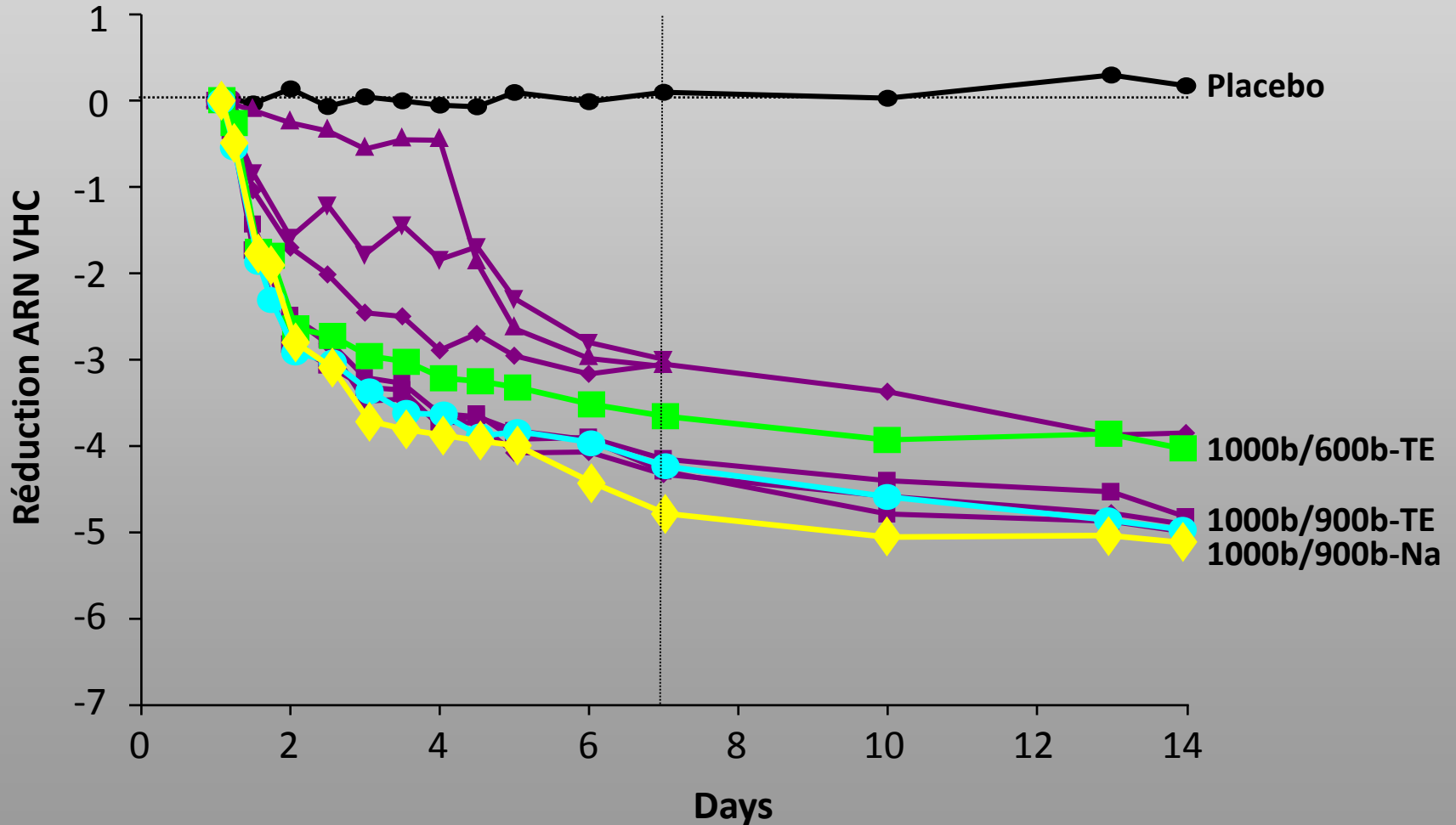


**NS5A  
Inhibitors**



**NS5B  
Polymerase  
Inhibitors**

# IFN-free regimen: "Proof of concept"



# IFN free regimens

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- Introduction (background)
- Direct acting antivirals (DAAs)
- **IFN-free ongoing trials**
- Conclusion

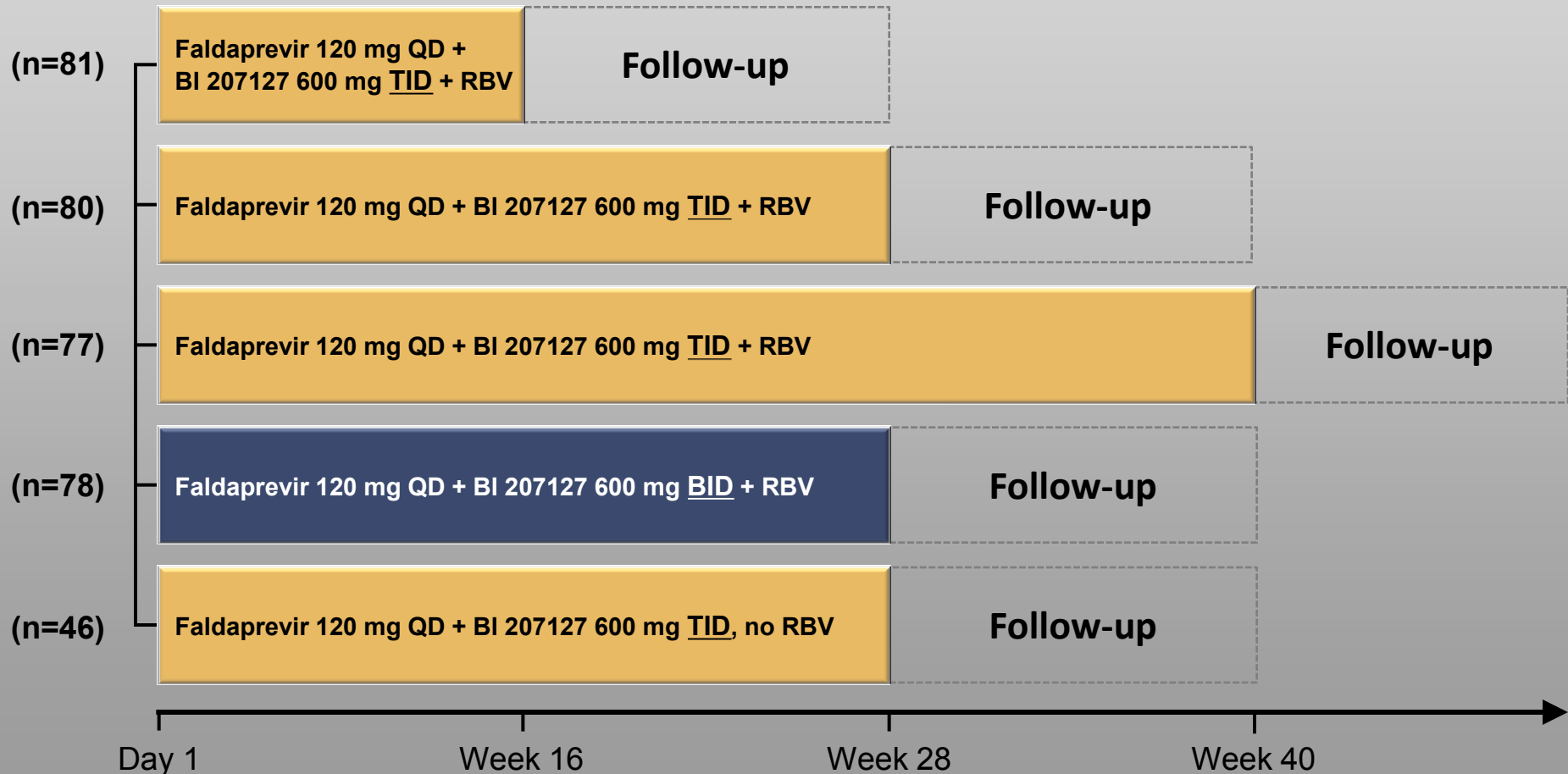
# IFN-free ongoing trials

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- Faldaprevir + BI 207127 (Boehringer-Ingelheim)
- ABT-450/r + ABT-333 +/- ABT-267 +/- RBV (Abbott)
- Sofosbuvir + GS 5885 + RBV (Gilead)
- Sofosbuvir + GS 5885 + RBV (Gilead) (G2 and G3)
- Asunaprevir + daclastavir + BMS 791325 (BMS)

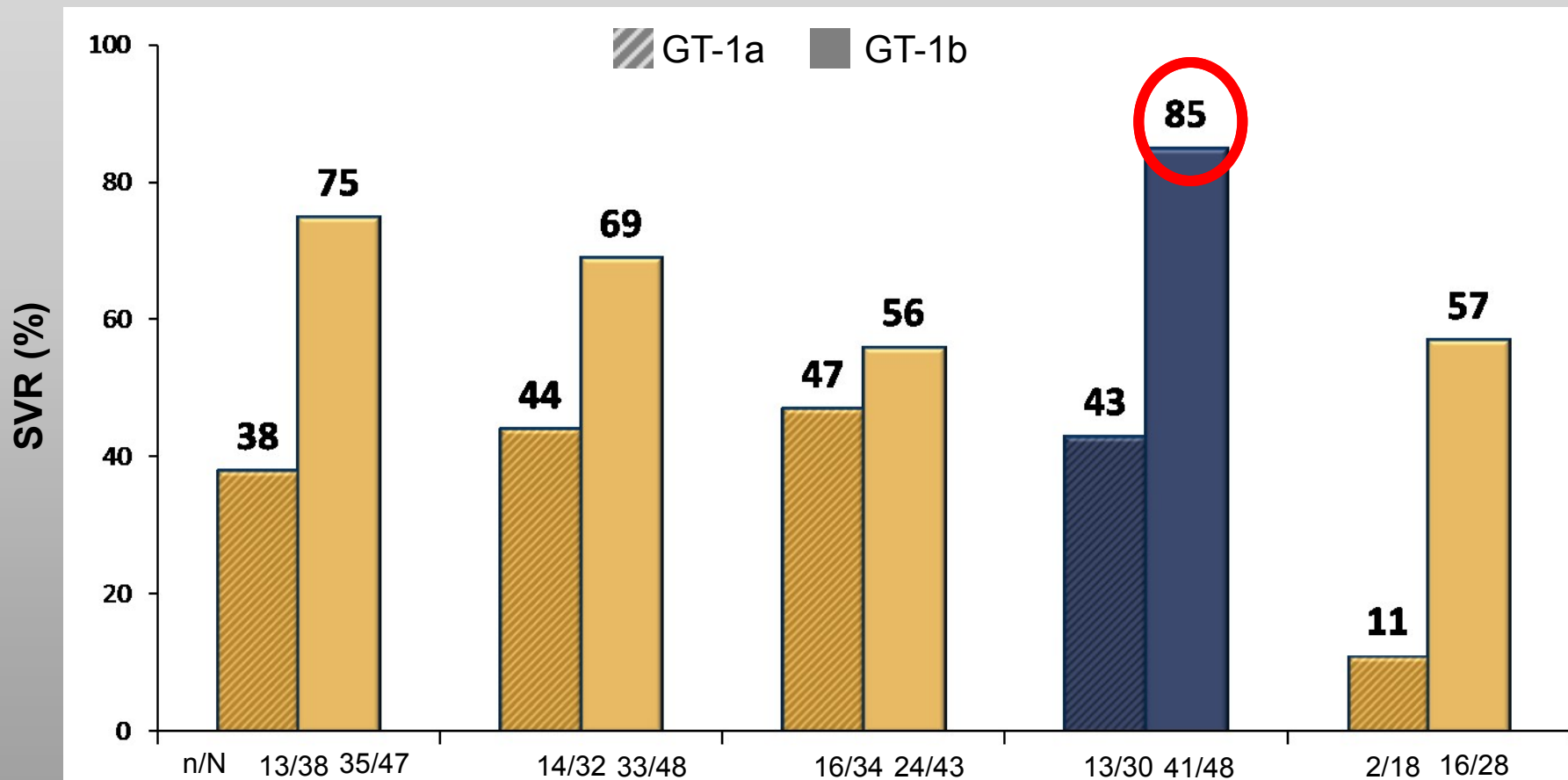
# Faldaprevir (PI) + BI 207127 (NS5BI) (Boehringer-Ingelheim)

## G1 Naive patients



# Faldaprevir (PI) + BI 207127 (NS5BI)

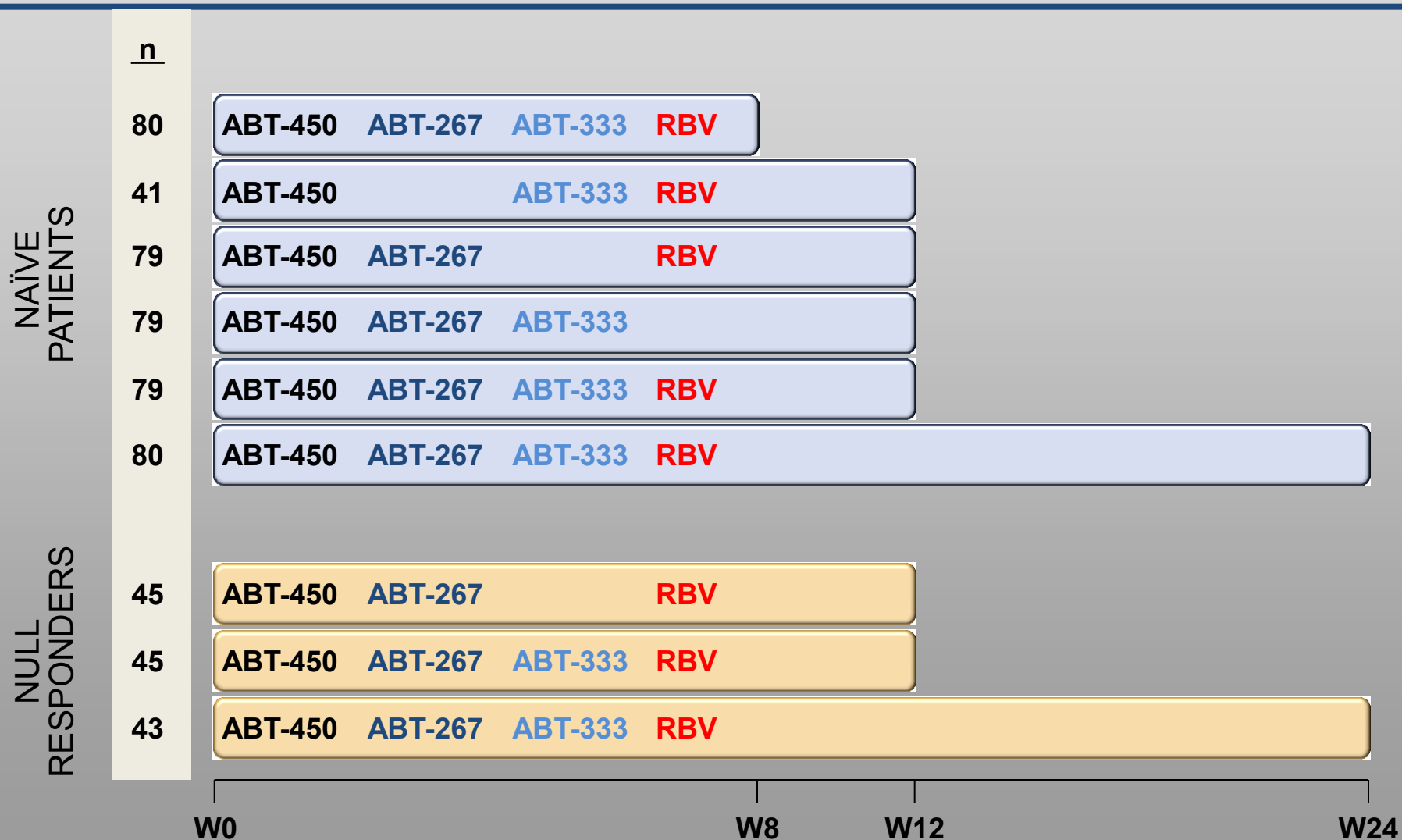
(Boehringer-Ingelheim)



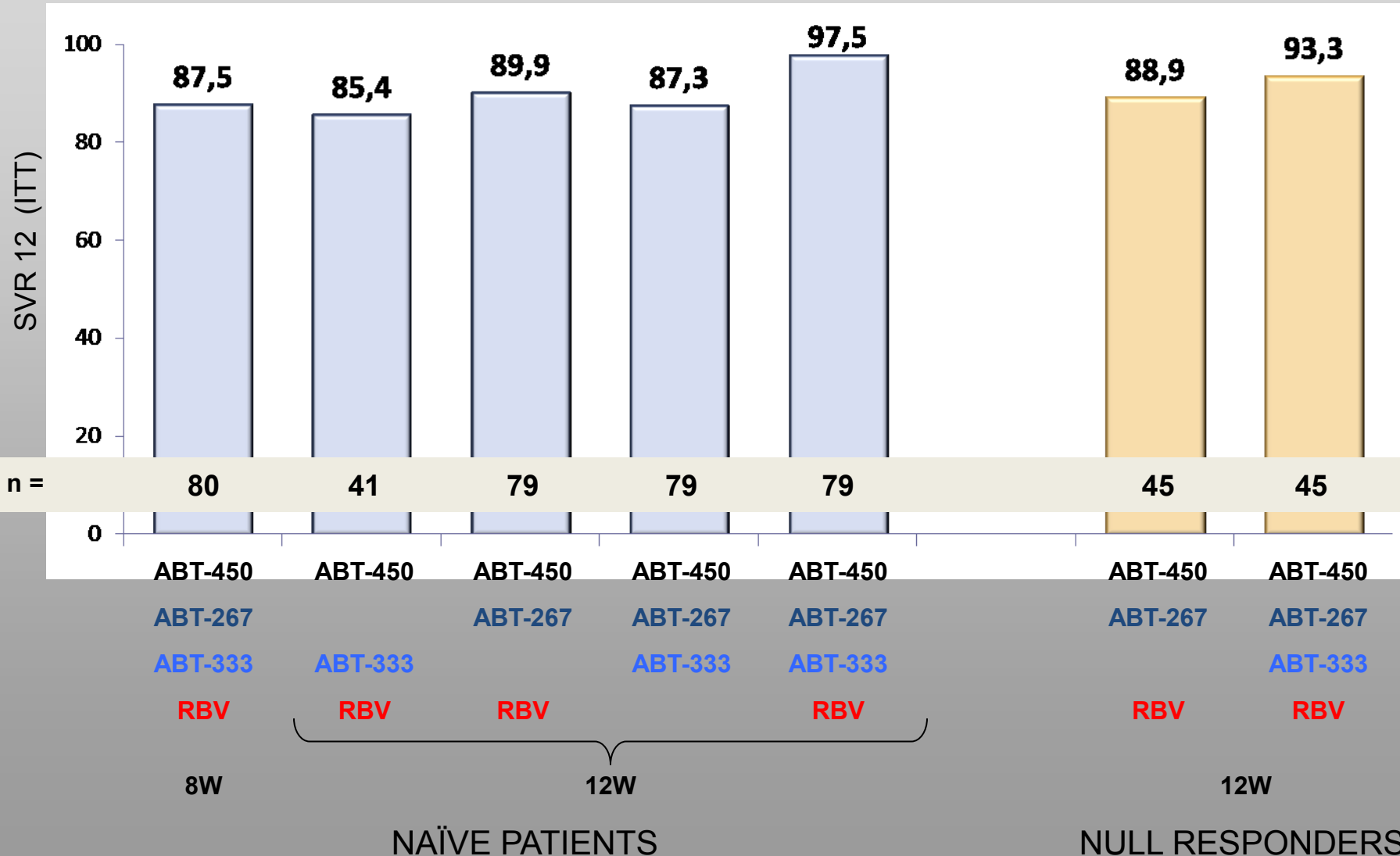
BI 207127 dosing	TID	TID	TID	BID	TID
Duration (weeks)	16	28	40	28	28
RBV +/-	+	+	+	+	-



# ABT-450/r (PI) +/- ABT-333 (NS5AI) +/- ABT-267 (NS5BI) +/- RBV (Abbott)



# ABT-450/r (PI) +/- ABT-333 (NS5AI) +/- ABT-267 (NS5BI) +/- RBV (Abbott)

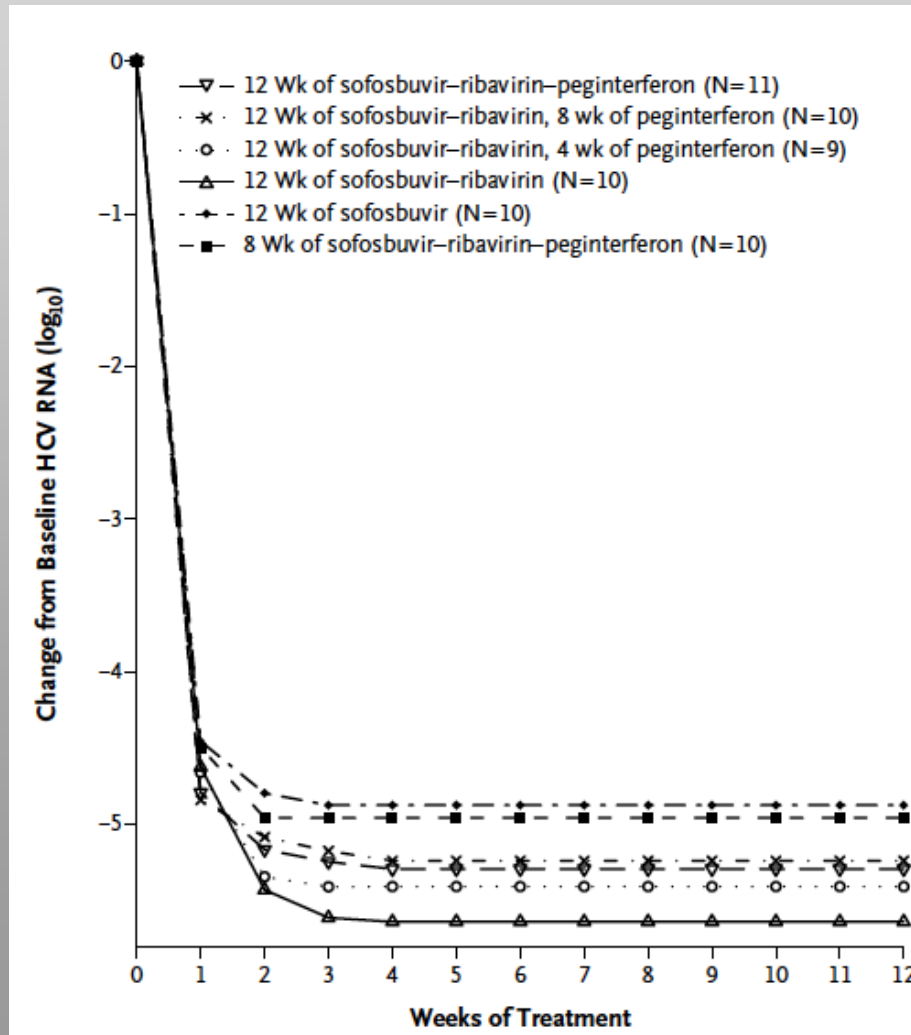


# Sofosbuvir (NS5BI) + GS 5885 (NS5AI) + RBV (Gilead)

HCV RNA < 15 UI/mL	SOF + RBV		SOF + GS-5885 + RBV	
	Treatment-naïve (n = 25)	Null responder (n = 10)	Treatment-naïve (n = 25)	Null responder (n = 9)
<b>Week 1</b>	<b>8/25 (32)</b>	<b>1/10 (10)</b>	<b>11/25 (44)</b>	<b>0/9 (0)</b>
<b>Week 2</b>	<b>17/25 (68)</b>	<b>7/10 (70)</b>	<b>22/25 (88)</b>	<b>4/9 (44)</b>
<b>Week 4</b>	<b>25/25 (100)</b>	<b>10/10 (100)</b>	<b>25/25 (100)</b>	<b>8/9 (89)</b>
<b>EOT</b>	<b>25/25 (100)</b>	<b>10/10 (100)</b>	<b>25/25 (100)</b>	<b>9/9 (100)</b>
<b>SVR4</b>	<b>22/25 (88)</b>	<b>1/10 (10)</b>	<b>25/25 (100)</b>	<b>9/9 (100)</b>
<b>SVR12</b>	<b>21/25 (84)</b>	<b>1/10 (10)</b>	<b>--</b>	<b>--</b>

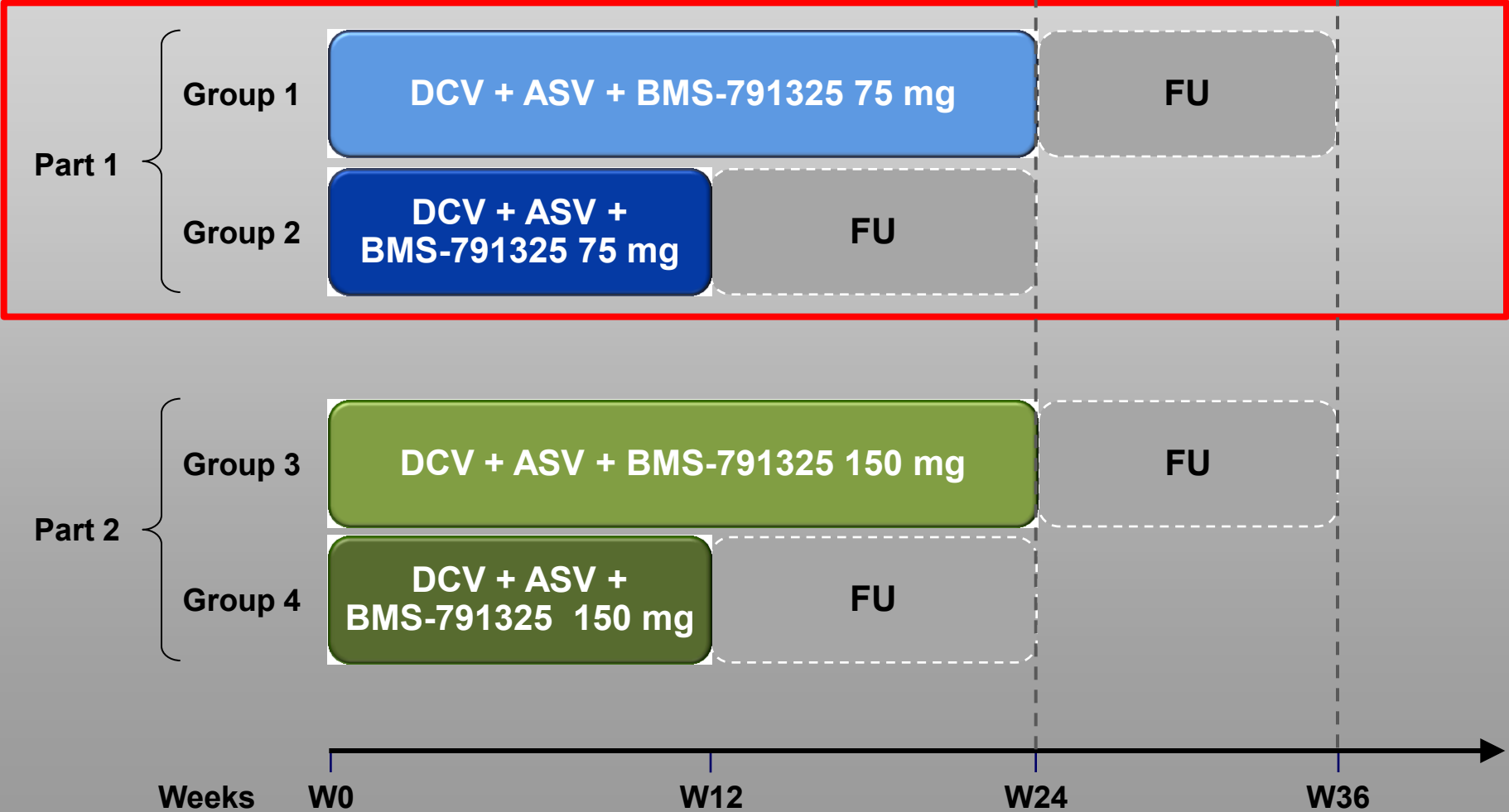
# Sofosbuvir + RBV (Gilead)

## G1 and also Genotype 2 and 3

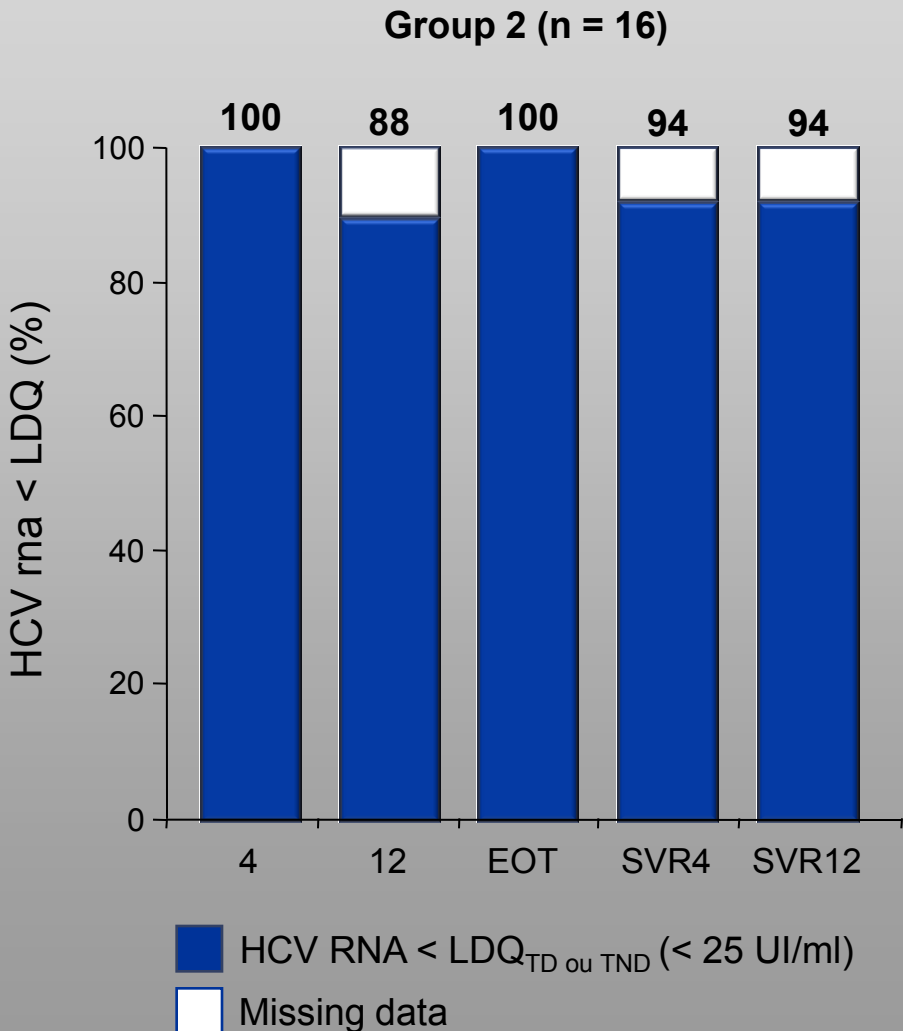
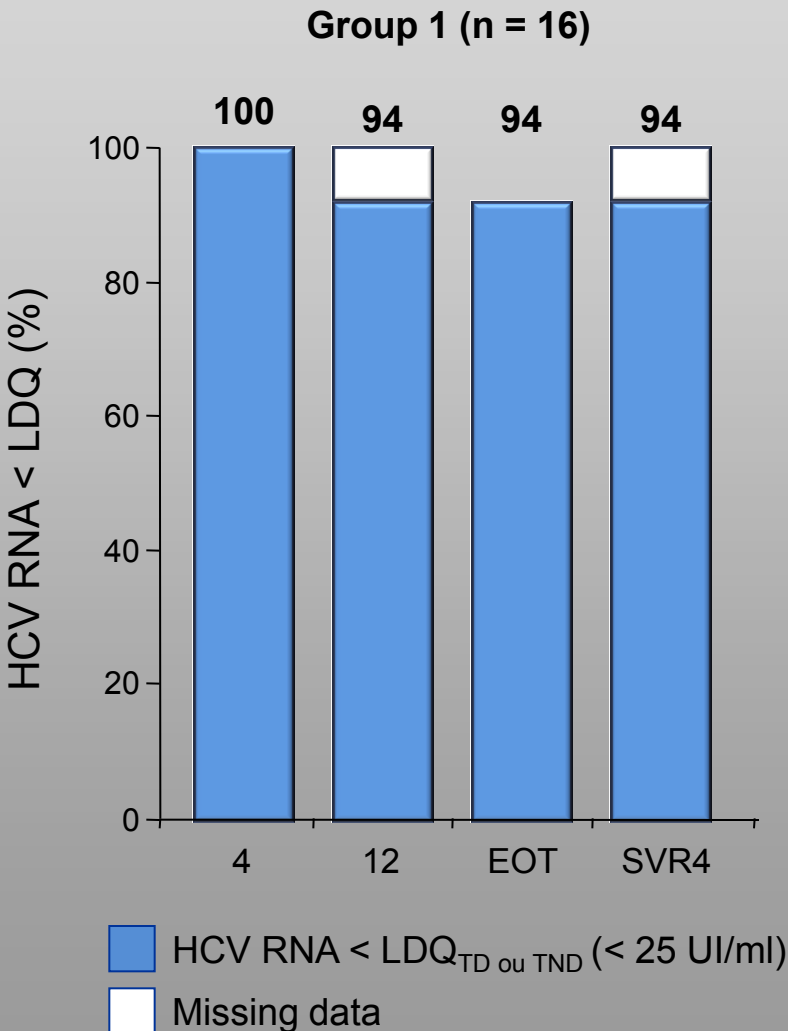


# Asunaprevir (PI) + daclastavir (NS5AI) + BMS 791325 (NS5BI) (BMS)

## G1 naive

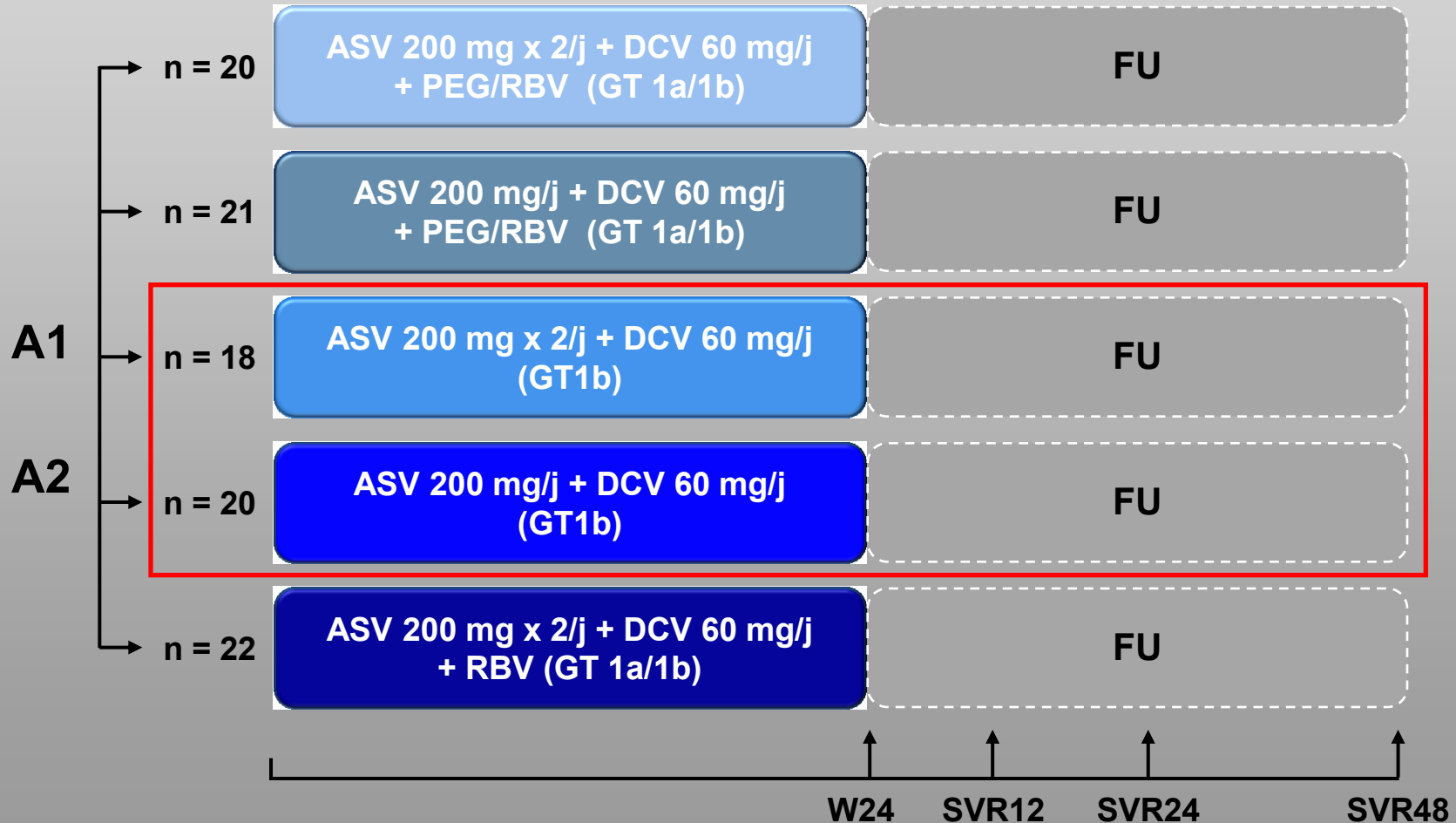


# Asunaprevir (PI) + daclastavir (NS5AI) + BMS 791325 (NS5BI) (BMS)

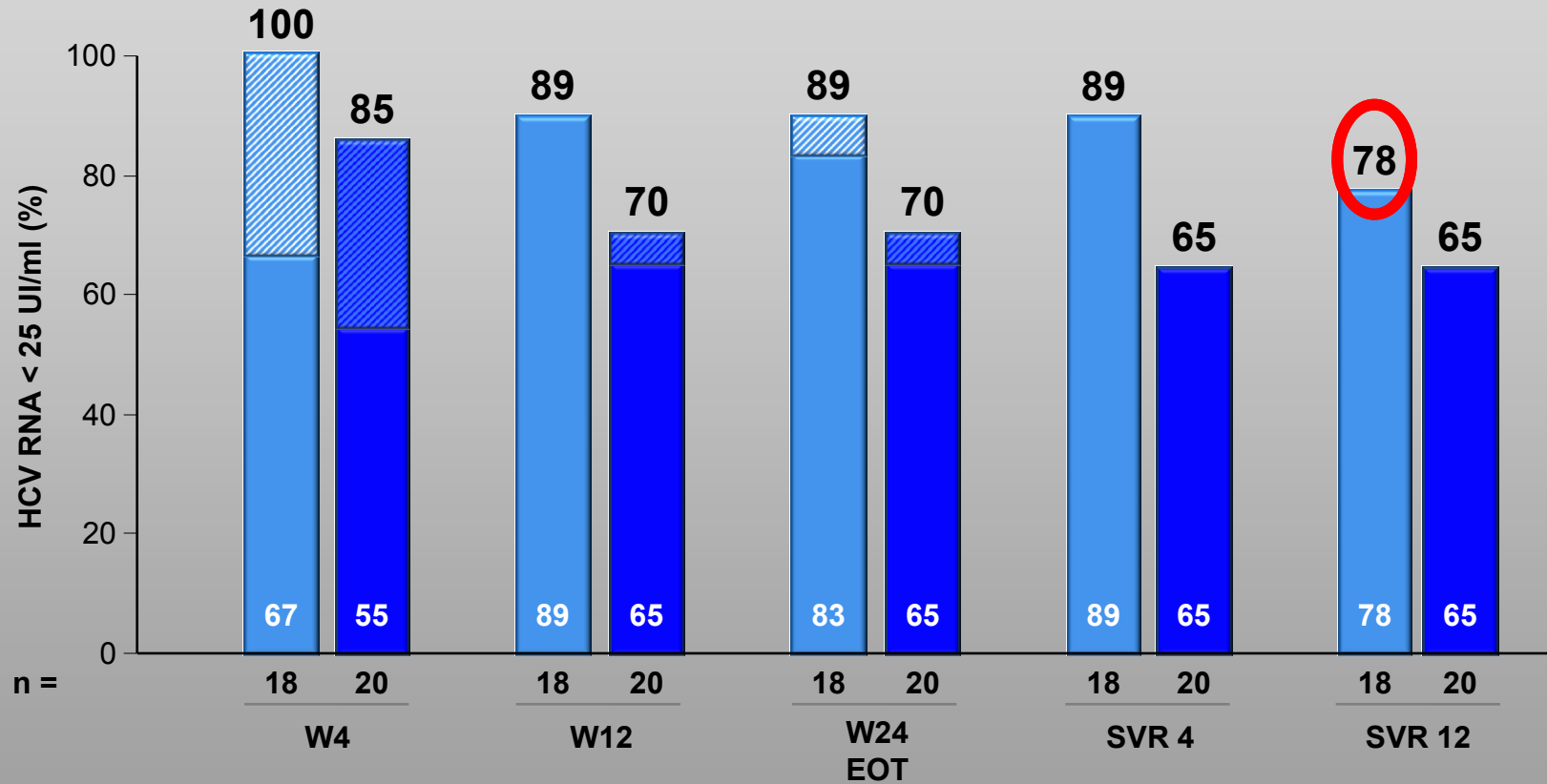


# Asunaprevir (PI) + daclastavir (NS5AI) (BMS)

A1 and A2: G1b Null responders, without cirrhosis



# Asunaprevir (PI) + daclastavir (NS5AI) (BMS)



ASV 200 mg x 2/j + DCV  
ASV 200 mg x 1/j + DCV

Detectable and < LOD (25 UI)  
< LOD (10 UI)



# IFN-free ongoing trials: summary

First drug (company)	Second drug	Third drug	Fourth drug
<b>Boehringer Ingelheim</b>			
Faldaprevir (BI201335) Protease inhibitor	BI207127 NS5B NNI	Ribavirin	
<b>Abbott</b>			
ABT-450/r Protease inhibitor	ABT 267 NS5B NNI	ABT 333 NS5A inhibitor	Ribavirin
<b>Gilead</b>			
Sofosbuvir (GS 7977)	Ribavirin		
Sofosbuvir (GS 7977) NS5B NI	GS 5885 NS5A inhibitor		
<b>Gilead/BMS</b>			
Sofosbuvir (GS 7977) NS5B NI	Daclastavir NS5A inhibitor	± Ribavirin	
<b>BMS</b>			
Asunasprevir Protease inhibitor	Daclastavir NS5A inhibitor		
<b>Vertex</b>			
Telaprevir Protease inhibitor	VX 222 NS5B NNI	Ribavirin	

# Conclusion:

## A realistic hope for an oral regimen

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- More than 6 IFN free ongoing trials
- Majority of trials in HCV Genotype 1
- Several DAAs (different class of action)
- Some with efficacy for all genotypes
- Concern: safety issues

# **We still have a dream**

Martin Luther King J (1963, Washington)

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# Where we go: The Future

## Ten Commandments for the Magic Drug

- 1 HIGH **E**FFICACY
- 2 LOW **R**ESISTANCE (high genetic barrier)
- 3 FOR **A**LL-GENOTYPES
- 4 SHORT **D**URATION
- 5 TOLERAB**I**LITY
- 6 PHARMA**C**OKINETIC (Low pill burden)
- 7 ONLY OR**A**L REGIMEN (IFN free)
- 8 DRUGS IN**T**ERRACTION
- 9 AVAILABLE : C**I**RRHOSIS, ELD, HIV-HCV...
- 10 **C**OST REDUCTION**N** (access program)

HCV **ERADICATION** WORLDWIDE