



***Pharmacology of IDX184, a Liver-Targeted  
Nucleotide Prodrug for the Treatment of HCV***

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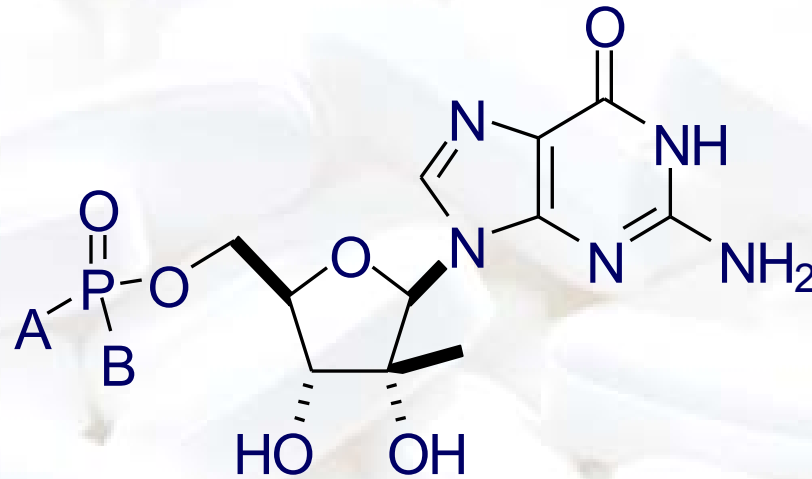
***HepDart  
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# IDX184: HCV Liver-Targeted Nucleotide Polymerase Inhibitor

- IDX184 is a novel liver-targeted prodrug of 2'-methylguanosine monophosphate
- IDX184 has demonstrated potent and selective inhibition of HCV *in vitro*
  - Active against HCV genotypes 1, 2, 3 and 4
- Liver-targeted
  - >95% of absorbed IDX184 is extracted by the liver *in vivo*
  - Low systemic exposure of parent drug (IDX184) and nucleoside metabolite (2'-methylguanosine)
  - High levels of 2'-methylguanosine triphosphate (2'-MeGTP) in liver demonstrated in animal models

# Partial Chemical Structure of IDX184

2'-C-Methylguanosine monophosphate prodrug



# 2'-MeGTP Shows Potent and Selective Antiviral Activity *in vitro*

- Against purified viral polymerases (HCV and BVDV) or cellular polymerases

HCV NS5B	IC <sub>50</sub> (μM)
HCV 1a	0.08
HCV 1b	0.29
HCV 2a	0.14
HCV 3a	0.12
HCV 4a	0.19
BVDV	0.14

Cellular Enzyme	IC <sub>50</sub> (μM)
Human DNA pol α	>50
Human DNA pol β	>50
Human DNA pol γ	>100
Human RNA pol II	>100

No activity against human cellular polymerases

Pan-genotypic activity against HCV

# IDX184 Shows Potent Antiviral Activity in Genotype 1b HCV Replicon Model

	Prodrug (Drug)	EC <sub>50</sub> (μM)	CC <sub>50</sub> (μM)
Nucleoside	NM283 (NM107)	4.1	>100
	R7128 (PSI-6130)	5.6	>100
	R1626 (R1479)	4.7	>75
Nucleotide	<b>IDX184</b>	<b>0.4</b>	<b>&gt;100</b>

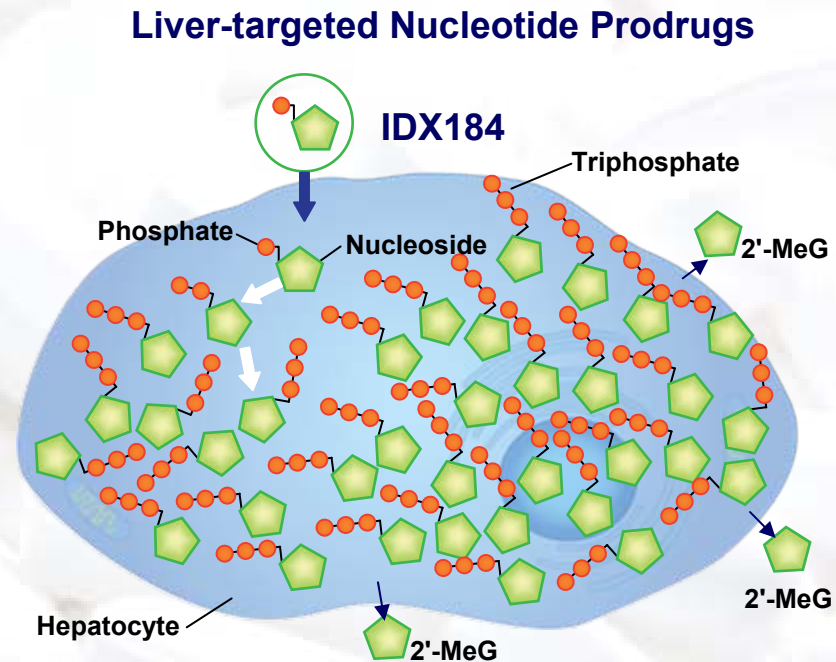
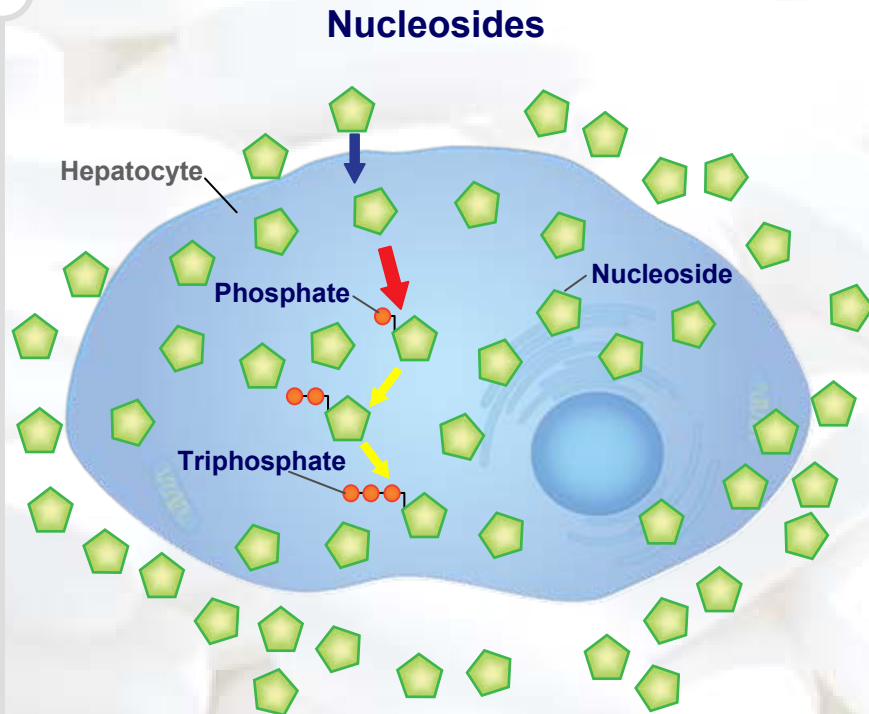
- Protein binding does not affect antiviral activity of IDX184
- Human plasma protein binding of IDX184 is 42-44% and is concentration independent

# Antiviral Potency of IDX184 on HCV Genotypes 1a, 1b and 2a by HCV Luciferase Replicon Assay

	HCV genotype 1a		HCV genotype 1b		HCV genotype 2a (JFH-1)	
	n	EC <sub>50</sub> ± SD (μM)	n	EC <sub>50</sub> ± SD (μM)	n	EC <sub>50</sub> ± SD (μM)
<b>IDX184</b>	14	<b>0.036 ± 0.007</b>	13	<b>0.106 ± 0.024</b>	5	<b>0.11 ± 0.03</b>

# Advantages of Liver-Targeted HCV Nucleotides

Nucleoside()Triphosphate() Inhibits Viral Replication



2'-methylguanosine (2'-MeG) is generated by hydrolysis of 2'-methylguanosine nucleotides in hepatocytes.

# IDX184: High Level Production of 2'-MeGTP in Primary Hepatocytes

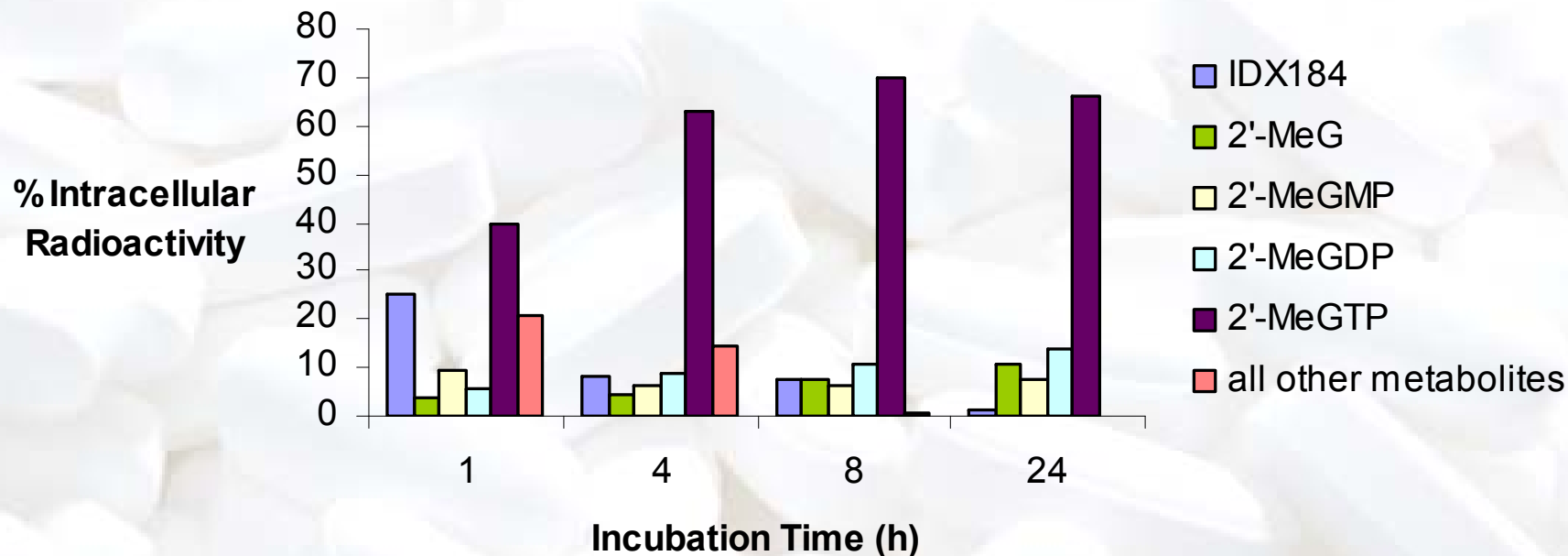
2'-MeGTP levels (pmol/10<sup>6</sup> cells)

		Primary Hepatocytes			Cell Lines	
	Compound	Human	Monkey	Rat	Huh-7	HepG2
Nucleoside	PSI-6130	22.7	24.5	ND	28.6	55.9
	R1479	2.26	4.27	ND	5.60	3.55
	NM107	14.4	14.0	BLD	10.7	41.5
Nucleotide	IDX184	<b>590</b>	<b>915</b>	<b>1640</b>	15.7	18.9

IDX184 is preferentially metabolized/activated in liver cells

# 2'-MeGTP is the Predominant Intracellular Metabolite of IDX184 in Human Hepatocytes

IDX184 and its metabolites in human hepatocytes incubated with 10  $\mu\text{M}$   $^{14}\text{C}$ -IDX184



- Mouse, rat and monkey hepatocytes give similar profiles.

# Stability of IDX184 in Whole Blood

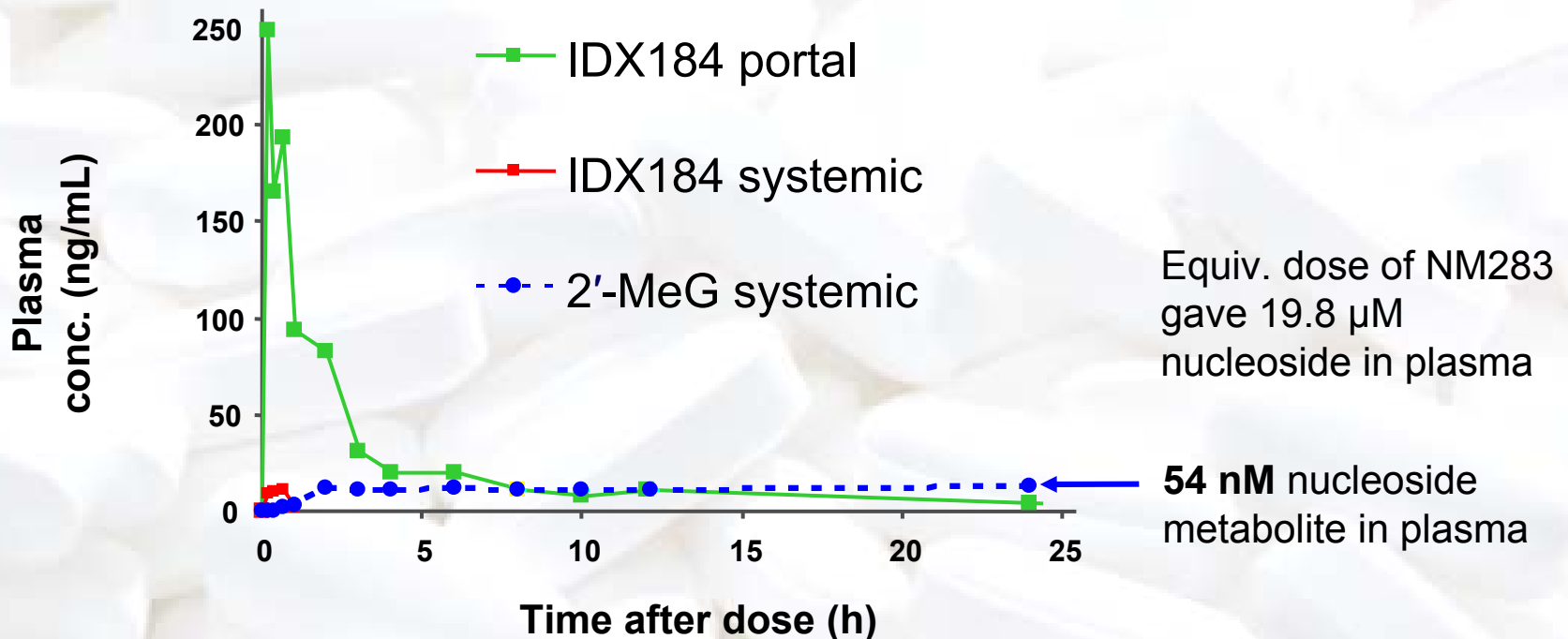
## Half-life of IDX184 in Fresh Whole Blood at 37°C

Mouse	Rat	Monkey	Human
4.6 hr	3.2 hr	9.4 hr	11 hr

- IDX184 is stable in whole blood (especially human).

# IDX184 is Efficiently Extracted by the Liver *in vivo*

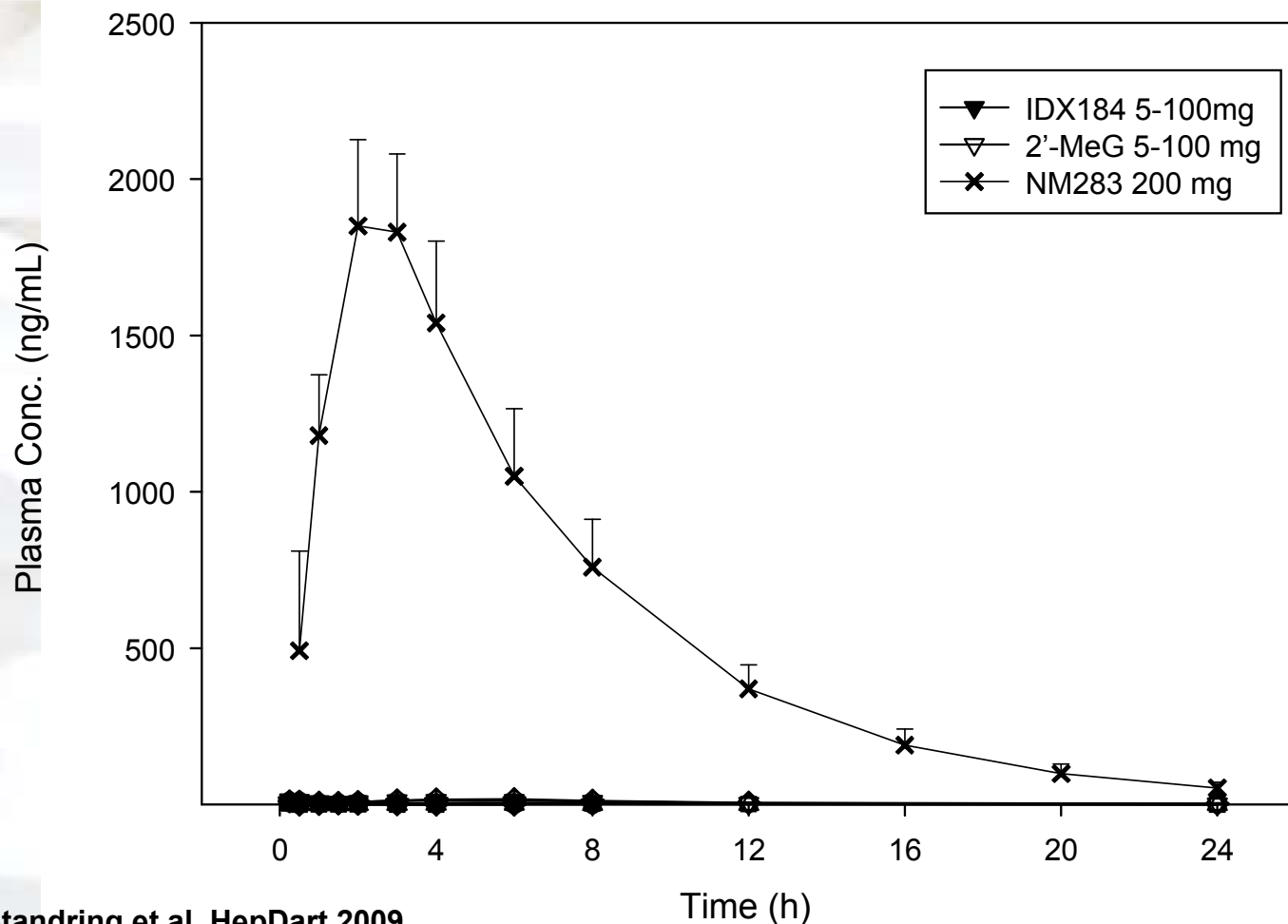
PK study in portal vein-cannulated cynomolgus monkeys: 50 mg/kg PO dose of IDX184



- IDX184 appears transiently in the portal system; very low systemic exposure
- >95% hepatic extraction
- 2'-MeG appears slowly in plasma and remains at low levels

# PK of IDX184/2'-MeG vs NM283/NM107 in Human Subjects

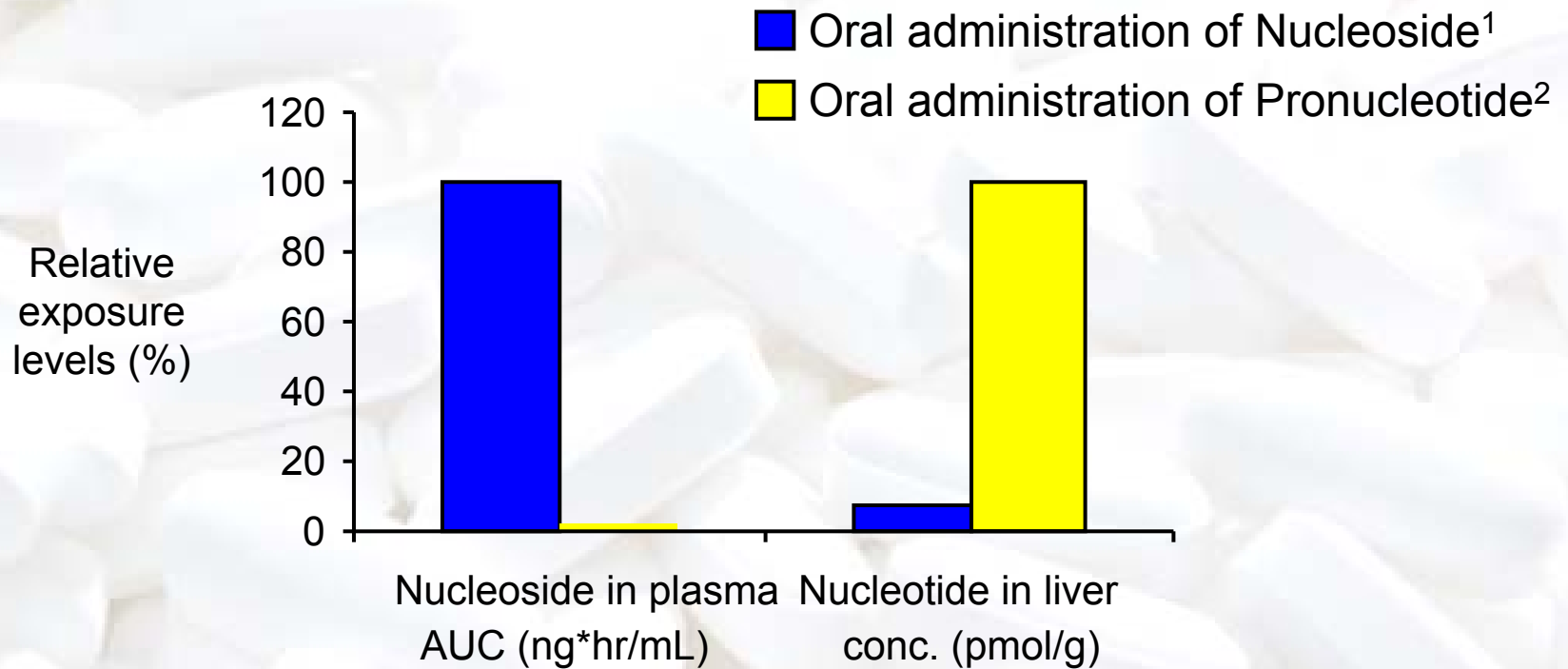
Mean (+SD) Single-Dose Plasma IDX184/2'-MeG vs. NM283/NM107



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# Idenix Liver-Targeting Technology Delivers High Hepatic Nucleotide Levels *in vivo*

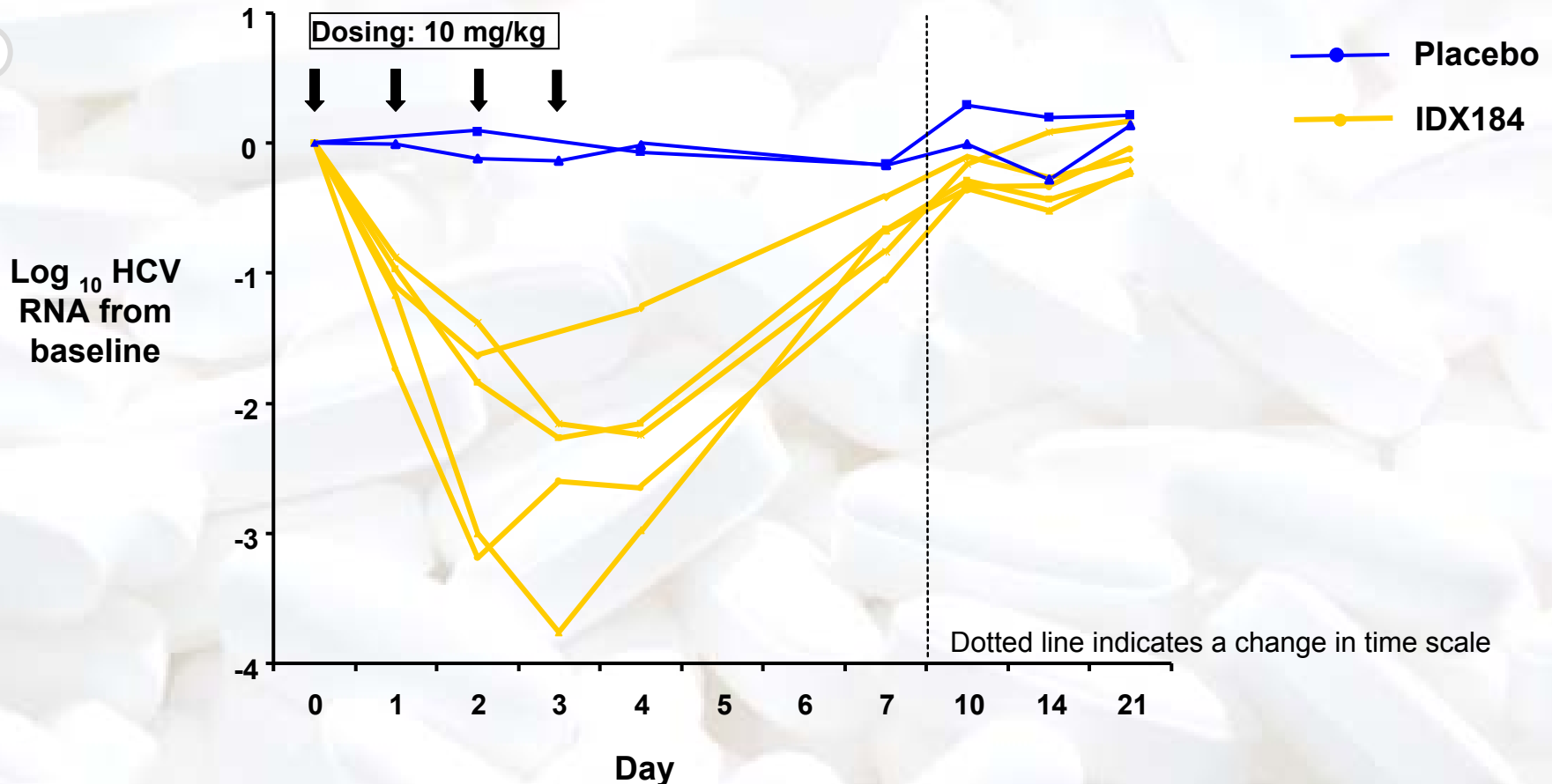
Steady-state PK in cynomolgus monkeys



<sup>1</sup>Nucleoside (2'MeC, NM107): high systemic nucleoside levels, low liver nucleotide levels

<sup>2</sup>Pronucleotide of 2'MeC: low systemic nucleoside levels, high liver nucleotide levels

# IDX184 Delivers Potent Antiviral Effects in HCV-1 Infected Chimpanzees



- Median and mean viral load decline ~ 2.3 log<sub>10</sub> at Day 3 and Day 4
- IDX184 was well tolerated in all animals

# Conclusions: IDX184, a Liver-Targeted Nucleotide Prodrug

- IDX184 nucleotide prodrug is preferentially cleaved in hepatocytes
  - Generates circa 30-fold more triphosphate than the nucleoside
- Liver targeting delivers more triphosphate in the liver
  - Dramatic increase in liver TP, decrease in systemic nucleoside for the nucleotide prodrug versus the nucleoside
  - Increased liver TP levels delivers potent antiviral effects in HCV-1 infected chimpanzees and patients
- IDX184 is efficiently extracted by the liver *in vivo*
  - >95% hepatic extraction in the monkey
  - Low systemic levels of parent drug (IDX184) and its metabolite (2'-MeG) demonstrated in monkeys and in man

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