Roche Pharma Day 2020

Infectious Diseases: A close look at our HBV pipeline

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Late stage pipeline update

1. **Hematology franchise**
   - DLBCL: Polivy, glofitamab, mosunetuzumab
   - FL: mosunetuzumab, glofitamab, Polivy
   - AML: Venclexta
   - MM: Venclexta
   - MDS: Venclexta

2. **Breast Cancer franchise**
   - TNBC: Tecentriq, ipatasertib
   - HR+: SERD (RG6171), PI3Kαi (RG6114)
   - HER2+: Tecentriq

3. **Lung Cancer franchise**
   - NSCLC: Tecentriq, tiragolumab
   - SCLC: Tecentriq, tiragolumab
   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek
   - RET+: Gavreto
   - KRAS *G12C*+: GDC-6063

4. **Other oncology**
   - CRPC: ipatasertib
   - Thyroid cancer: Gavreto
   - Esophageal cancer: tiragolumab
   - Melanoma: Tecentriq, Cotellic, Zelboraf

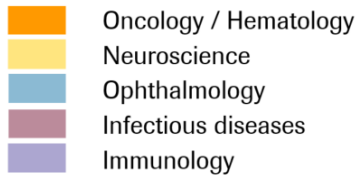
5. **Non-malignant hematology**
   - Hemophilia A: Hemlibra
   - Hemophilia A: Factor VIII Gene Therapy
   - PNH: crovalimab

6. **Neuroscience**
   - MS: Ocrevus; fenebrutinib
   - SMA: Evrysdi
   - NMOSD: Enspryng
   - AD: gantenerumab, anti-Tau, brain shuttle
   - Huntington's disease: tominersen
   - DMD: Micro-dystrophin Gene Therapy
   - Parkinson's disease: prasinezumab

7. **Immunology**
   - IPF: rhPentraxin-2, Esbriet
   - Myelofibrosis: rhPentraxin-2
   - Lupus nephritis: Gazyva
   - Crohn's disease: etrolizumab

8. **Ophthalmology**
   - nAMD, DME, DR: Port Delivery System
   - nAMD, DME, RVO: faricimab

9. **Infectious diseases**
   - HBV: TLR7 agonist, CpAM, RG6346, RG6084
   - Influenza A/B: Xofluza
   - SARS-CoV2: Actemra
   - SARS-CoV2: REGN-COV2

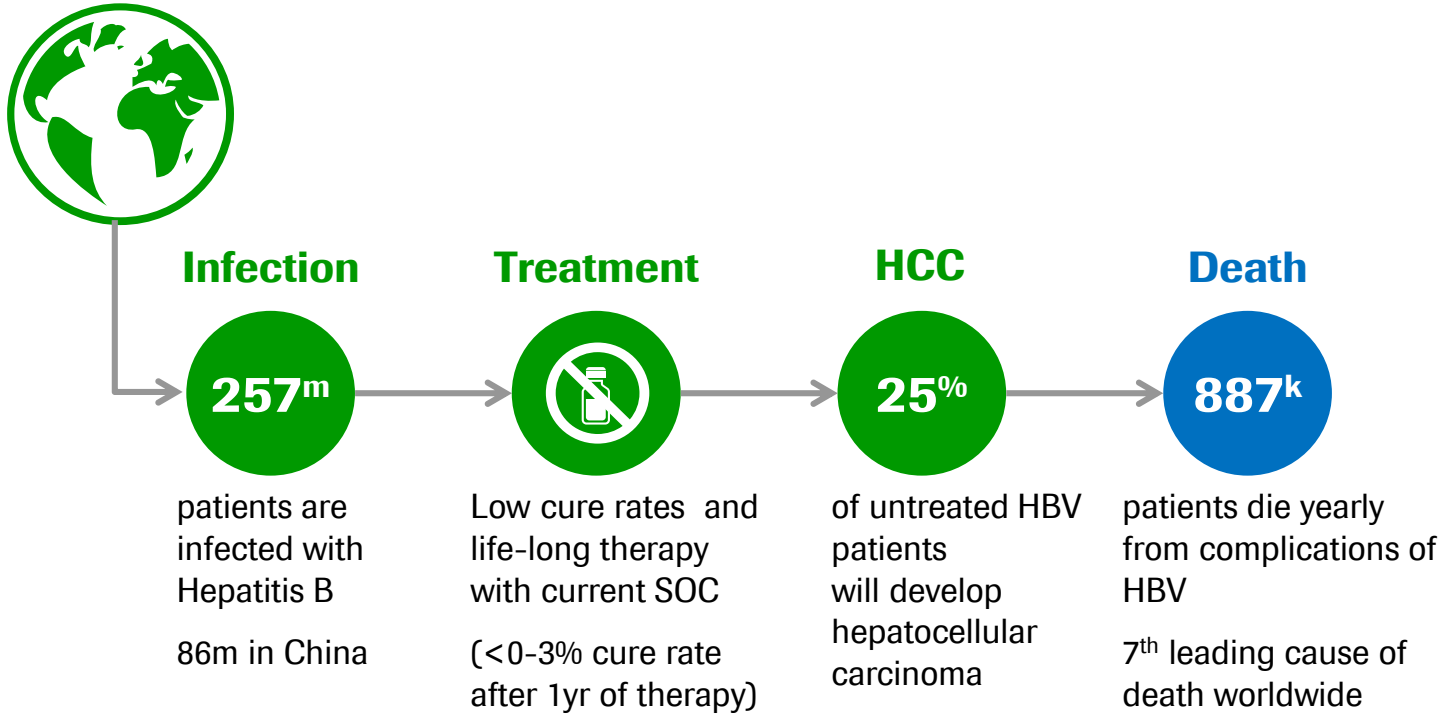


* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage

Hepatitis B: High global unmet need

High burden of disease with life-threatening complications

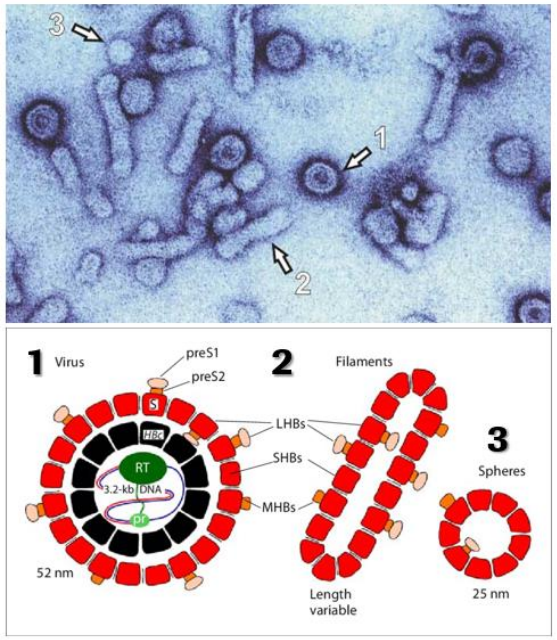
Hepatitis B Virus (HBV)



Reference: WHO July 2018

Hepatitis B surface Antigen (HBsAg) loss is the most important endpoint for functional cure with finite treatment duration

HBsAg detection



- Total HBsAg is quantatively measured by Immunoassay (Elecsys HBsAg II quant II, Roche)

HBsAg decline associated with signitifcantly improved patient outcomes

	Relative Risk	Lower limit	Upper limit	P-value
Liver decompensation	**0.28**	0.13	0.59	0.001
HCC	**0.30**	0.20	0.44	<0.001
Transplant/Death	**0.22**	0.13	0.39	<0.001
Composite first clinical event	**0.31**	0.23	0.43	<0.001

- Meta-analysis of 28 studies with nearly 190,000 chronic HBV patients
- Clear association between HBsAg seroclearance and improved outcome
- HBsAg seroclearance as primary endpoint in clinical trials supported

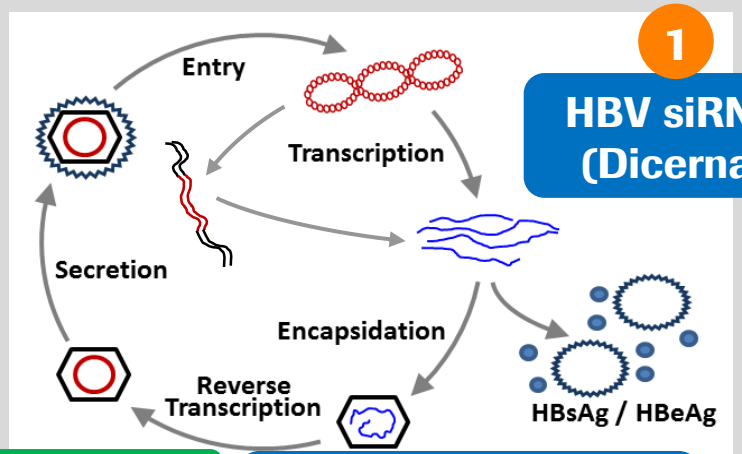
Figure: Gerlich HG Dig Dis. 2010; https://www.klinikum.uni-heidelberg.de/zentrum-fuer-infektiologie/molecular-virology/research-area/hbv/1-morphology-genome-organization; table: Anderson et al. Clin Gastroenterol Hepatol 2020; in press, online available at https://doi.org/10.1016/j.cgh.2020.05.041; HCC=hepatocellular carcinoma

Roche HBV strategy

Combining antiviral and immunomodulatory agents

Antiviral agents

HBV life cycle



1 HBV siRNA (Dicerna)

Nucleos(t)ide

CpAM (Core protein Allosteric Modulator) 2

Immunomodulators

Virus mediated suppression

Novel Immunomodulator

3 TLR7 Agonist

Peg-IFNα

Activation

Standard of Care

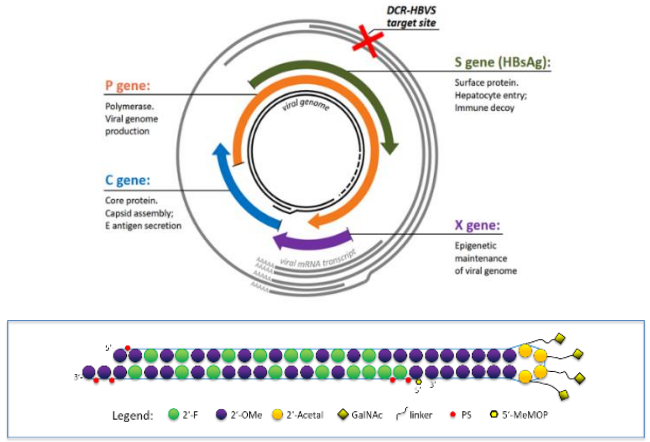
Functional cure

1

HBV siRNA (RG6346)

Inhibiting HBV gene expression by targeting the viral genome

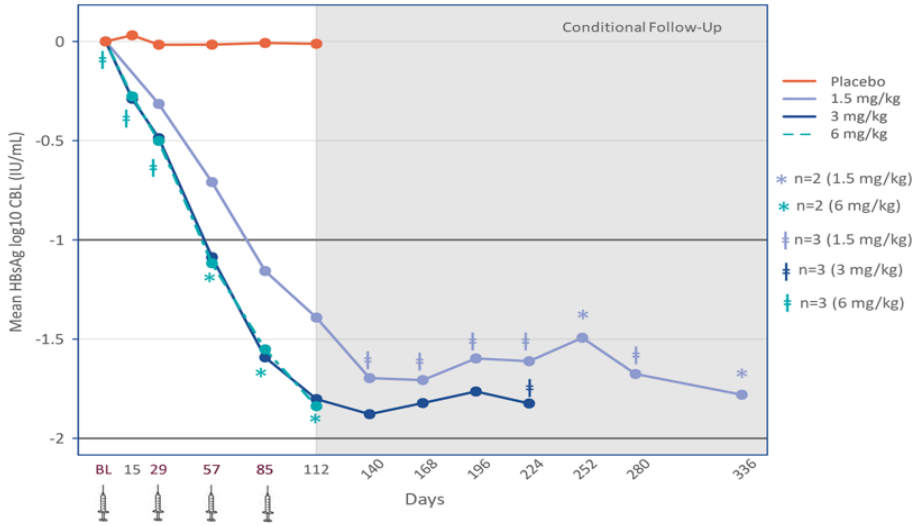
siRNA simultaneously inhibiting multiple HBV genes



- Proprietary liver-targeted RNAi technology (GalXC™) with unique 'tetraloop' folded design
- Designed to inhibit HBV gene expression through targeting of S open reading frame of the HBV genome

Ph I (dose finding) interim results

HBsAg decline in patients receiving siRNA (RG6346) + nucleos(t)ide*



- Durable HBsAg decline up to day 336
- 6 out of 10 patients, who completed day 112, had HBsAg < 100 IU/mL
- Safe and well tolerated

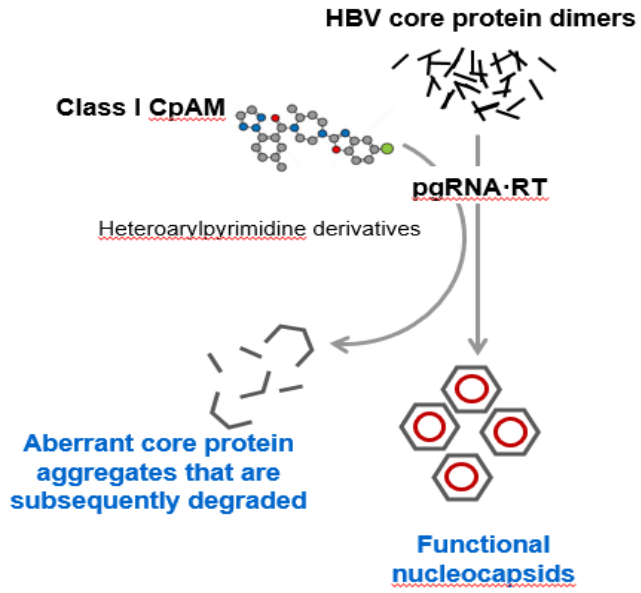
* Interim analysis from 25 June 2020 data cutoff; https://investors.dicerna.com/static-files/0507fc43-4023-4a40-92fb-0c06b9c4a4b7; In collaboration with Dicerna

2

CpAM (RG7907)

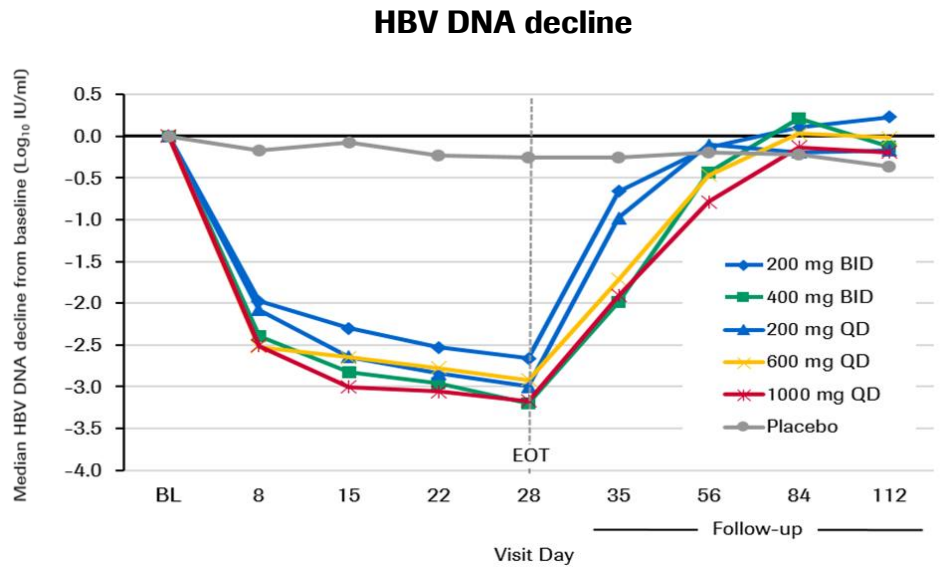
Leads to incorrect assembly of HBV core protein followed by degradation

Core protein allosteric modulator (CpAM)



- Effective against all major HBV genotypes
- Showing successful HBsAg reduction in preclinical mouse model

Ph I (dose finding)



- Strong HBV DNA decline in all patients within first week of treatment
- 81% (13/16) HBeAg-negative patients achieved HBV DNA levels below LLOQ (20 IU/ml)

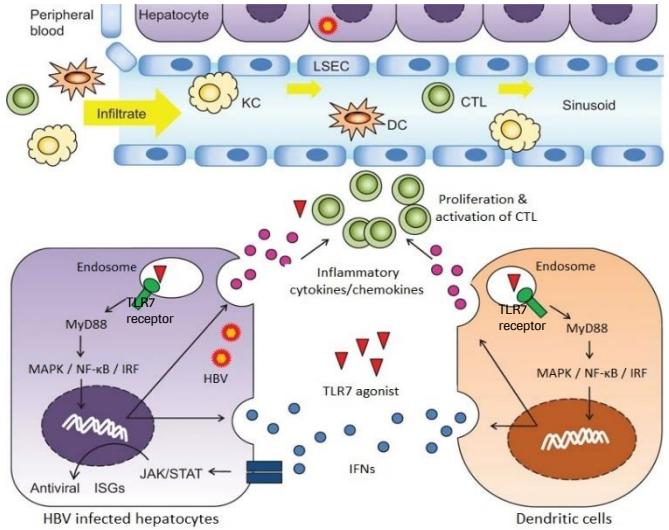
EASL 2019 poster FRI-219; HBeAg=Hepatitis B e-antigen; LLOQ=lower limit of quantification

3

TLR7 agonist (RG7854)

Stimulating innate and adaptive antiviral response via TLR7 pathway

Toll like receptor 7 (TLR7) agonist



- TLR7 detects single-stranded viral RNA and mediates anti-viral cytokine production and dendritic cell activation
- Unique double pro-drug selectively activated in the liver

Ph I (dose finding) results

Dose (mg)	ISG15		OAS1	
	Fraction responding	Geometric mean fold change (range)	Fraction responding	Geometric mean fold change (range)
Placebo	0/16	-	0/16	-
3	1/8	2.4 (2.4–2.4)	0/8	-
10	0/8	-	0/8	-
20	1/8	2.6 (2.6–2.6)	0/8	-
40	1/8	2.9 (2.9–2.9)	0/8	-
60	1/8	2.6 (2.6–2.6)	2/8	2.4 (2.0–2.9)
100	6/8	5.9 (2.3–29.3)	5/8	3.8 (1.9–6.9)
140	8/8	11.6 (2.3–48.0)	8/8	5.5 (2.2–18.1)
170	8/8	11.2 (2.5–132.2)	8/8	5.5 (2.0–19.0)

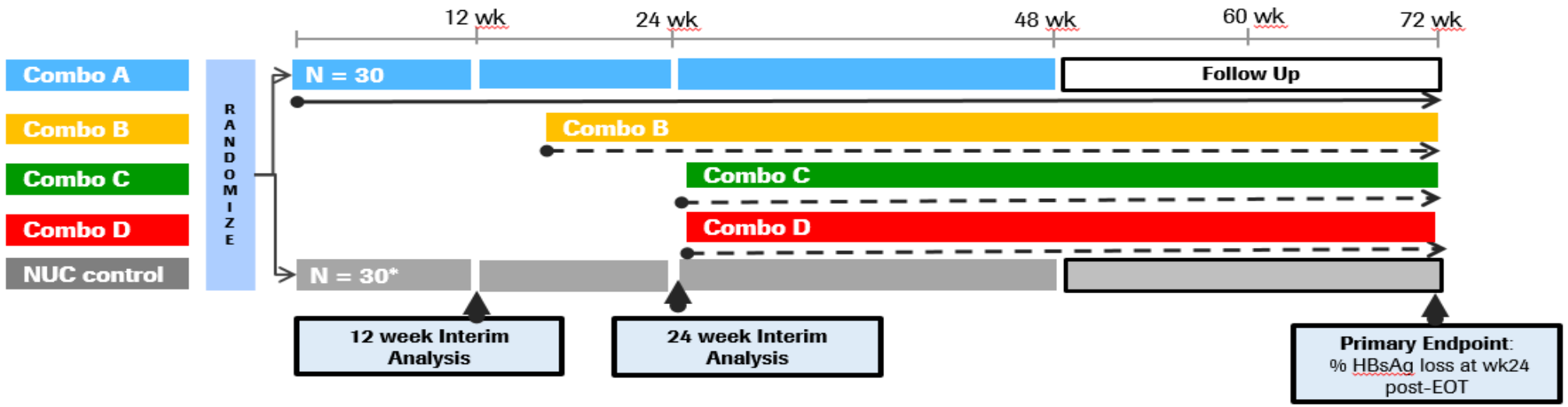
- Dose dependent immunomodulatory activity established
- TLR7 activation induces mRNA expression of interferon-inducible genes (e.g. ISG15, OAS1) first observed at 100 mg dose and plateaued at 170 mg dose

Modified from Ma Z et al. Cell Mol Immunol 2015, 12(3):273-82; Gane E et al. EASL 2018; ISG15=Interferon-stimulated gene 15; OAS1=2'-5'-oligoadenylate synthetase 1

Highly adaptive HBV combination platform

Screening novel drug combinations efficiently

Combination platform trial design



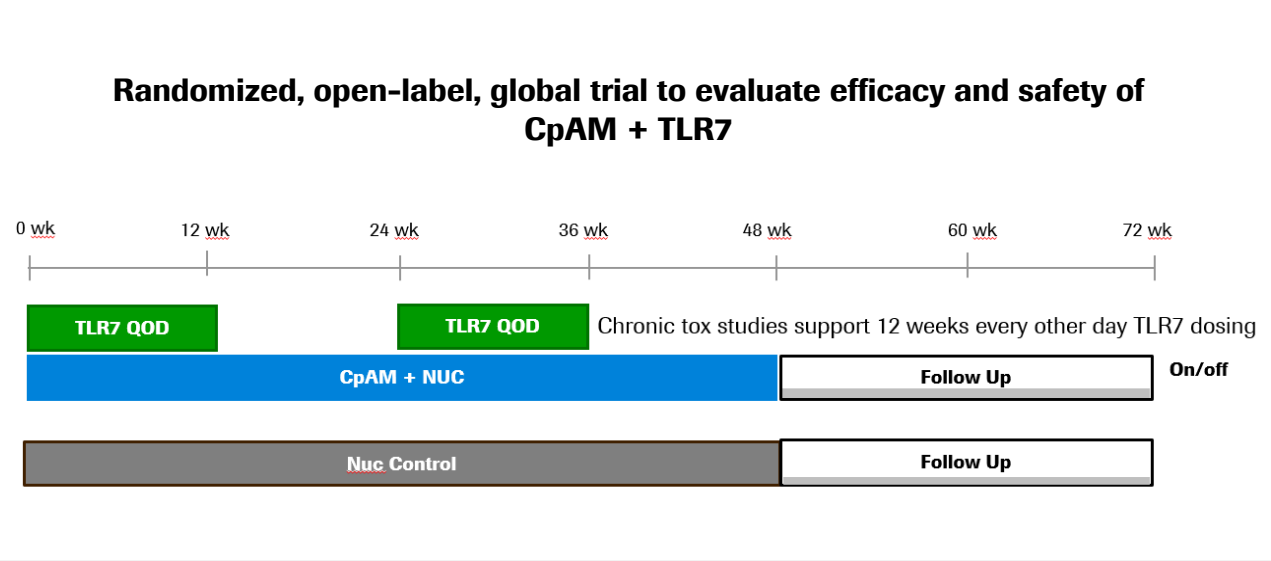
- Nimble and adaptive platform for Ph II screening with shared control arm
- First interim analysis after 12 weeks; second interim analysis after 24 weeks; interim analysis helps inform combos B, C and D
- Opportunity to seamlessly add and terminate different drug combinations

2 + 3

CpAM + TLR7 agonist in HBV

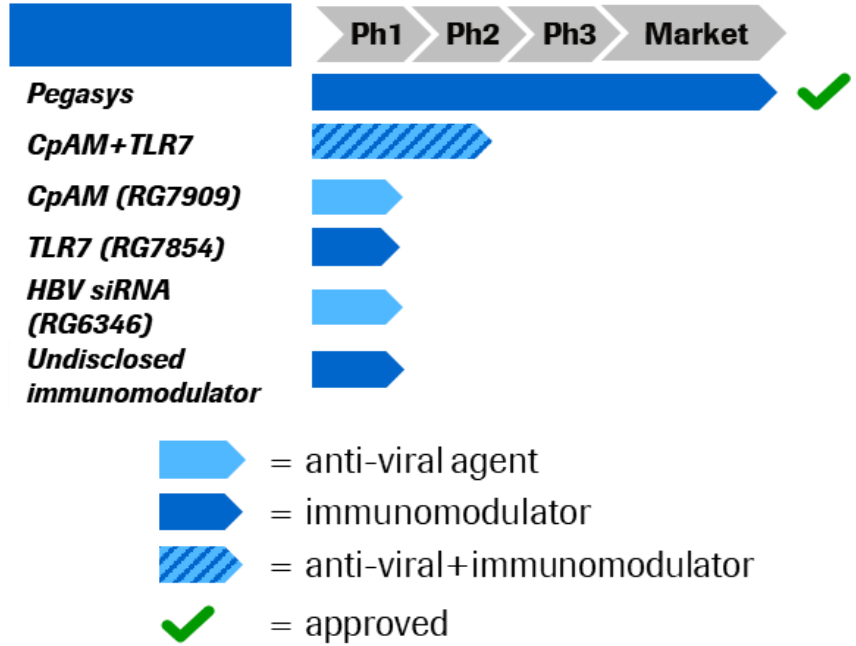
First combination to move into Ph II testing

Ph II combination trial design



- Ph II combination trial (n=60) started in Q3 2020
- First 12-week interim analysis planned for Q2 2021
- A 4th HBV program molecule (undisclosed novel immunomodulator) moved into Ph I testing

Overview HBV development program



Doing now what patients need next