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Curing Chronic Hepatitis B

Abstract # PS-027

Preclinical antiviral drug combination studies utilizing novel orally bioavailable agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, an HBV RNA destabilizer

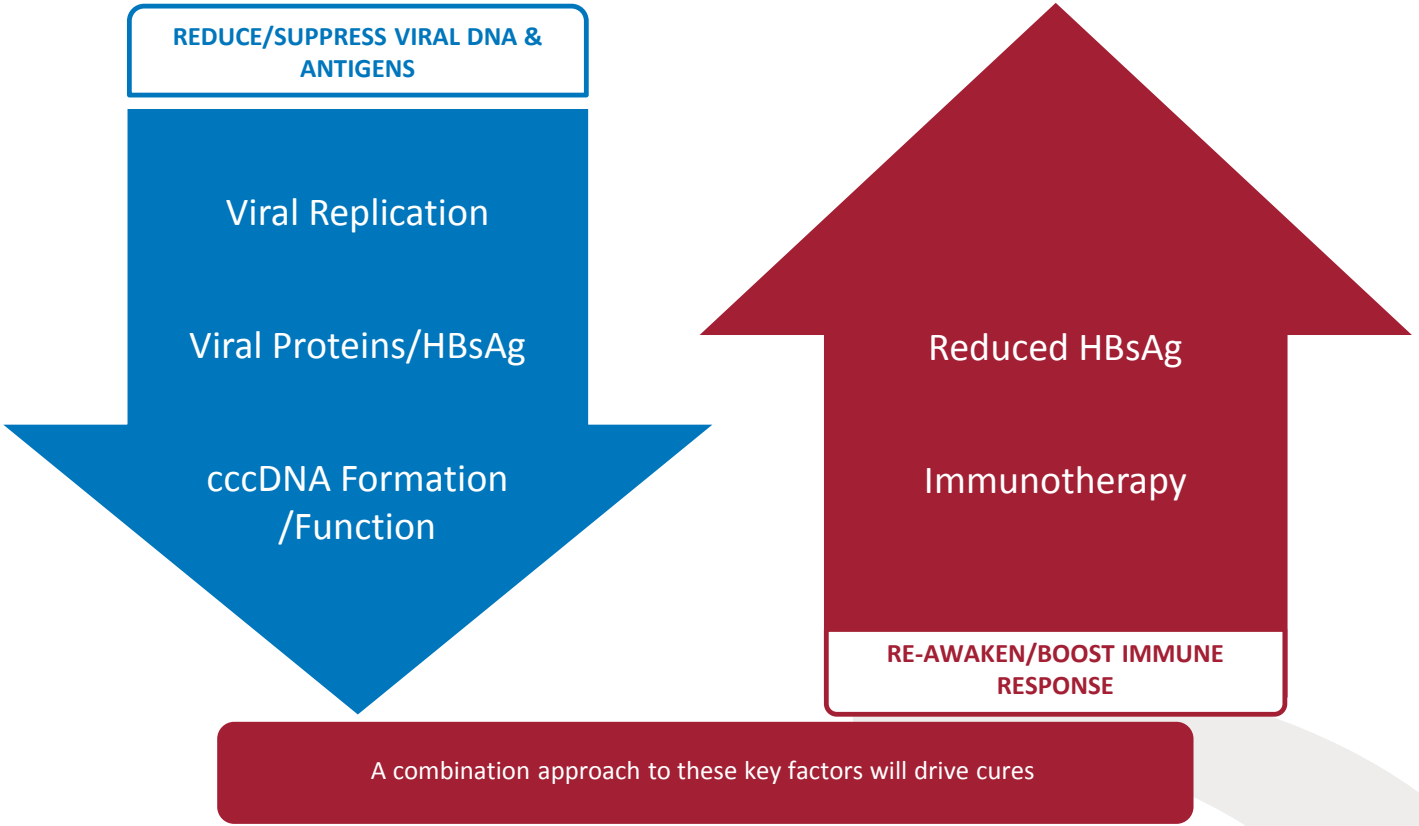
Rene Rijnbrand

Arbutus Biopharma Inc.

The International Liver Congress 2018,

April 11 – 15, 2018, Paris, France

Key to Therapeutic Success in HBV



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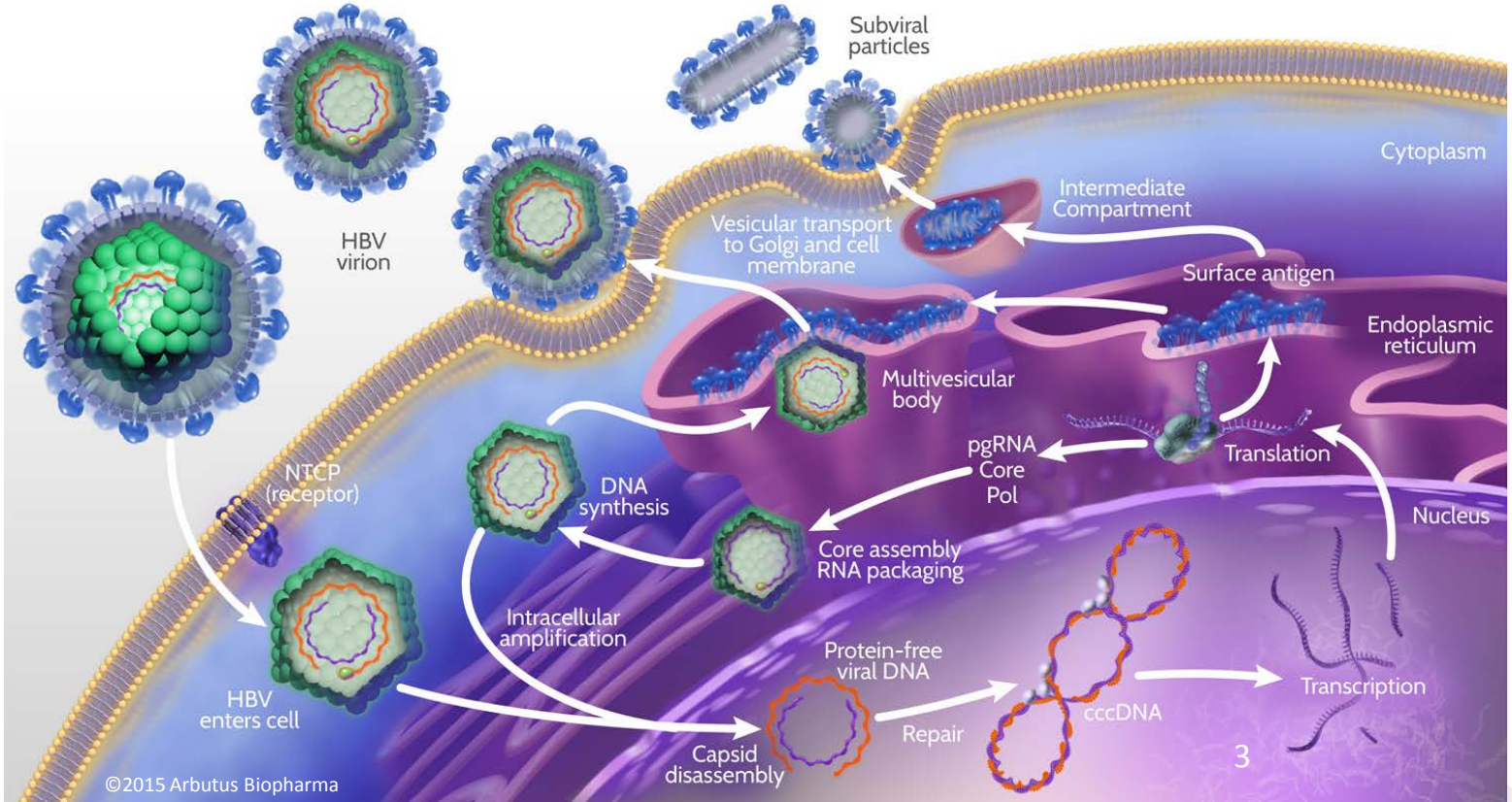
HBV Lifecycle

Keys to therapeutic success: combining agents with different mechanism of action



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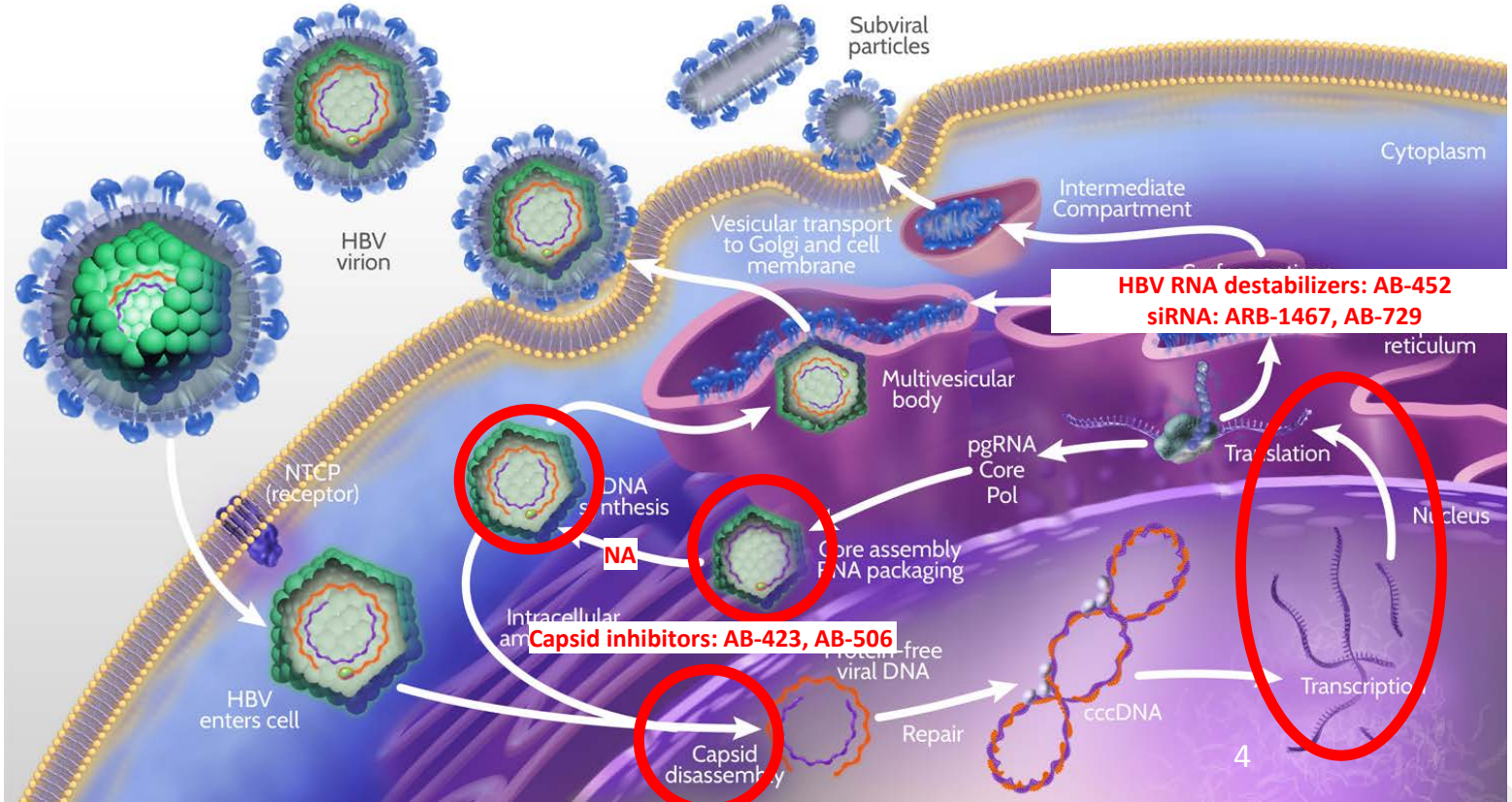
Keys to therapeutic success: combining agents with different MOA



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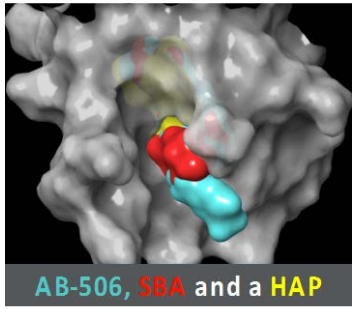
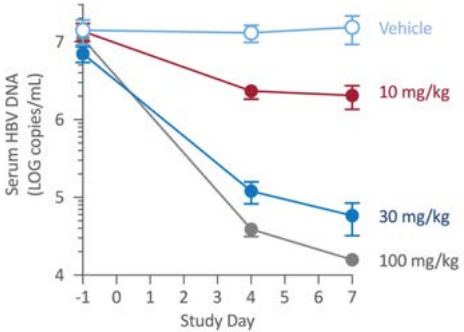
AB-506: A Next Gen HBV Capsid Inhibitor

Potent inhibitor of HBV replication *in vitro*

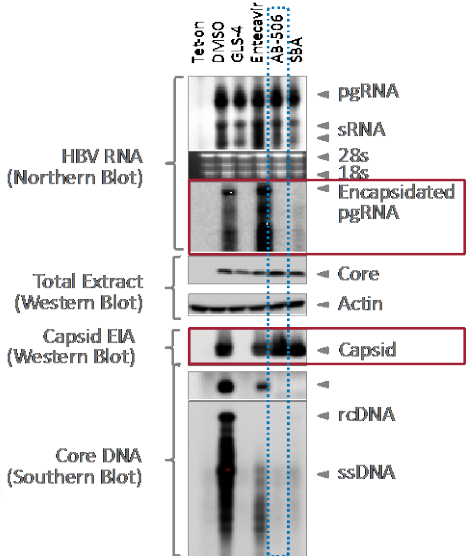
Binding site overlaps with other capsid inhibitors



Antiviral activity in an HDI mouse model of HBV



AB-506 forms empty capsids devoid of pgRNA or rcDNA



- **Potent inhibition of viral replication in HBV cell culture models (EC_{50} = 35-80 nM, EC_{90} = 200-275 nM; PHH EC_{50} of 32 nM)**
  - **Binds at the dimer:dimer interface of core protein**
  - **Forms capsids devoid of pgRNA**
  - **Inhibits formation of rcDNA**
  - **Pan-genotypic activity (HBV genotypes A-H)**
  - **No cross-resistance with Nuc^R variants**
  - **High degree of antiviral selectivity for HBV**
  - **Modest ~6 fold increase in EC_{50} in 40% human serum**
- **Dose Dependent Reduction in serum HBV DNA in an HDI mouse model of HBV**
- **Preclinical data supports potential for QD dosing**
- **AB-506 is being advanced into clinical development (mid 2018)**

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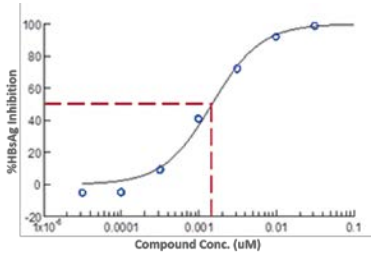
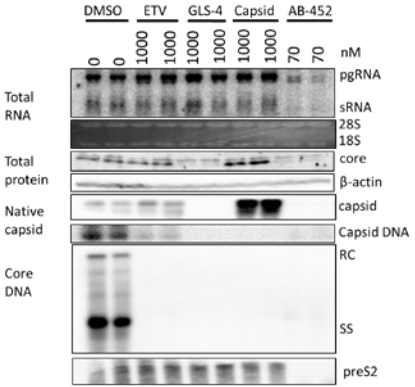
AB-452: A Potent HBV RNA Destabilizer

Novel small molecule HBV RNA Destabilizer

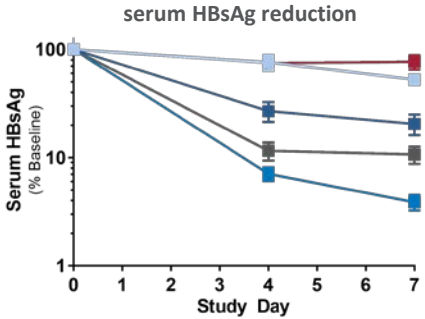
Inhibits HBsAg expression in HepG2.2.15 cells with an EC_{50} of 1.5 nM

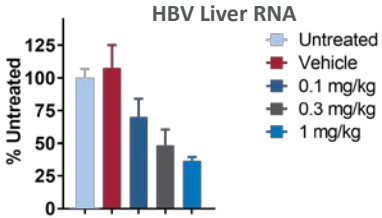


Multiple aspects of the HBV lifecycle affected by AB-452.



BID PO dosing resulted in up to 1.4 log10 serum HBsAg reduction. Correlated with liver HBV RNA levels.





- **AB-452 is a potent, highly selective small molecule inhibitor of HBV replication through destabilization of HBV RNA (EC_{50} 1.5 nM)**
- ***In vitro* AB-452 showed:**
  - **Drop in viral RNA levels**
    - **Drop in viral s/e/c Ag levels**
  - **Pan-genotypic activity**
  - **No cross-resistance with Nuc^R variants**
  - **Highly degree of antiviral selectivity for HBV**
- **AB-452 significantly inhibited HBV replication and reduced viral RNA and antigens in an immunocompetent AAV mouse model**
- **AB-452 is being evaluated for advancement into clinical development**

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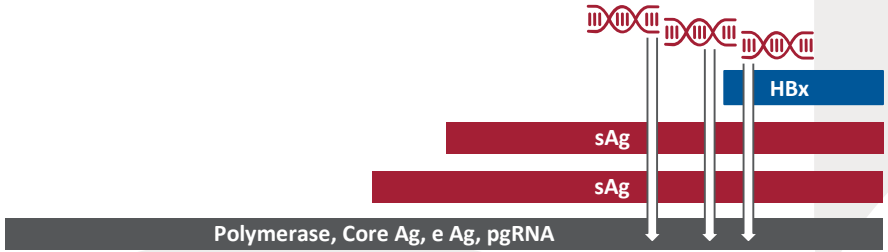
ARB-1467

A LNP siRNA agent targeting all HBV transcripts

- **Novel RNA interference product**
- **Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens**
- **Delivered via proprietary lipid nanoparticle (LNP) technology**
- **Generally safe and well tolerated to date**
- **Currently in Phase 2 trials**



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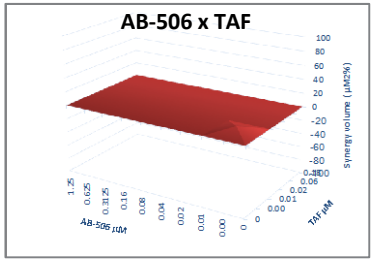
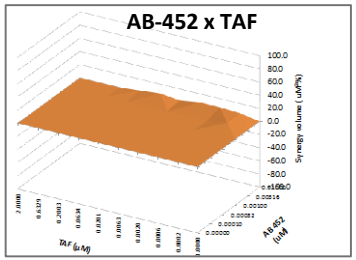
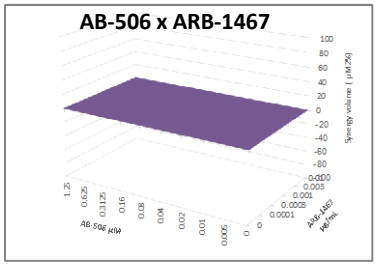
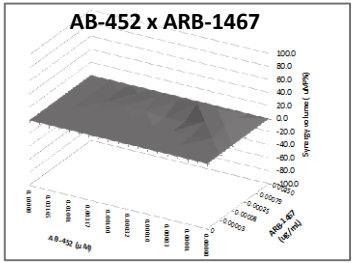
Combination of AB-506 and AB-452 With NAs and LNP siRNA (ARB-1467)

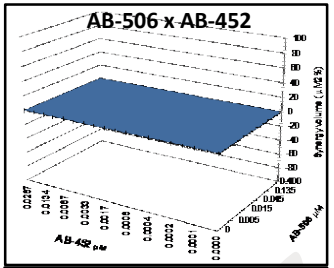
Molecules are mechanistically compatible

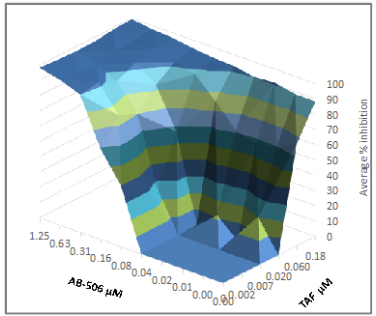


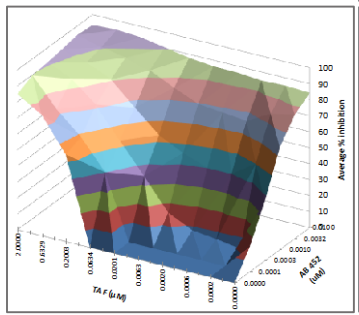


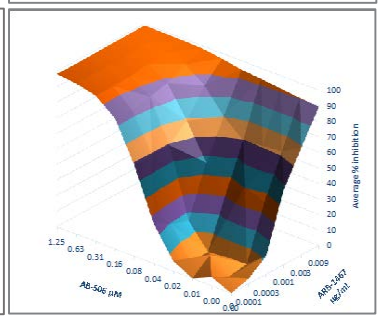


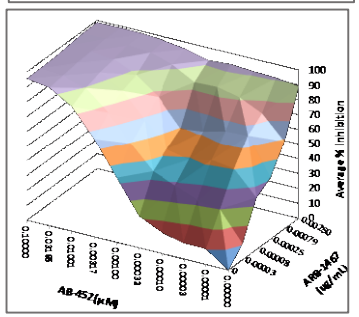


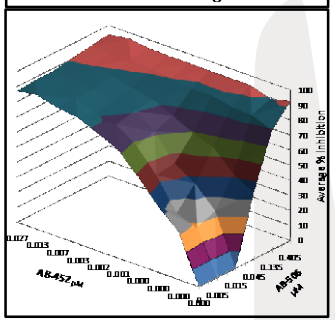


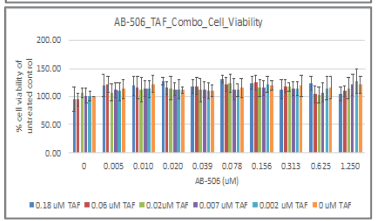


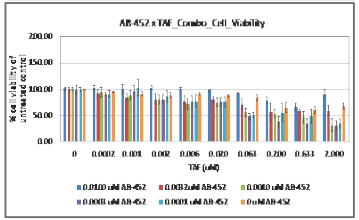


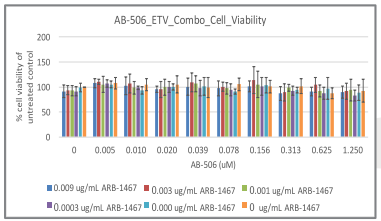


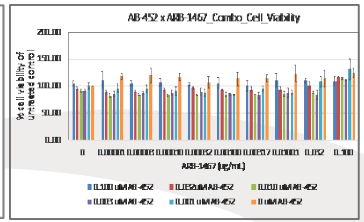


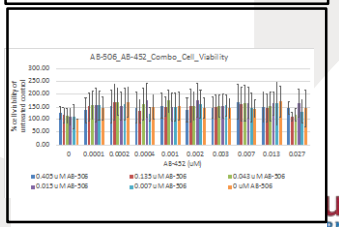












HepDE19 (rcDNA/bDNA) | HepG 2.2.15 (rcDNA/bDNA) | HepDE19 (rcDNA/bDNA) | HepG 2.2.15 (sAg) | HepG 2.2.15 (rcDNA/bDNA)

In Vitro Combination Studies: Summary

Molecules are mechanistically compatible

HBV Inhibitor		ETV	TDF	TAF	ARB-1467	AB-506
AB-506 Next Gen Capsid Inhibitor*		Additive	Additive	Moderate Synergy	Additive	NA
AB-452 HBV RNA Destabilizer**	sAg	ND	ND	ND	Minor Synergy	ND
	HBV DNA	Moderate Synergy	Additive	Additive	ND	Additive

- *HepDE19 HBV cell culture model with rcDNA quantitation
- **HepG2.2.15 HBV cell culture model with HBV DNA and HBsAg quantitation

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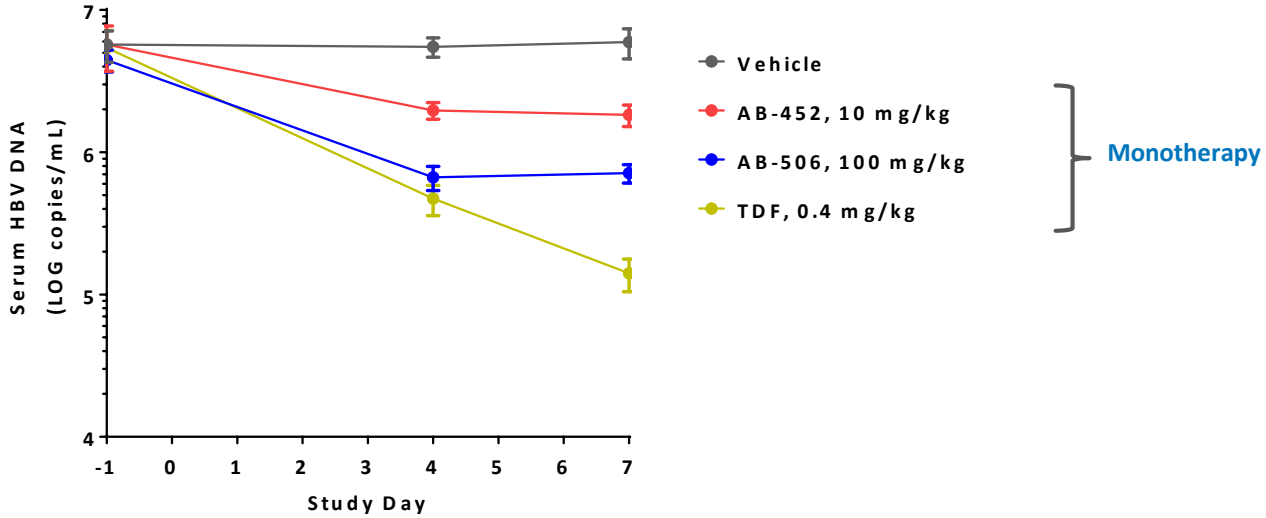
In Vivo Dual and Triple Combination of AB-506, AB-452 and TDF

HDI Mouse Model of HBV: Serum HBV DNA and HBsAg Reductions



- **Dual combinations of AB-506 + AB-452, AB-506 + TDF, and AB-452 + TDF showed strong antiviral activity with mean 1.4, 1.9 and 2.2 $\log_{10}$ reductions in serum HBV DNA *vs* the vehicle control, respectively**
- **Triple combination effected larger serum HBV DNA reduction of 2.8 $\log_{10}$ *vs* the vehicle control**
- **As expected, serum HBsAg reductions observed only in AB-452 groups**

Once-Daily Oral Dose × 7 Days
Mean (n=7-8) ± SEM
Open symbol indicates close to LLOQ

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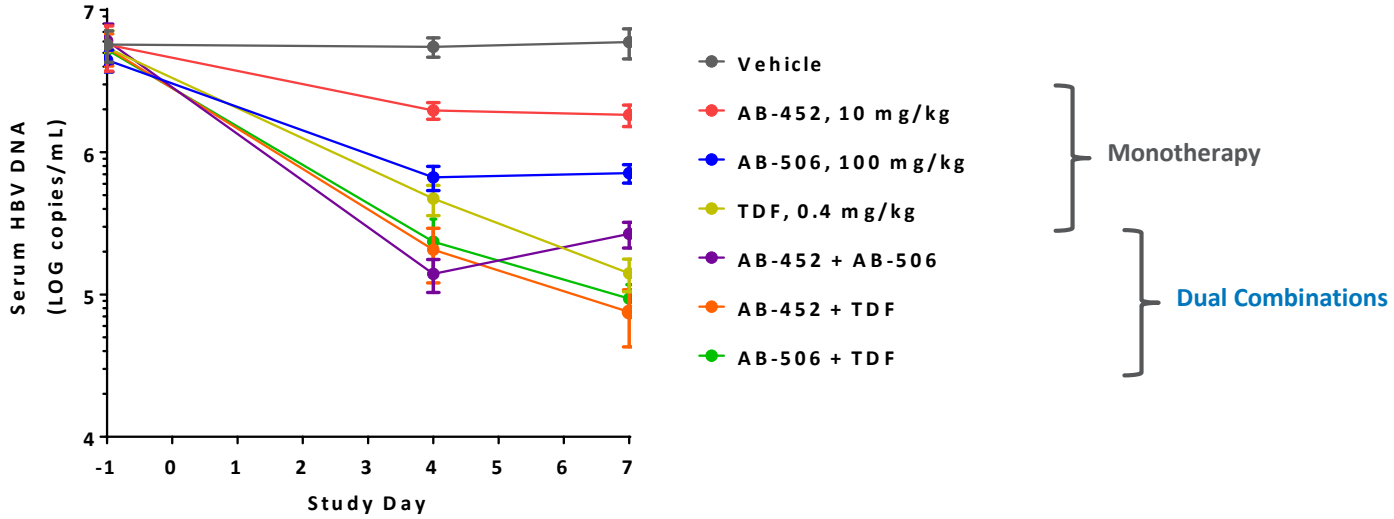

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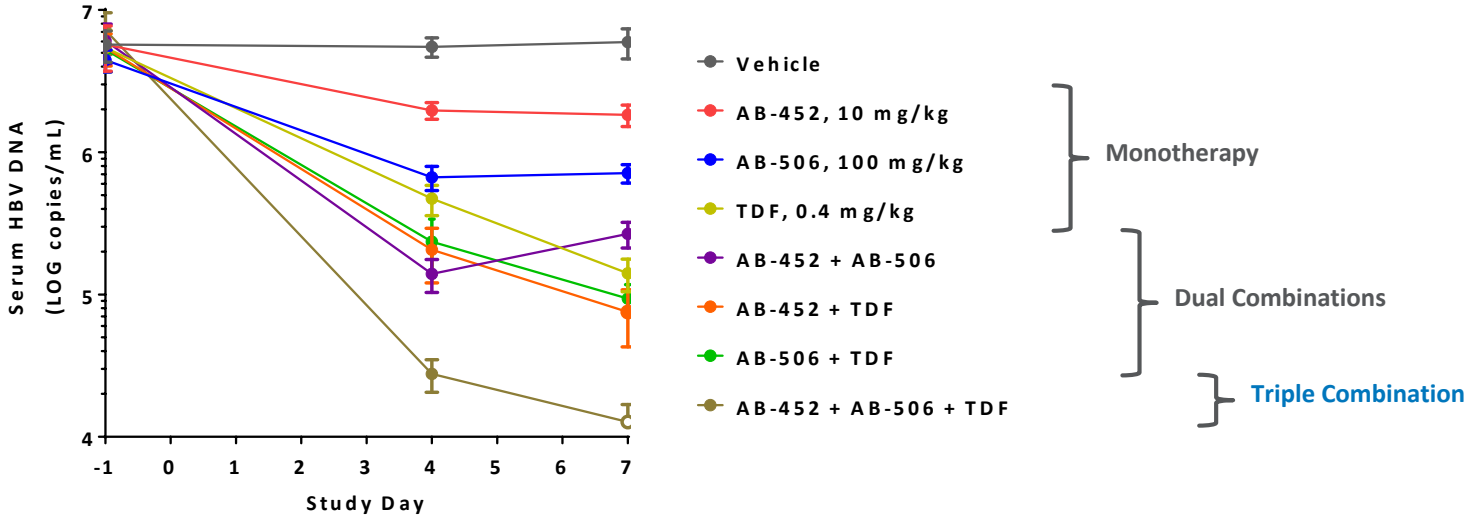

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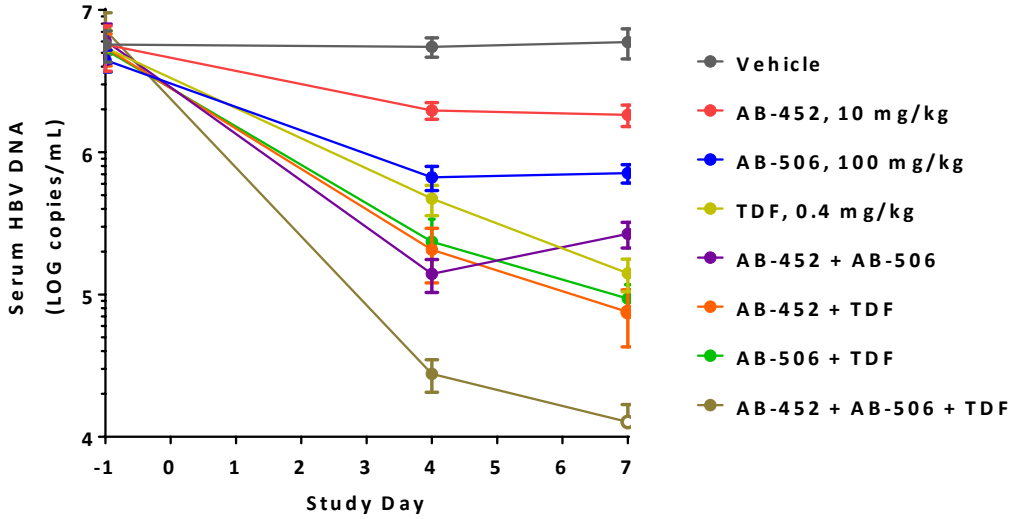

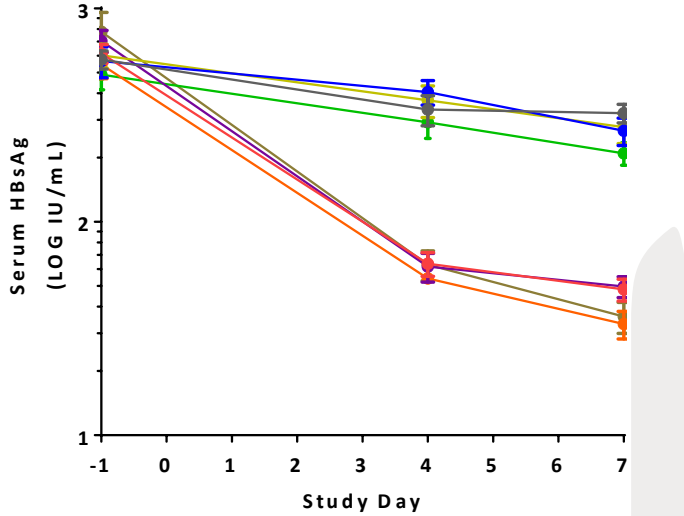

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Mean (n=7-8) ± SEM
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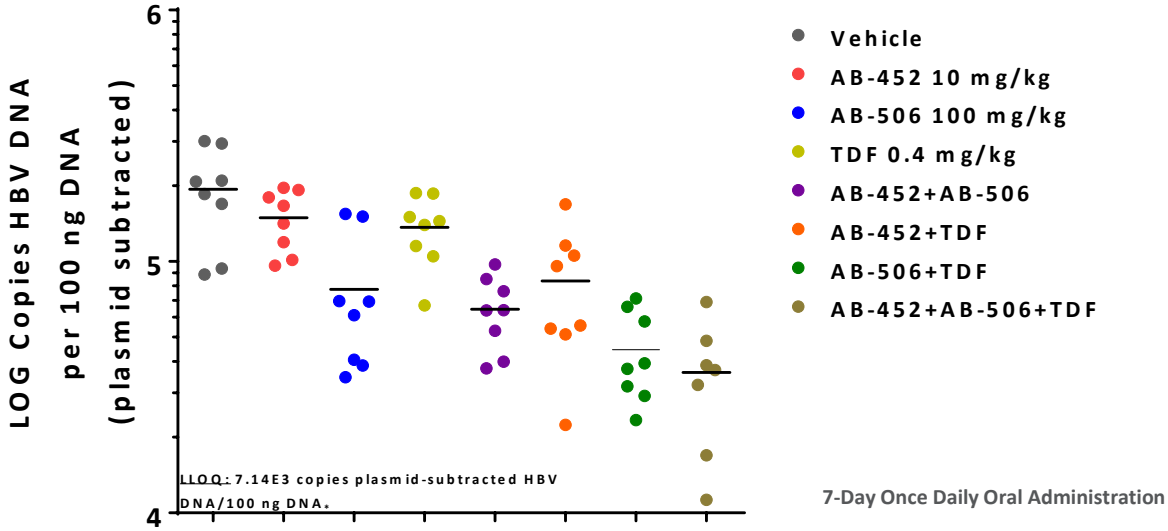
In vivo Dual and Triple Combination of AB-506, AB-452 and TDF

HDI Mouse Model of HBV: Liver HBV DNA and HBsAg Reductions



- Liver HBV DNA reductions reflect serum HBV DNA reductions
- AB-506 showed greater effect on liver HBV DNA reduction than TDF
- Only AB-452 containing groups showed liver HBsAg reductions

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Summary

- Key to therapeutic success will involve combination of different MoA agents
  - Reduce/Suppress Viral DNA and Antigens
  - Reawaken/Boost host immune responses
- Agents with novel MoA undergoing clinical evaluation; more in preclinical stages
  - eg: Capsid Inhibitors, HBV RNA Destabilizers, RNAi Agents, NA, others
- *In vitro* and *in vivo* antiviral evaluations of Capsid Inhibitor AB-506, RNA Destabilizer AB-452, LNP siRNA ARB-1467 and NA agents show favorable additive to synergistic effects in combination

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Acknowledgments

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