GILEAD
Creating Possible

Liver Safety Learnings

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Safety Considerations

Target	Mechanism	Type of Toxicity	Example
	Direct acting antivirals	On-target toxicity	*Accumulation of viral proteins leading to cellular stress*
		Off-target toxicity	*Unintended interaction with mitochondrial respiration*
	Host-interacting antivirals		
	Immune agonists	On-target toxicity	*Expression of inflammatory cytokines leading to liver inflammation*

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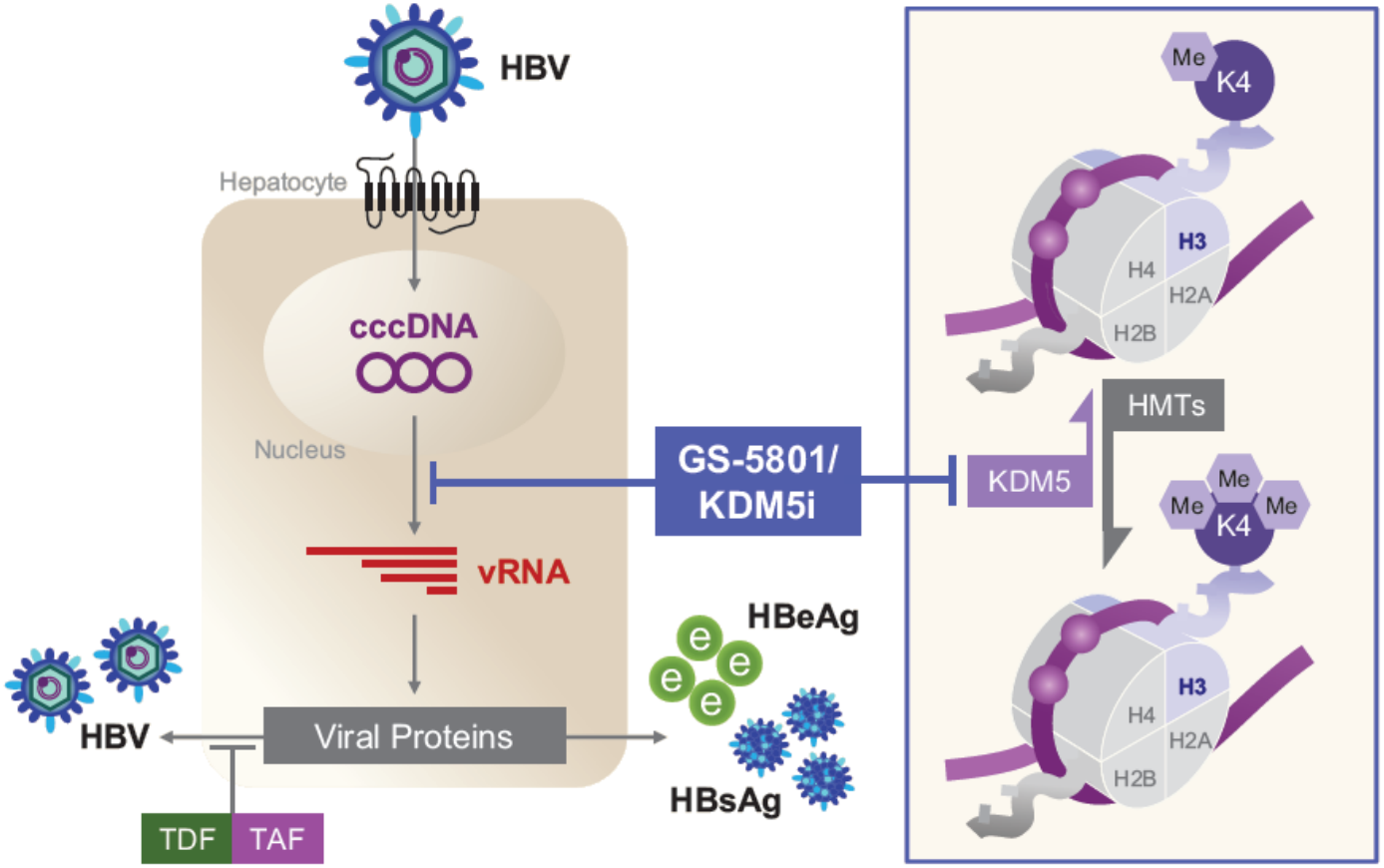
	Host-interacting antivirals	On-target toxicity	*Expression of inflammatory cytokines leading to liver inflammation*
	Immune agonists		

GS-5801 Mechanism of Action



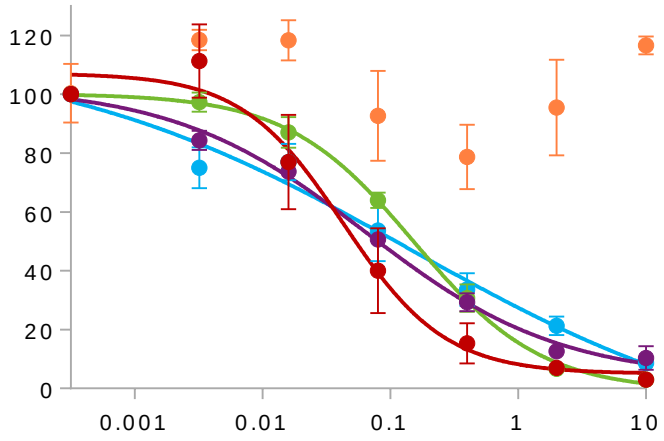
cccDNA, covalently closed circular DNA; H, histone; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HMTs, histone methyltransferases; K4, lysine 4; KDM5i, lysine demethylase-5 inhibitor; Me, methyl; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; vRNA, viral RNA.

- GS-5801 is a liver-targeted prodrug that inhibits the lysine demethylase 5 enzyme (KDM5)
- Inhibiting KDM5 results in the accumulation of methylation at K4 on the tail of H3 histone

Gilmore SA et al. THU-171, ILC 2017; Gilmore SA et al. SAT-160, ILC 2017;

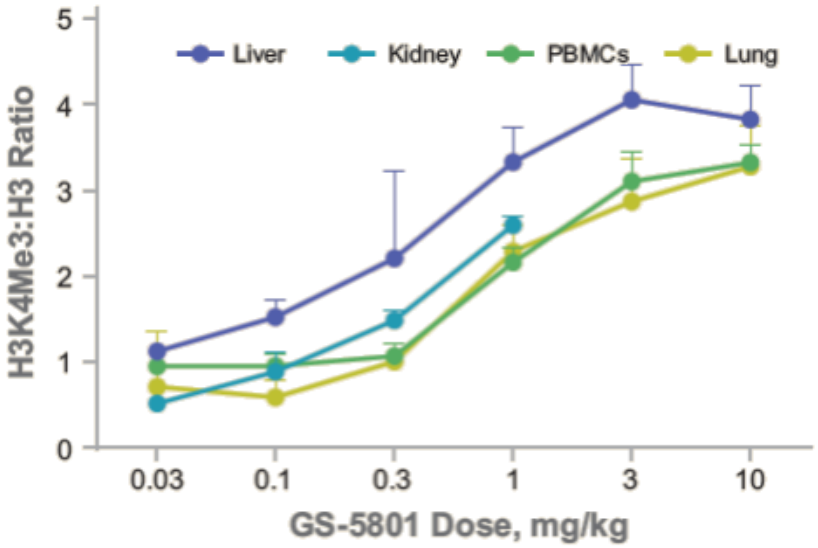
GS-5801 inhibits HBV replication through epigenetic modulation

Activity in PHH System



	EC_{50}, µM
HBV RNA	0.043
HBV DNA	0.065
HBeAg	0.154
HBsAg	0.142
B actin (toxicity)	> 10

In vivo Cyno Pharmacodynamics



In vitro activity across multiple PHH donors

In vivo accumulation of methylation in liver at greater levels than other tissues

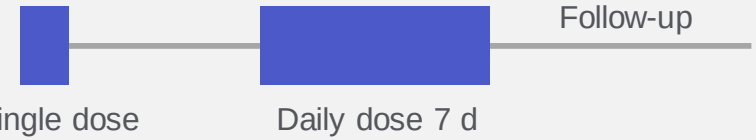
Liver not identified as target organ in preclinical toxicology studies

Gilmore SA et al. THU-171, ILC 2017; Gilmore SA et al. SAT-160, ILC 2017;

GS-5801 Evaluation in Healthy Volunteers and Patients

Phase 1a

N=10/cohort



- Doses of 2mg and 6mg evaluated
- Increase in PD response with 6 mg dosing
- ALT increases seen with 7-day dosing

Phase 1b

N=10/cohort

- Increase in PD response with 4 mg dosing
- No change in viral parameters with 7-day dosing
  - ALT increases seen with 7-day dosing

Confidential

GS-5801 Additional Analyses

Competing cause	Recommended evaluation[a]	Interpretation
1st line testing		
Liver directed medical history and physical exam	Recent travel/ exposures Alcohol consumption Exercise & activity Concomitant medications & HDS product consumption	Consider HAV, HCV, HDV, HEV If excessive or AST/ ALT >2 consider lab testing[a] Possible rhabdomyolysis Drug hepatotoxicity and acetaminophen hepatotoxicity
Acute HAV	Anti-HAV (IgM)	Acute HAV infection
Acute HCV	Anti- HCV HCV RNA (PCR)	Parenteral exposure/ risk factor Acute HCV may be anti-HCV (–) but HCV RNA (+)
Muscle injury	Excessive muscle use history Serum CPK, aldolase	Compare to baseline values, AST frequently elevated as well
Alcoholic liver damage	Urinary ethylglucuronide Serum Phosphatidylethanol	Alcohol use in past 3-5 d Alcohol use in past 3 wk
Pancreaticobiliary disease, HCC	Liver imaging such as ultrasound/ CT or MRI[a]	Evaluate for gallstones, pancreatitis, PV thromboses, malignancy If cholestatic, MRCP recommended

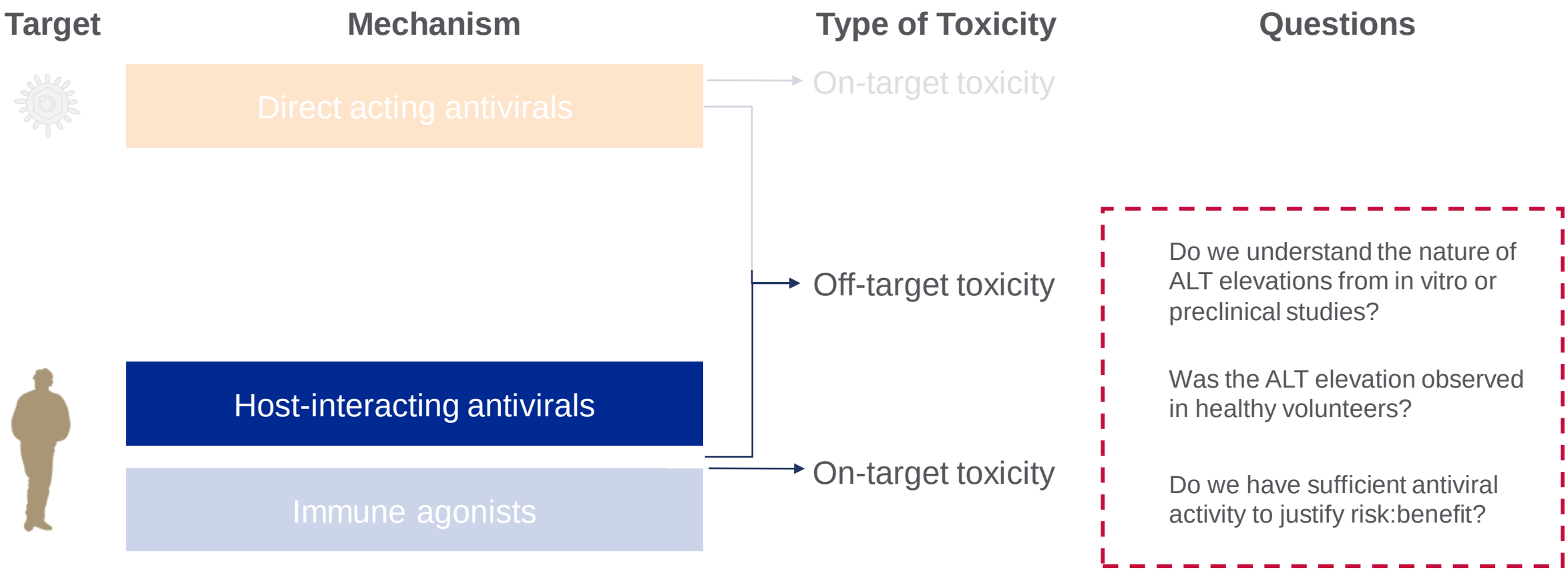
No Adverse Events associated with ALT elevations

No change in Alkaline Phosphatase, total bilirubin, albumin or HBV DNA in subjects treated with GS-5801

Liver imaging, autoimmune panel, viral serology panel not evaluated

1. Fontana RJ et al. J. Viral Hepat. 2019.

Safety Considerations



GS-5801 clinical development was concluded after completion of Ph1b study