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FUNCTION MATTERS

Moving the Needle (literally) in Drug Development

November 30, 2022

Safe Harbor and “Forward-looking Statements”

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The Problem of Chronic Liver Disease

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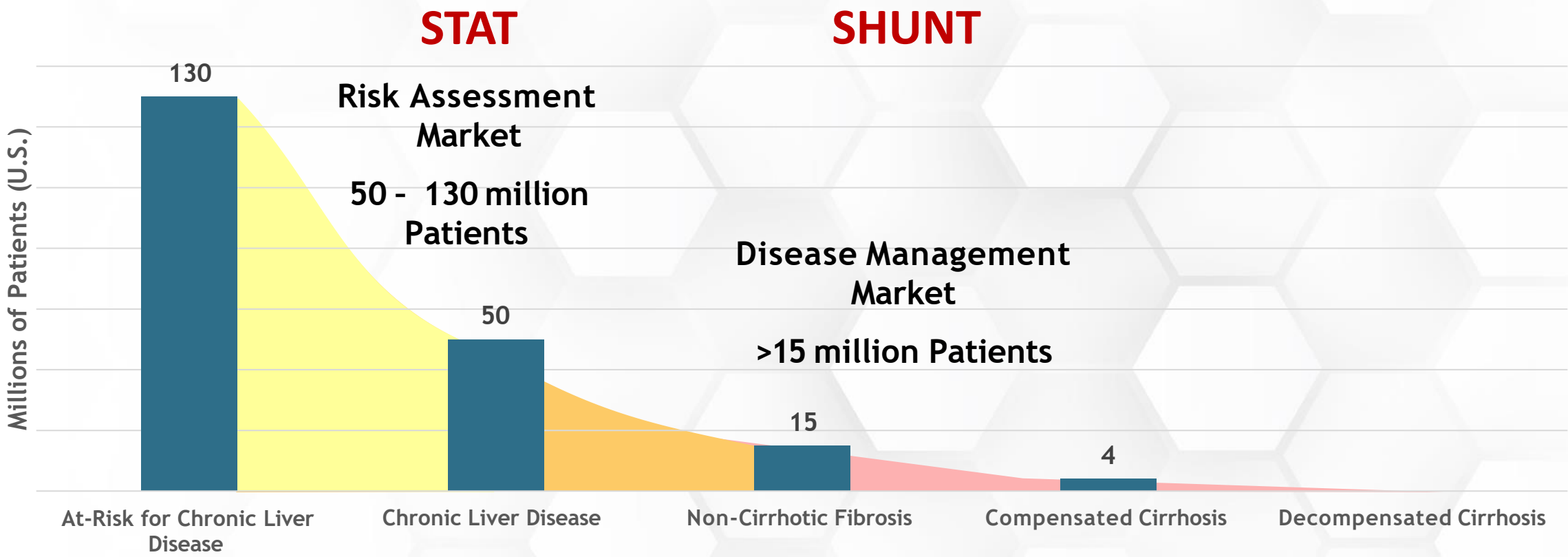
Substantial Need for Better Liver Testing



Sources: See Appendix.

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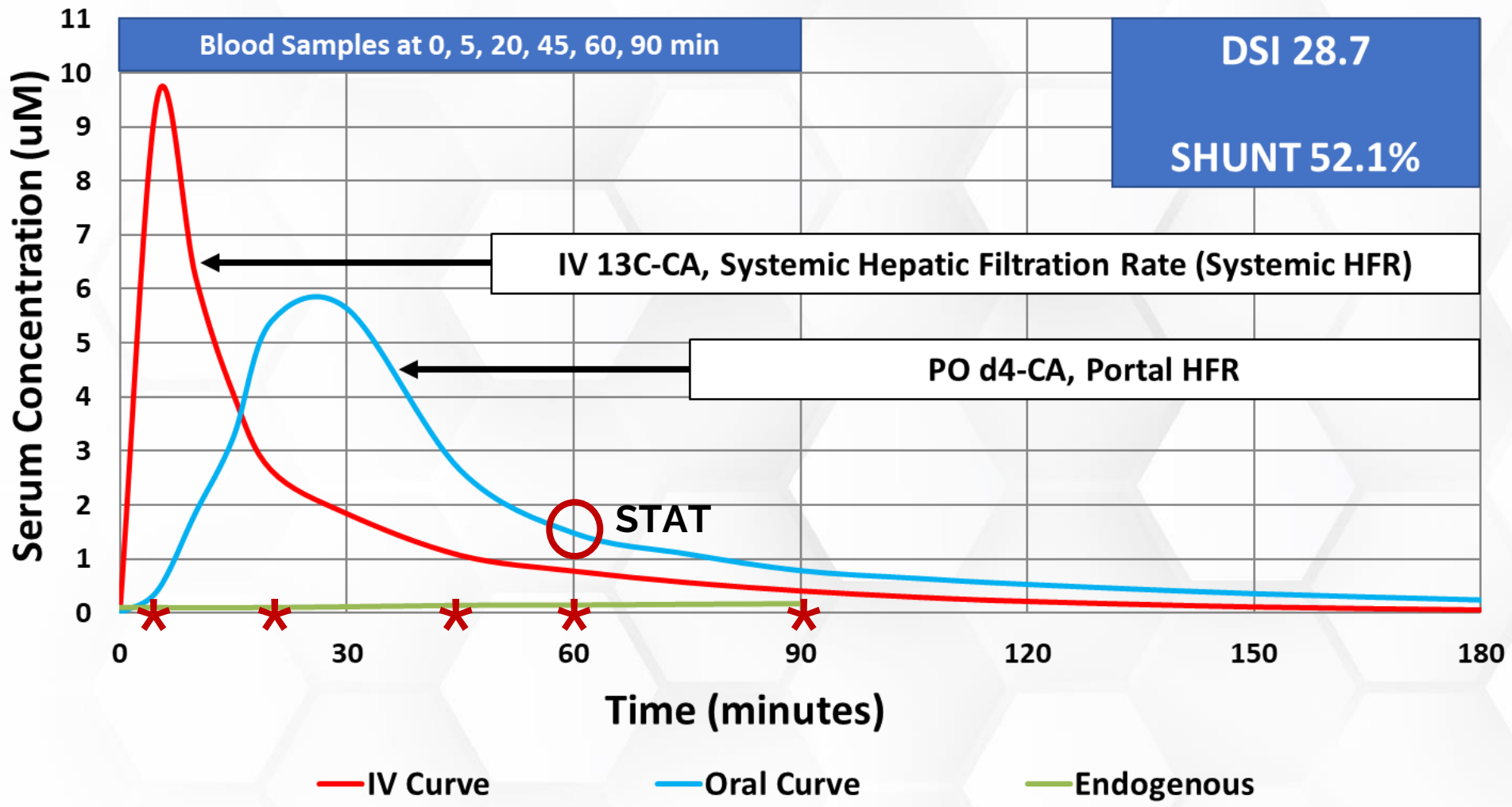
The Dual Cholate Test in a Patient with Liver Disease



Key Discussion Points

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- Recent Experience in Clinical Trials
- Update on Regulatory Pathways
- New research and development

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Recent Experience in Clinical Trials

Hepion Pharmaceuticals Announces Initiation of Dosing in Phase 2 'ALTITUDE-NASH' Liver Function Trial

ALTITUDE-NASH is a Phase 2, randomized, multi-center, open-label study to evaluate the safety and efficacy of rencofilstat in 60 adult subjects. Subjects included in the trial will be presumed F3, based on either historical biopsy or by using the AGILE 3+ criteria as defined by a screening Fibroscan score alongside common clinical and laboratory parameters. Subjects will be randomized to receive a once daily, oral dose of 75, 150, or 225 mg rencofilstat soft gelatin capsules (20 subjects in each dosing cohort) over a period of four months. The **HepQuant 'SHUNT' test, a measure of hepatic function,** will be performed at baseline, and changes in **Disease Severity Index ("DSI")** relative to baseline measurements will be determined at days 60 and 120. Other NASH biomarkers will be collected throughout the study duration.

"When evaluating hepatic drug efficacy, clinicians and regulatory agencies rely on the assessment of many parameters, including liver fat content, inflammation, ballooning, and fibrosis, which require an invasive liver biopsy," stated **Greg Everson, MD, CEO and Chief Medical Officer of HepQuant.** "Although biopsy is the gold standard, it measures only surrogates to liver function and does not truly determine the extent of hepatic impairment or improvement with clinical interventions. HepQuant's non-invasive, blood-based technology determines a DSI score that relies on liver-specific uptake of cholate to measure hepatic and portal blood flow; and portal-systemic shunt in patients with chronic liver disease, providing a direct assessment of liver function and physiology. To date, HepQuant's procedure has been successfully utilized in 26 studies with over 1,100 subjects."

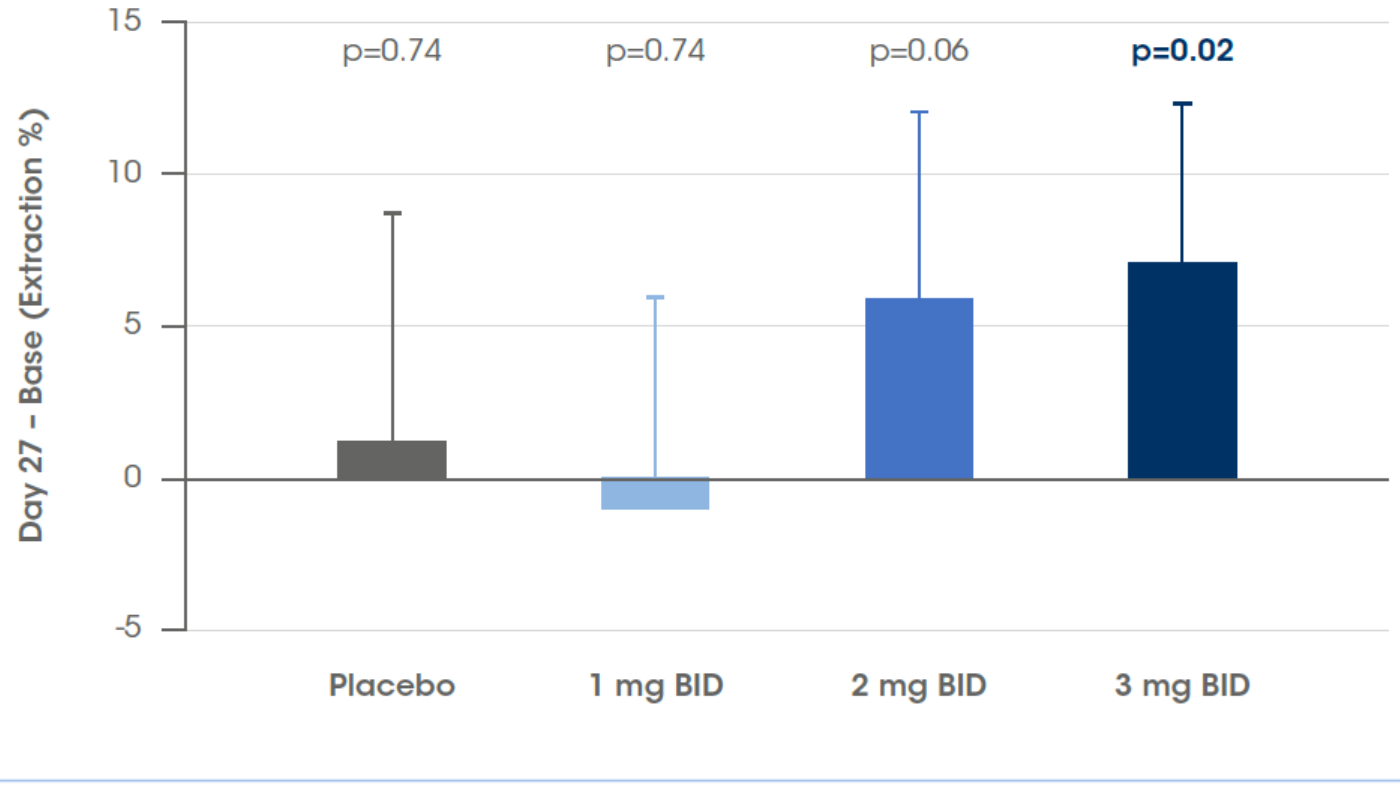
Boehringer Ingelheim

BI 685509 improves first-pass hepatic extraction of cholate in a dose-dependent manner within 27 days: A randomized controlled trial with 6 subjects per arm

Detecting early signal Small Sample Size

First-pass extraction of d4-CA increased in a dose-dependent manner with BI 685509

Figure 2. Change in the first pass extraction % of d4-CA (1 – SHUNT %) from the portal inflow



BID, twice daily; CA, cholate.

Hepatology 2021
Presented at AASLD 2021

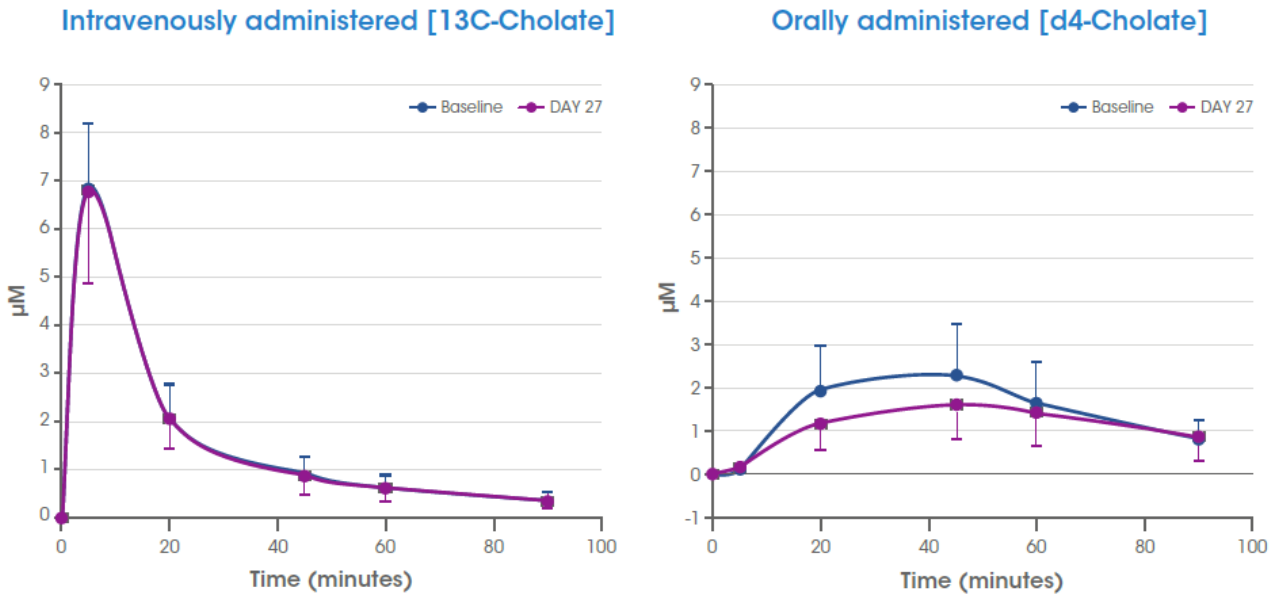
BI 685509 selectively enhanced hepatic uptake of cholate from the portal circulation

Hitting the drug target

Hepatology 2021
Presented at AASLD 2021

BI 685509 selectively lowered the peripheral venous concentration of orally administered d4-Cholate, consistent with a selective effect of enhanced uptake of cholate by the liver from the portal circulation

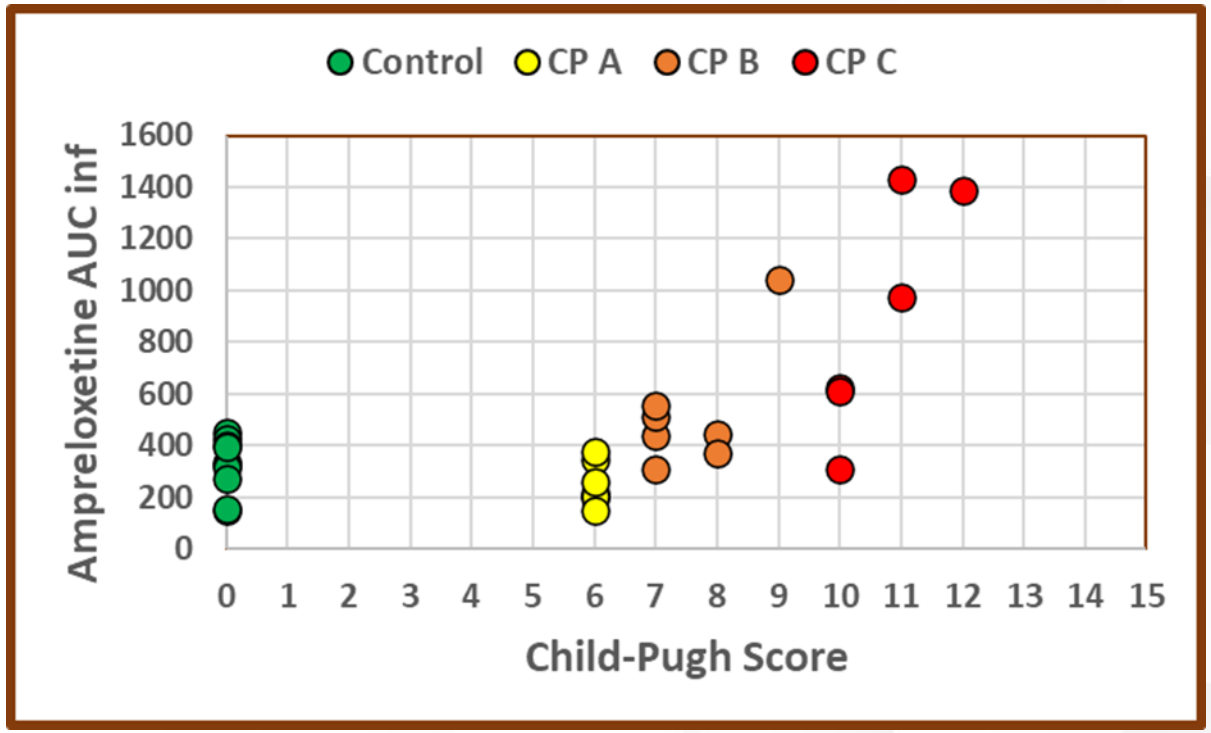
Figure 3: Effect of 3 mg BID BI 685509 on serum concentrations of cholates



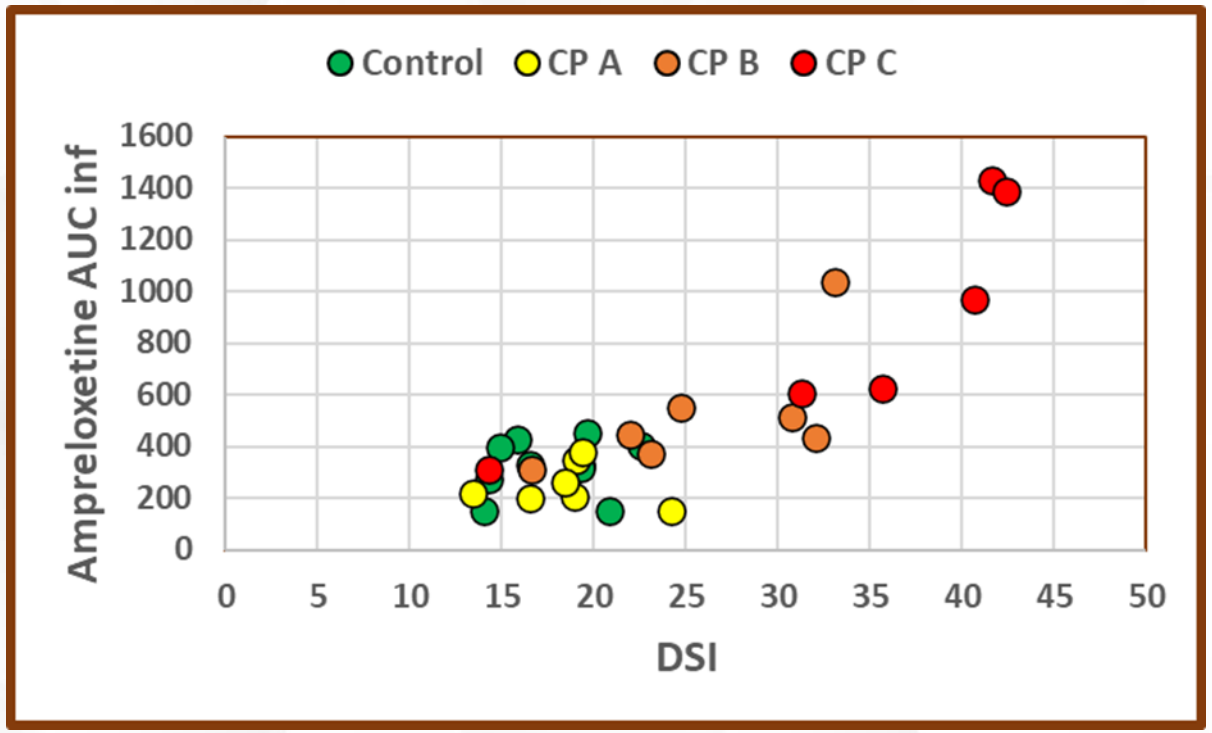
		Systemic HFR	Portal HFR	SHUNT %	Hepatic reserve	DSI
Baseline	Mean	2.96	6.81	49.0	45.9	27.1
	SD	0.54	3.21	14.8	10.7	5.4
DAY 27	Mean	3.10	8.22	42.0	49.4	25.3
	SD	0.91	4.02	12.3	11.9	6.0

BID, twice daily; DSI, disease severity index; HFR, hepatic filtration rate; SD, standard deviation.

Child-Pugh Score



HepQuant DSI



Hepatology 2022; Presented at ACP and AASLD Meetings in 2022.

HepQuant Test Parameters are more predictive of Drug AUC than Child-Pugh Score

Multivariable Regression	Port HFR	STAT	DSI	SHUNT
HQ Variable	**0.06**	**0.0101**	**0.0143**	**0.0024**
CP Score	0.09	0.89	0.31	0.40
Age	0.14	0.89	0.36	0.73
Gender	0.34	0.15	0.30	0.16
Ethnicity	0.57	0.30	0.59	0.49
BMI	0.43	0.44	0.32	0.95
Coeff of Determination, r^2	**0.8187**	**0.8591**	**0.8519**	**0.8851**

Hepatology 2022; Presented at ACP and AASLD Meetings in 2022.

Unique Attributes of Our PIVOTAL Study

(Representative of the current population in the United Stages undergoing EGD Screening for Varices)

- US only – 27 clinical study sites throughout the US
- The etiology of liver disease was nonalcoholic fatty liver disease in 50% of the cases (total n=306)
- Average BMI 35 kg/m^2
- Average age 62 years

- **PIVOTAL Study– older, heavier US population with NAFLD**

- **Literature – younger, leaner Europeans/Asians with viral hepatitis**

SHUNT-V Pivotal Study: STATIN / Metformin Treatment Effect

In Multivariable Analysis the Use of STATINs or METFORMIN were Independently Associated with Lower SHUNT% and Lower DSI

	Impact on SHUNT%		Impact on DSI	
	Decline in SHUNT%	p	Decline in DSI	p
Statin	**-6.3%**	**0.0132**	**-3.3269**	**0.0025**
Metformin	**-5.9%**	**0.0475**	**-2.4337**	**0.0574**
Diabetes Diagnosis	-1.4%	0.64	-0.7239	0.5736
NASH Diagnosis	-1.3%	0.61	-0.2246	0.8343

The combined effect of the use of STATINs plus METFORMIN was 20% less portal-systemic shunting (lower SHUNT%) and 20% better function (lower DSI).

AASLD The Liver Meeting®

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Update on Regulatory Pathways

STAT and SHUNT Timelines*

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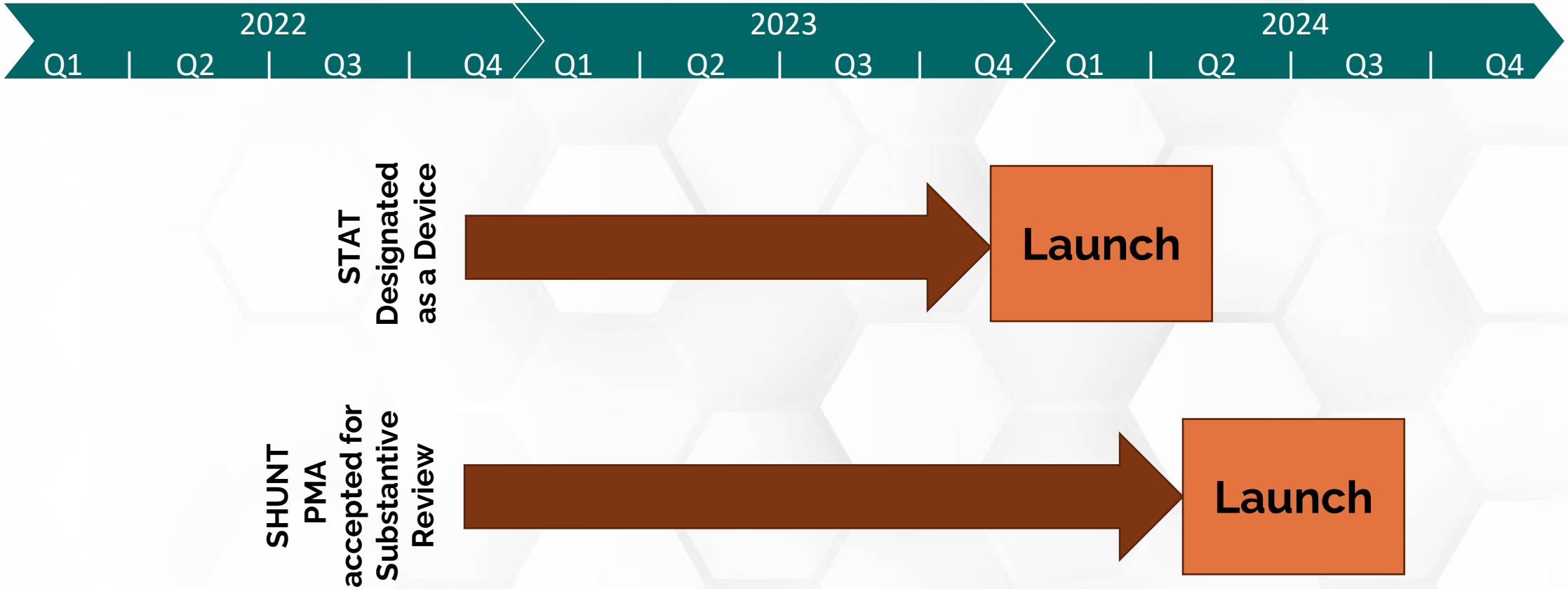

*** Contingent upon FDA review and decisions.**

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New Research and Development

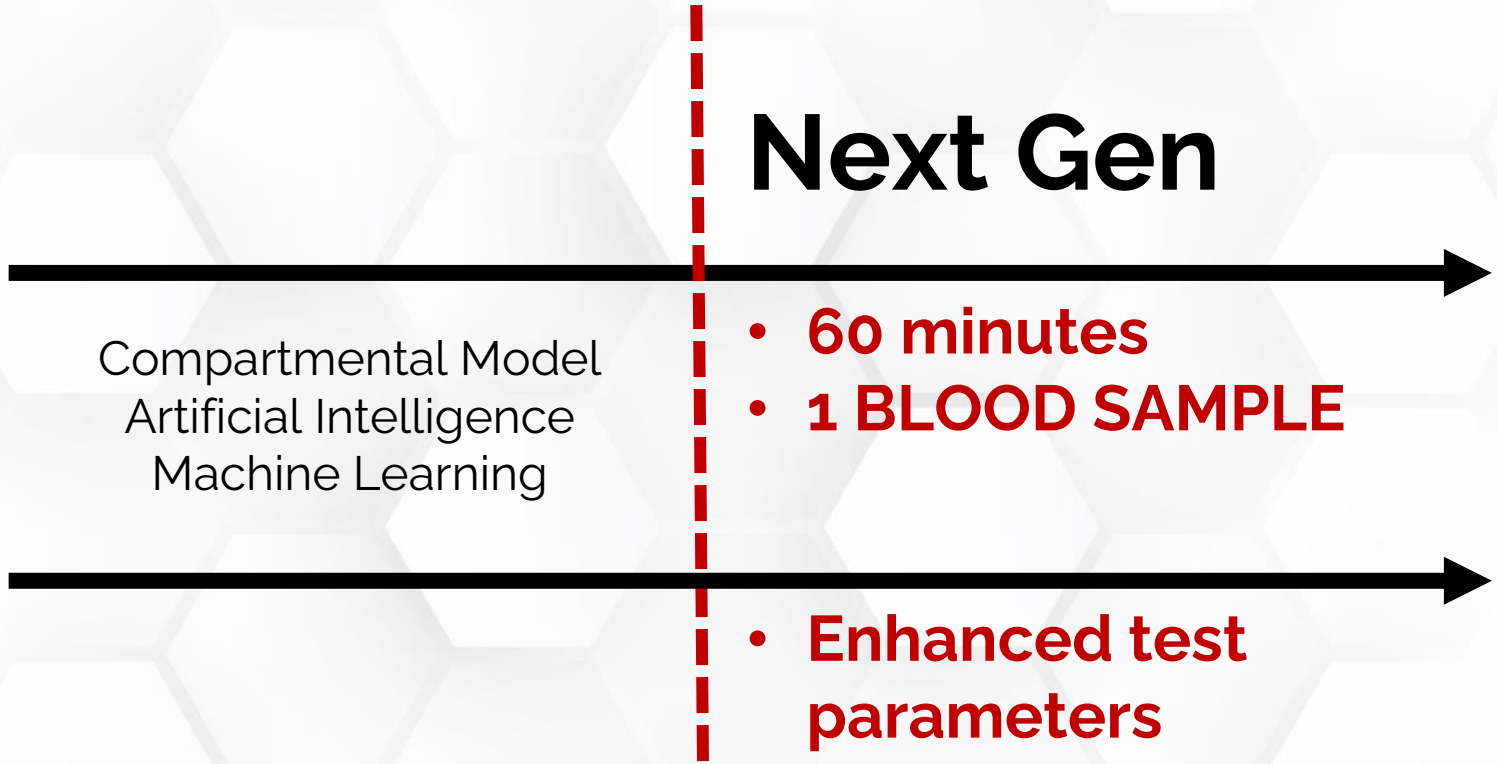
Next Generation Tests: Reducing Samples and Testing Time

SHUNT

- 90 minutes
- 5 BLOOD SAMPLES

STAT

- 1 BLOOD SAMPLE



Appendix: Sources for TAM Estimates

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2) Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018;67(1):123-133. doi:10.1002/hep.29466

3) Schweitzer, Aparna et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013 The Lancet, Volume 386, Issue 10003, 1546 – 1555 DOI: https://doi.org/10.1016/S0140-6736(15)61412-X

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5) Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology*. 2015;62(5):1353-1363. doi:10.1002/hep.27978

6) Wong T, Dang K, Ladhani S, Singal AK, Wong RJ. Prevalence of Alcoholic Fatty Liver Disease Among Adults in the United States, 2001-2016. *JAMA*. 2019;321(17):1723-1725. doi:10.1001/jama.2019.2276