Emricasan (IDN-6556) administered orally for 28 days lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension

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Background

Caspases play a central role in apoptosis and inflammation

Caspases produce hemodynamically-active, pro-inflammatory microparticles from apoptotic cells

In cirrhosis, these microparticles appear to contribute to the splanchnic and systemic vasodilatation that maintains and enhances portal hypertension **Rautou PE et al. Gastroenterology 2012;143:166-176**

Emricasan (IDN-6556), an oral pan-caspase inhibitor has been shown to reduce portal pressure and improve survival in a murine model of portal hypertension **Eguchi A, et al. Hepatology 2015 62(S1):1522 [AASLD abstract 953A]**

Objectives

To evaluate, in patients with compensated cirrhosis and portal hypertension, the effect of emricasan on:

- **portal pressure (determined by the hepatic venous pressure gradient or HVPG)**
- **safety and tolerability**

Hypothesis

Emricasan lowers portal pressure and is safe in patients with compensated cirrhosis and portal hypertension

Methods

Prospective, proof-of-concept, multi-center (9 U.S. sites), open-label study

Emricasan administered orally at a dose of 25 mg twice a day for 28 days

Hepatic venous pressure gradient (HVPG) assessed before and after emricasan

One expert (J.B.) read all HVPG tracings

Investigators had access to all the data

Methods:
Inclusion and Exclusion Criteria

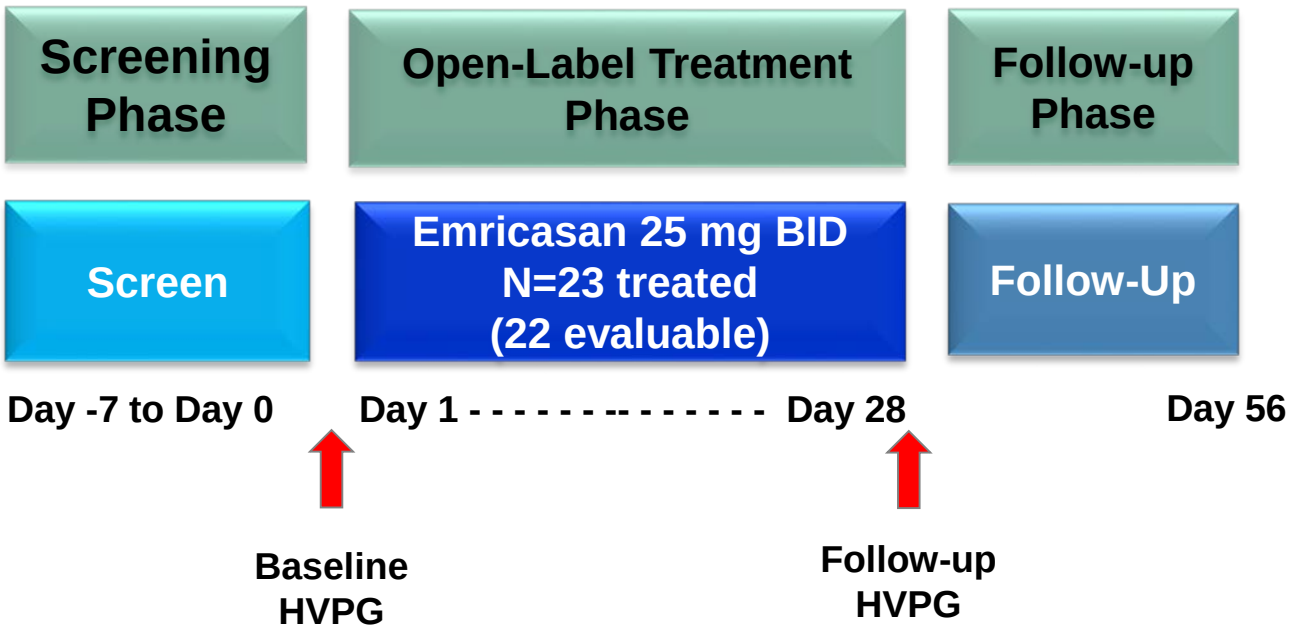
Inclusion criteria

- **Cirrhosis (HCV, NASH, limiting alcoholic etiology to <40%)**
- **Portal hypertension, i.e. HVPG > 5 mmHg**

Main exclusion criteria

- **Decompensation or HCC at entry**
- **Use of vasoactive drugs (beta-blockers, nitrates, PDE inhibitors)**
- **HCV-infected subjects receiving or planning on receiving anti-viral therapy during the course of the study**
- **Concomitant HIV infection**
- **Unwillingness to undergo contraception from screening to one month after last dose of emricasan**

Study Schema



Methods:
Study Outcomes

Primary (Baseline to Day 28)

- Change in HVPG
- Change in cCK18 serum levels (marker of apoptosis and indicator of caspase activity)

Secondary (Baseline to Day 28)

- Change in liver enzymes (ALT, AST), caspase 3/7, MELD, Child-Pugh score
- Development of decompensation

Safety Variables (Baseline to Day 56)

- Adverse events
- Vital signs
- Laboratory tests
- EKG (QTc interval)

Statistical Analyses

- **Analysis in the entire group**
- **Post-hoc analyses of baseline HVPG subgroups: <12 or ≥12 mmHg (severe portal hypertension)**
  - Post-hoc sensitivity analysis conducted using an HVPG cutoff of 10 mmHg
- **Analyses of primary endpoints used parametric tests given no major violations of normality**
  - Sensitivity analyses using non-parametric tests yielded similar results

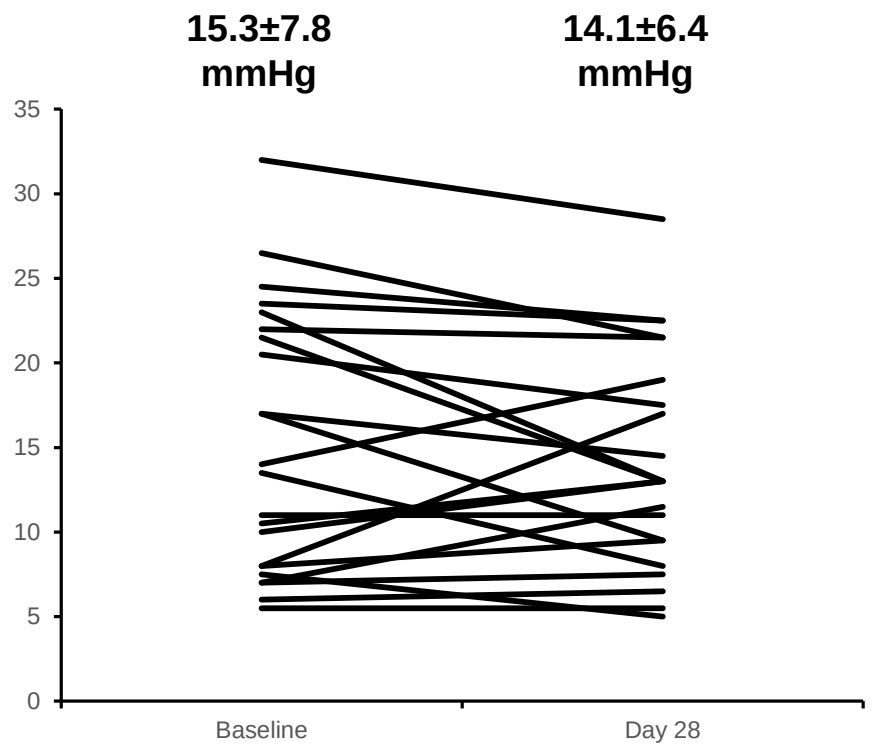
Results:
Baseline Characteristics of the Cohort (N=23)

	Median*	Range (min, max)
Age (yrs)	59	48-80
Gender (% male)	16 (69.6%) male	N/A
Race (% Caucasian)	21 (91.3%) Caucasian	N/A
Etiology of cirrhosis		
- NASH	13 (56.5%)	N/A
- HCV (± alcohol)	9 (39.1%)	N/A
- Alcohol alone	1 (4.3%)	N/A
BMI (kg/m^2)	32.4	17.9 – 44.9
Platelet count (K/mm^3)	104	43 - 199
ALT (U/L)	25	10 - 99
AST (U/L)	35	16 - 83
Total bilirubin (mg/dL)	0.73	0.31 – 3.08
Albumin (g/dL)	4.2	2.7 – 4.9
INR	1.1	0.9 – 1.6
Number with Child Class A	20 (87%)	N/A
MELD score	8	6 - 15
HVPG (mmHg)	13.5	5.5 – 32.0

*Except where percentages are in parentheses

Results:
Overall, there were no significant differences in HVPG

Entire Group (N=22*)



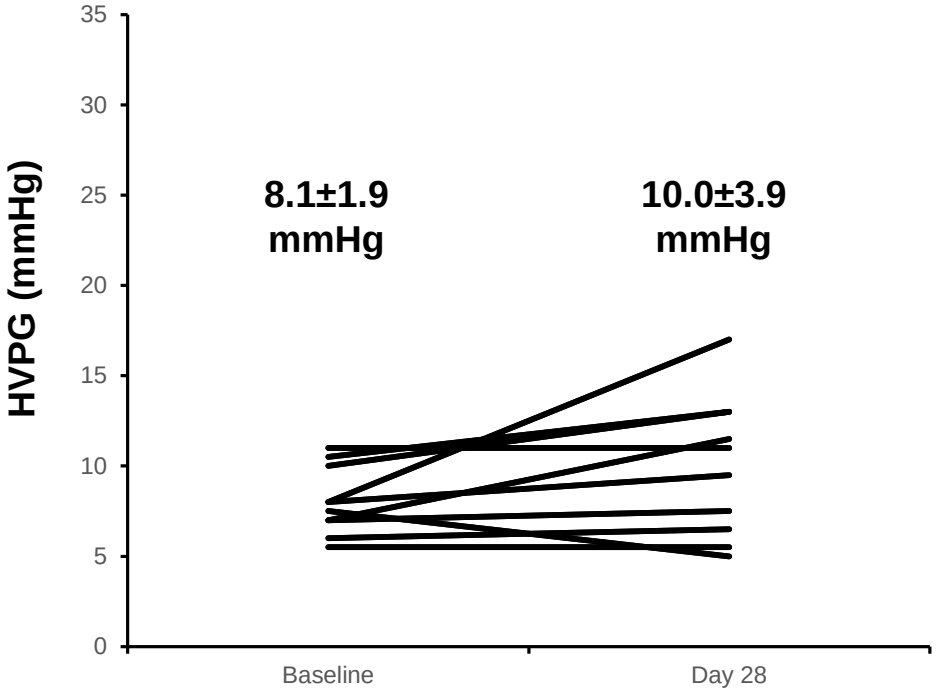
Mean change: ↑ 1.2% (↓ 1.1±4.6 mmHg), p=0.26

***1 subject withdrew after 1 week due to adverse events of abdominal bloating and conjunctivitis (no follow-up HVPG)**

Results:

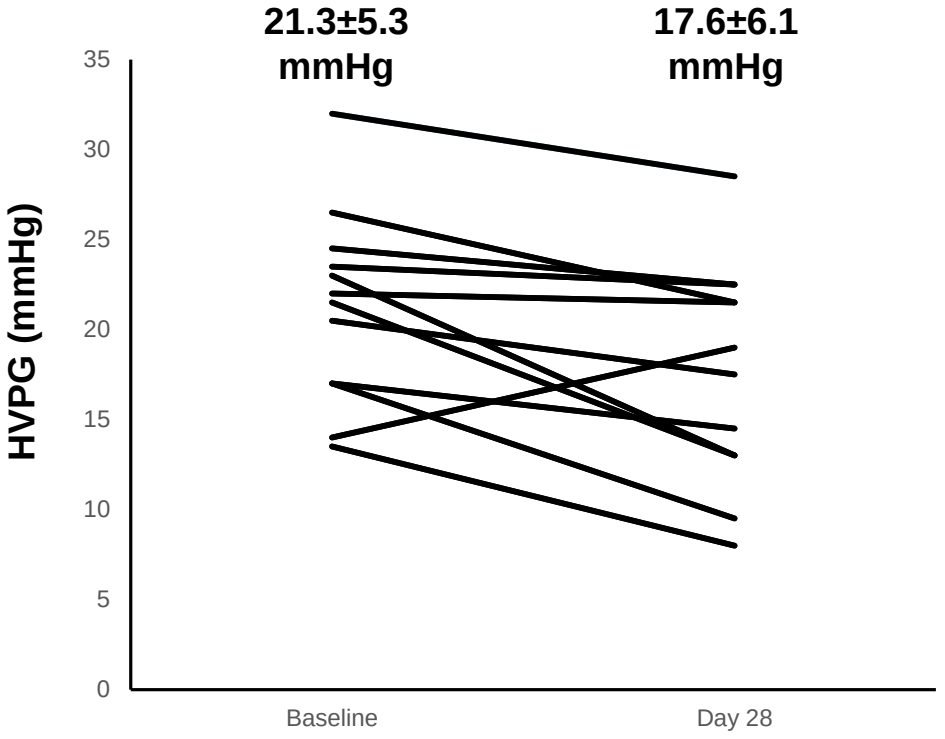
A clinically meaningful reduction in HVPG was observed in patients with severe portal hypertension (HVPG ≥12 mmHg) at baseline

Baseline HVPG < 12 mmHg (N=10)



Mean change: ↑ 23.1% (↑ 1.9±3.2 mmHg), p=0.12

Baseline HVPG ≥ 12 mmHg (N=12)



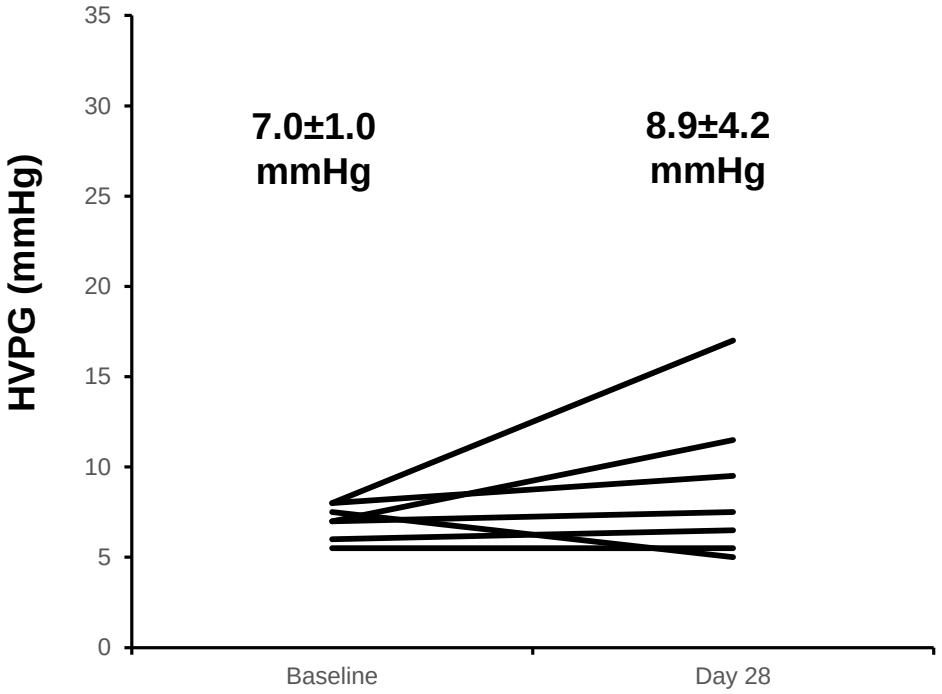
Mean change: ↓ 17.2% (↓ 3.7±4.0 mmHg), p<0.003*

8/12 had a ≥10% decrease;
4/12 had a ≥20% decrease;
2/12 HVPG ↓ below 12 mmHg

***p-value not adjusted for multiple testing**

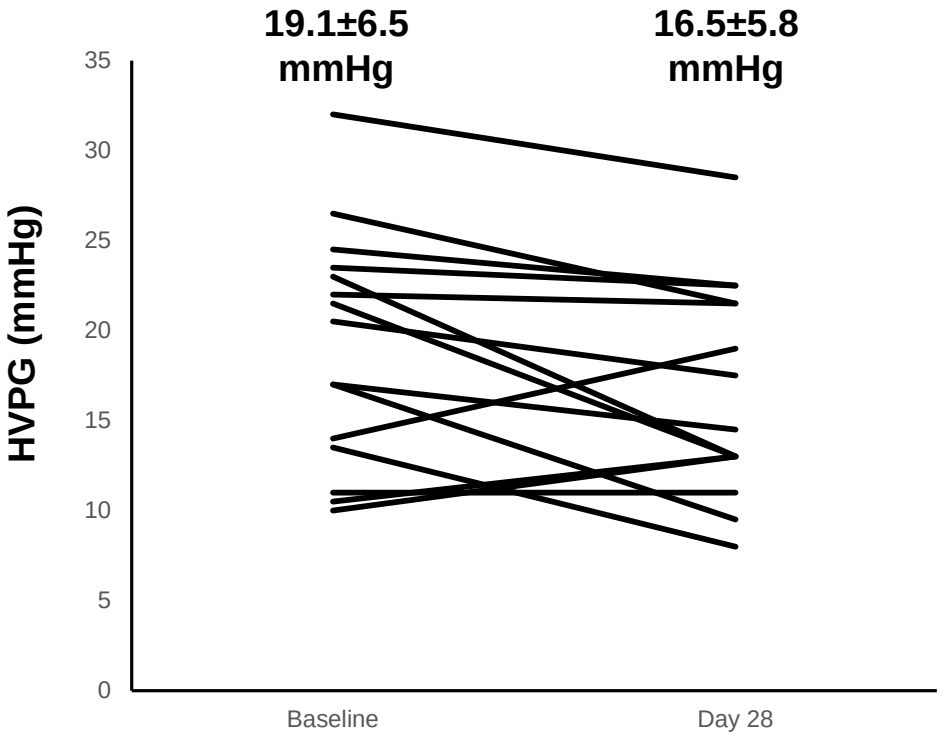
Results:
Sensitivity analyses using HVPG cut-off of 10 mmHg (clinically significant portal hypertension) showed similar results

Baseline HVPG < 10 mmHg (N=7)



Mean change: ↑ 25.4% (↑1.9±3.7 mmHg), p=0.23

Baseline HVPG ≥ 10 mmHg (N=15)

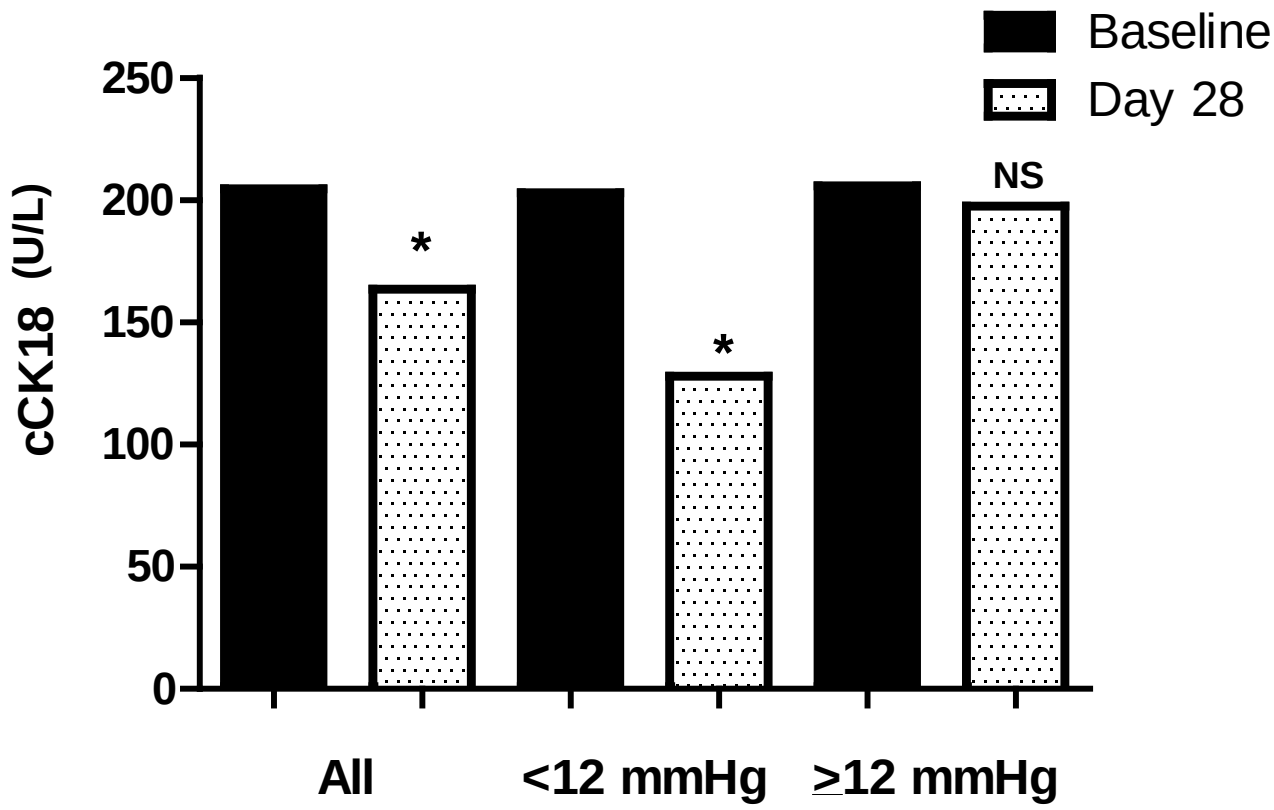


Mean change: ↓ 10.1% (↓ 2.6±4.3 mmHg), p=0.03*

***p-value not adjusted for multiple testing**

Results:

cCK18 levels decreased in entire group but were relatively low at baseline



*p<0.05, not adjusted for multiple testing
NS=not significant
Data are geometric means

Results:
Changes in clinical, biochemical and biomarker parameters

	HVPG < 12 mmHg (N=10)	p	HVPG ≥ 12 mmHg (N=13)	p
	Median (Range)		Median (Range)	
Systolic BP (mmHg)	-2 (-12, 16)	0.85	0 (-14, 17)	0.99
Heart rate (bpm)	-4 (-22, 10)	0.20	0 (-29, 24)	0.98
BMI (kg/m^2)	+0.3 (-0.2, 1.5)	0.05	0 (-1.9, 1.4)	1.0
Platelet count (K/mm^3)	0 (-31, 24)	0.77	-8 (-33, 13)	0.08
AST (U/L)	-2.5 (-23, 68)	0.32	-4 (-29, 8)	0.03
ALT (U/L)	0 (-61, 43)	0.44	-5 (-15, 4)	0.008
Total bilirubin (mg/dL)	-0.1 (-0.6, 0.3)	0.29	0 (-0.4, 0.5)	0.78
Albumin (g/dL)	-0.15 (-0.4, 0.3)	0.16	-0.1 (-0.5, 0.4)	0.40
INR	0 (-0.1, 0.1)	0.34	0 (-0.2, 0.1)	0.74
MELD score	0 (-2, 1)	0.38	0 (-2, 2)	0.43
Caspase 3/7* (RLU)	-746 (-3452, 424)	0.009	-655 (-2337, 1107)	0.06

No correlation was found between changes in these parameters and changes in HVPG

*Excludes 1 outlier

p-values not adjusted for multiple testing

Results:
Emricasan was generally well tolerated

	Baseline HVPG		
	<12 mmHg (N=10)	≥12 mmHg (N=13)	All Subjects (N=23)
Number of AEs	11	49	60*
Number of related AEs	7	8	15
Subjects with AEs	6 (60.0%)	9 (69.2%)	15 (65.2%)
Subjects with serious AEs	0	1 (7.7%)*	1 (4.3%)
Subjects with moderate AEs	4 (40.0%)	6 (46.2%)	10 (45.3%)
Subjects with severe AEs	0	1 (7.7%)**	1 (4.3%)
Subjects with AEs leading to discontinuation	0	1 (7.7%)	1 (4.3%)

AEs occurring in >5% subjects	All subjects N (%)
Fatigue	5 (21.7%)
Headache	3 (13.0%)
Peripheral edema	3 (13.0%)
Dehydration	2 (8.7%)
Diarrhea	2 (8.7%)
Constipation	2 (8.7%)
Nausea	2 (8.7%)

* One subject had 3 serious AEs (SIRS, acute respiratory failure, dyspnea) occurring 10 days after last dose of study drug, assessed unrelated, along with 24 other AEs

** All AEs except 2 (SIRS, anemia in the same subject with 3 SAEs) were mild to moderate in severity

- No clinically significant changes in routine labs, vital signs, or ECG (QTc)

No subject developed cirrhosis decompensation (ascites, encephalopathy, hemorrhage)

Limitations

Study is small, not placebo-controlled, relatively short duration

Classification of patients with severe portal hypertension was established post-hoc

Summary

Emricasan administered orally for 28 days was associated with a clinically meaningful decrease in portal pressure in patients with compensated cirrhosis and severe portal hypertension

- Although a hemodynamic mechanism cannot be ruled out, concomitant decreases in AST/ALT suggest an intrahepatic effect

Emricasan was generally well-tolerated

Future directions

Trials of longer duration will elucidate potential additional long-term effects due to microvascular remodeling or amelioration of vasodilatation

Randomized, placebo-controlled Phase 2 studies that will assess different doses of emricasan using an HVPG endpoint at 6 months are planned for 2016

Acknowledgements

Nine U.S. Sites Screened/Enrolled Subjects:

- **Albert Einstein Medical Center (PI: Dr. Feyssa)**
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