NCSCG AASLD Review 2016 Portal Hypertension and Complications of Cirrhosis

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Disclosures

- Advisory Board: Gilead, Intercept, Abbvie, Mallinckrodt, Salix
- Research: Gilead, Sequana, Mallinckrodt, Ocera, Conatus

LB-27: Quality of Life and Outcomes after Multiple Courses of Granulocyte-Colony Stimulating Factor (G-CSF) and Growth Hormone (GH) in Patients with Decompensated Cirrhosis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background:

- Decompensated cirrhosis carries a high mortality.
- Liver transplantation is the treatment of choice; however, the limited availability of donor organs, high costs, and limited expertise has resulted in widened donor-recipient mismatch and high waitlist mortality.
- The present study investigated whether granulocyte-colony stimulating factor (G-CSF) with or without growth hormone (GH) would promote liver regeneration and improve outcomes in patients with decompensated cirrhosis.

LB-27: Quality of Life and Outcomes after Multiple Courses of Granulocyte-Colony Stimulating Factor)G-CSF) and Growth Hormone (GH) in Patients with Decompensated Cirrhosis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Methods:

- 65 pts with decompensated cirrhosis openly randomized to:
  - (A, n=23) standard medical therapy (SMT) + G-CSF (5µg/kg sc Q12h x5 days then Q3 monthly for 3 days each x 4 cycles) plus GH (1 IU sc daily) or
  - (B, n=21) SMT plus G-CSF or
  - (C, n=21) SMT alone
- Followed monthly for 12 months
- Primary outcome was survival at 12 months
- Secondary outcomes: mobilization of CD34+ cells, CTP, MELD, liver stiffness, nutritional (Mid-arm-circumference [MAC]; Mid-arm muscle circumference [MAMC]), control of ascites, infection, QOL, and AEs at 12 months

LB-27: Quality of Life and Outcomes after Multiple Courses of Granulocyte-Colony Stimulating Factor (G-CSF) and Growth Hormone (GH) in Patients with Decompensated Cirrhosis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Results:

- Baseline characteristics were comparable between groups
- Significantly better 12-month survival in groups A and B than in group C (82.6%, 85.7%, 47.6%, respectively; p=0.019)
- Significant decrease in CTP and MELD scores in groups A and B compared to an increase in group C as compared to baseline ($p<0.05$)
- Improvement in MAC and MAMC in groups A and B ($p<0.05$) while they worsened in group C ($p<0.05$) as compared to baseline
- Ascites better controlled in groups A and B than in group C (p=0.000).
- More infection episodes in group C as compared to groups A and B (p= 0.008)
- Significant reduction in liver stiffness in groups A and B (p=0.000) while no change in group C
- QOL scores improved in groups A and B compared to group C (p=0.000)
- CD34+ cells increased in groups A and B compared to no change in group C (p=0.000, 0.000, and 0.119, respectively)
- The therapies were well tolerated with no major side effects

LB-27: Quality of Life and Outcomes after Multiple Courses of Granulocyte-Colony Stimulating Factor (G-CSF) and Growth Hormone (GH) in Patients with Decompensated Cirrhosis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Authors Conclusions:

- Multiple courses of G-CSF improve 12-month survival in decompensated cirrhosis
- G-CSF led to mobilization of hematopoietic stem cells, improved liver function, ascites control, nutrition, fibrosis, reduced infections
- Resulting in better QOL in patients with decompensated cirrhosis.
- Use of GH was not found to have any additional benefit beyond G-CSF

LB-4: Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background:

- Alcoholic hepatitis has very high short-term mortality
- Recently shown that G-CSF induced bone marrow-derived stem cells improve survival in alcoholic hepatitis [1]
- N-Acetyl Cysteine (NAC) could have a potential therapeutic role in the treatment of acute alcoholic hepatitis [2]
- Study Aims: to assess efficacy of combined G-CSF and NAC therapy in improving outcomes in patients with severe alcoholic hepatitis

1. Singh V et al. 2. Nguyen-Khac E er al. NEJM 2011

LB-4: Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Methods:

- 52 patients with severe alcoholic hepatitis randomized to either
  - SMT + G-CSF (5 µg/kg sc q12h x 5 days (A; n=15) or
  - SMT + G-CSF and IV NAC x 5 days (B; n=17) or
  - SMT alone (C; n= 20)
- Primary outcome: 90-day survival
- Secondary outcomes: mobilization of CD34+ cells, CTP score, MELD score, and modified discriminant function (mDF) scores to day 90

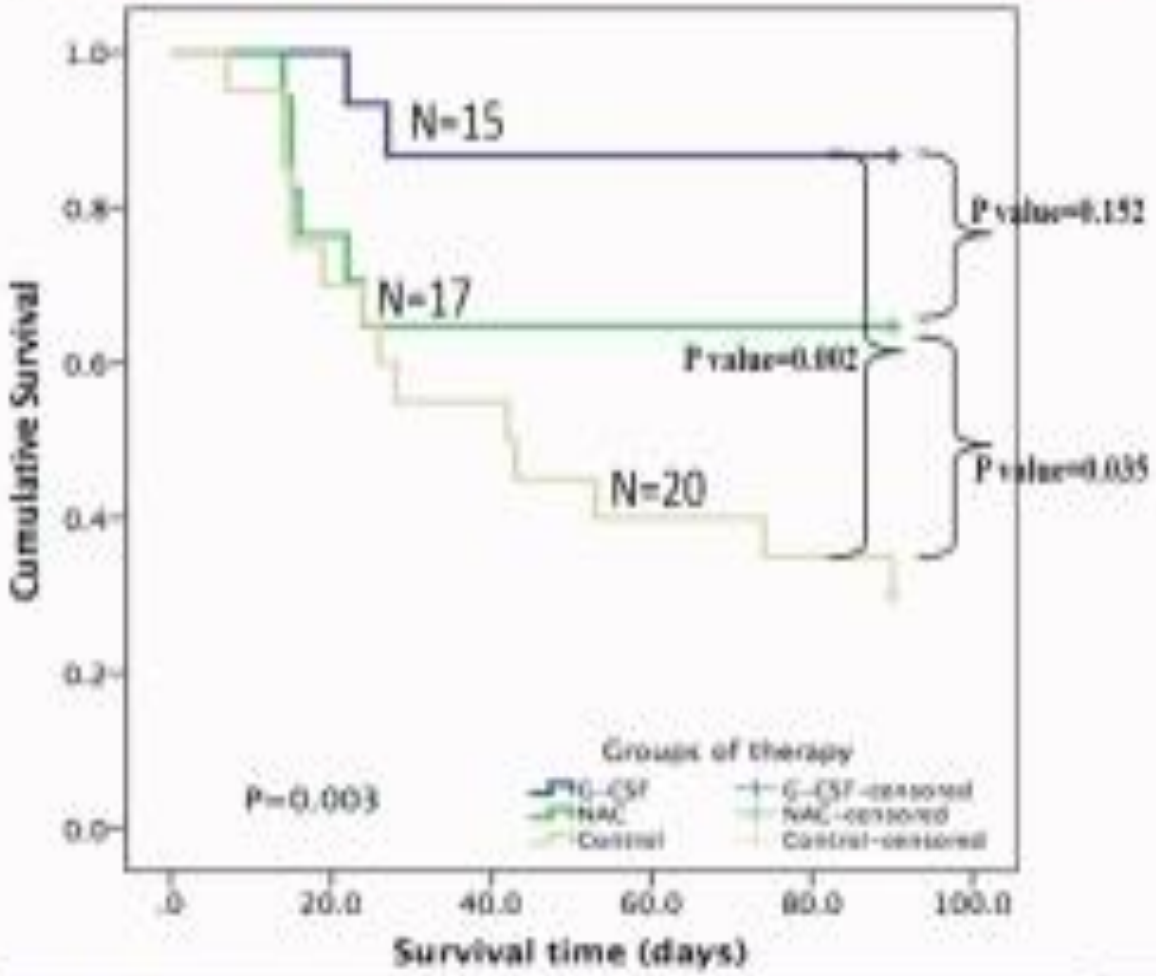
LB-4: Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Results:

- Significantly better survival in groups A and B compared to group C (86.7%, 64.7% vs. 30.0%, *p=0.002* and *p=0.035* respectively*)* at day 90
- Survival was similar in groups A and B
- Significant increase in CD34+ cells (*p=0.000)* in both G-GSF and combination therapy when compared to controls as well as baseline
- Significant reduction in median % change in mDF at 1, 2 and 3 months; in MELD at 2 and 3 months; and in CTP at 3 months in group A as compared to group C (*p<0.05)*
- Significant reduction in median % change in mDF at 3 months and in MELD at 2 months in group B as compared to group C (*p<0.05)*
- There was no significant difference in the frequency of various complications in different groups

Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis



LB-4: Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

Virendra Singh et al. Postgraduate Institute of Medical Education and Research, Chandigarh, India

Authors Conclusions:

- G-CSF improves survival in patients with severe alcoholic hepatitis
- The use of G-CSF led to mobilization of hematopoietic stem cells and improved liver function
- NAC was not found to have any additional benefit compared to G-CSF

LB-6: Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled RCT

Càndid Villanueva et al, Barcelona, Spain

Background:

- The prognosis of (compensated) cirrhosis is good until patients develop clinical decompensation (ascites, GI bleeding, hepatic encephalopathy)
- These complications are driven by the presence of clinically significant portal hypertension (CSPH), defined by a hepatic vein pressure gradient (HVPG) ≥10 mmHg
- The present double-blind, multicenter RCT hypothesized that early lowering of HVPG with β-blockers could decrease the risk of decompensation in patients with compensated cirrhosis and HVPG ≥ 10mmHg who had not yet developed high-risk varices

LB-6: Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled RCT

Càndid Villanueva et al, Barcelona, Spain

Methods:

- Baseline HVPG, during which the acute HVPG response to IV propranolol (0.15 mg/Kg) was investigated; responders (≥10 % decrease in HVPG) were randomized to propranolol vs. placebo and non-responders to carvedilol vs. placebo
- Primary end-point was probability of decompensation or death from any cause
- Pre-planned sensitivity analysis of the primary end-point considering non-liver related deaths as a competing event was also conducted
- Decompensation defined as development of ascites, GI bleeding, or overt encephalopathy
- Secondary end-points included all the above separately, HCC, changes in liver function and AEs

LB-6: Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled RCT

Càndid Villanueva et al, Barcelona, Spain

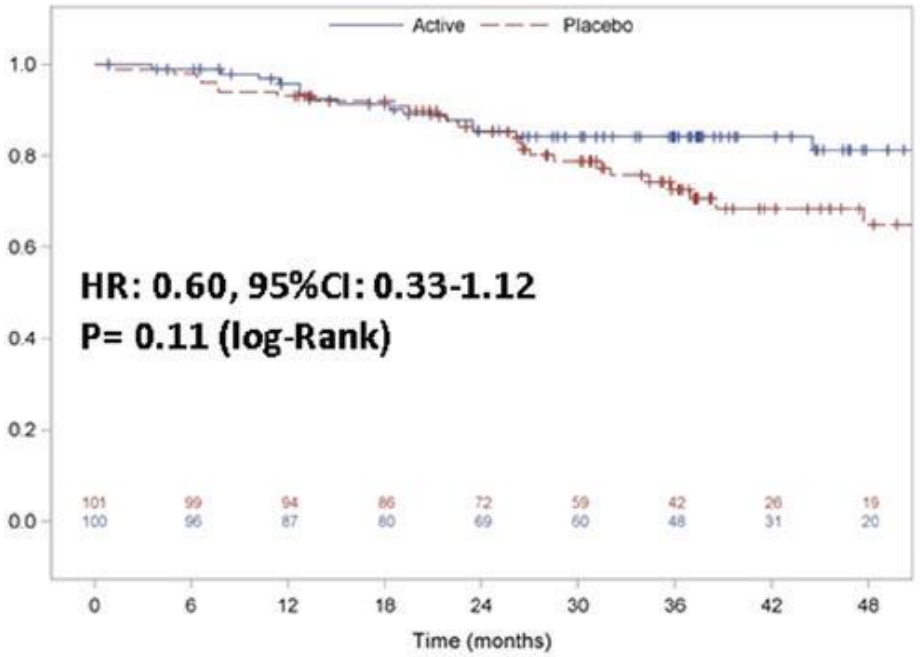
Results:

- 631 patients evaluated, 201 were randomized and followed until decompensation, death or transplantation (median of 36 months, IQR: 24-47 months)
- 101 patients were randomized to placebo and 100 to active treatment (67 responders received propranolol and 33 non-responders received carvedilol)
- Primary end-point occurred in 16% with propranolol/carvedilol vs. 27% with placebo (HR: 0.60, 95% CI: 0.33-1.12, *p=0.11*)
- When non-liver related death was analyzed as a competing event, the results became significant (HR: 0.51, 95%CI: 0.27-0.97, *p=0.041*)
- Significant reduction in the incidence of ascites, the most frequent decompensating event, occurring in 9% vs. 20% of cases (HR: 0.44, 95%CI:0.20-0.97, *p=0.037*)
- There were no differences in other end-points or according to etiology or to administration of propranolol vs. carvedilol

LB-6: Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled RCT

Càndid Villanueva et al, Barcelona, Spain

A



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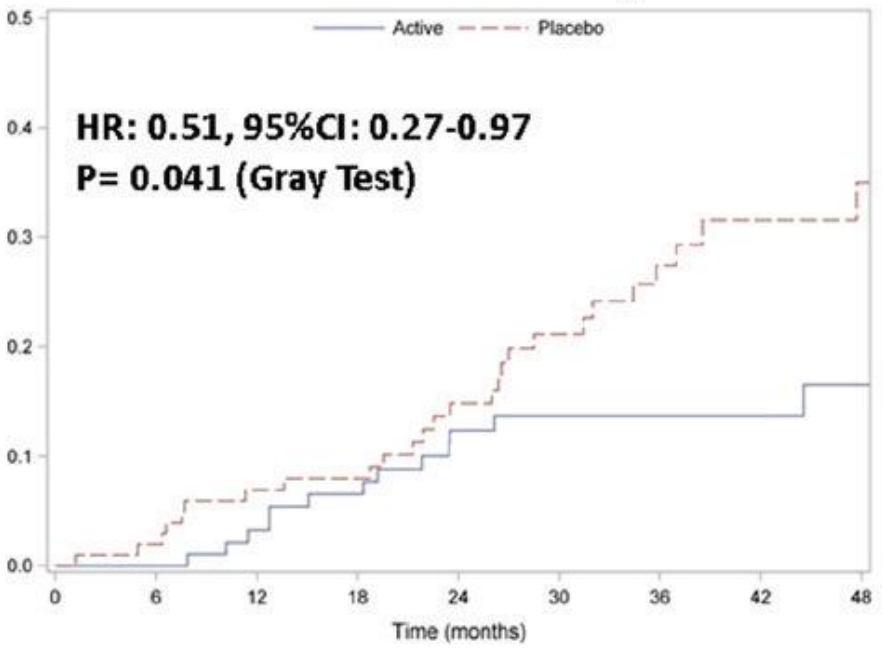


LB-6: Preventing the decompensation of cirrhosis with β-blockers in patients with clinically significant portal hypertension. A multicenter double-blind placebo-controlled RCT

Càndid Villanueva et al, Barcelona, Spain

Authors Conclusions:

- In patients with compensated cirrhosis and CSPH, long-term treatment with β-blockers did not significantly improve decompensation-free survival
- However, β-blockers significantly decreased the risk of decompensation or liver-related death, mainly by decreasing the incidence of ascites
- Suggests that these patients might benefit from β-blockers by reducing progression to decompensation

Abstract 247: A Randomized Controlled Trial Comparing Lactulose plus Albumin vs. Lactulose alone for Treatment of Hepatic Encephalopathy

Barjesh C. Sharma et al, ILBS, New Delhi, India

Background:

- Hepatic encephalopathy (HE) is associated with poor prognosis in cirrhosis
- Drugs used in the treatment of HE are primarily directed at the reduction of blood ammonia
- Lactulose and rifaximin have been shown to be effective in HE

Aim:

- Evaluate the efficacy and safety of albumin plus lactulose vs. lactulose alone for treatment of overt HE

Abstract 247: A Randomized Controlled Trial Comparing Lactulose plus Albumin versus Lactulose alone for Treatment of Hepatic Encephalopathy

Barjesh C. Sharma et al, ILBS, New Delhi, India

Methods:

- Prospective randomized controlled trial
- 120 patients with overt HE randomized to 2 groups
  - Group A: lactulose plus albumin 1.5 gm/kg/day (n=60)
  - Group B: lactulose alone (n=60)
- Primary end point: complete reversal of HE
- Secondary end points: mortality and duration of hospital stay

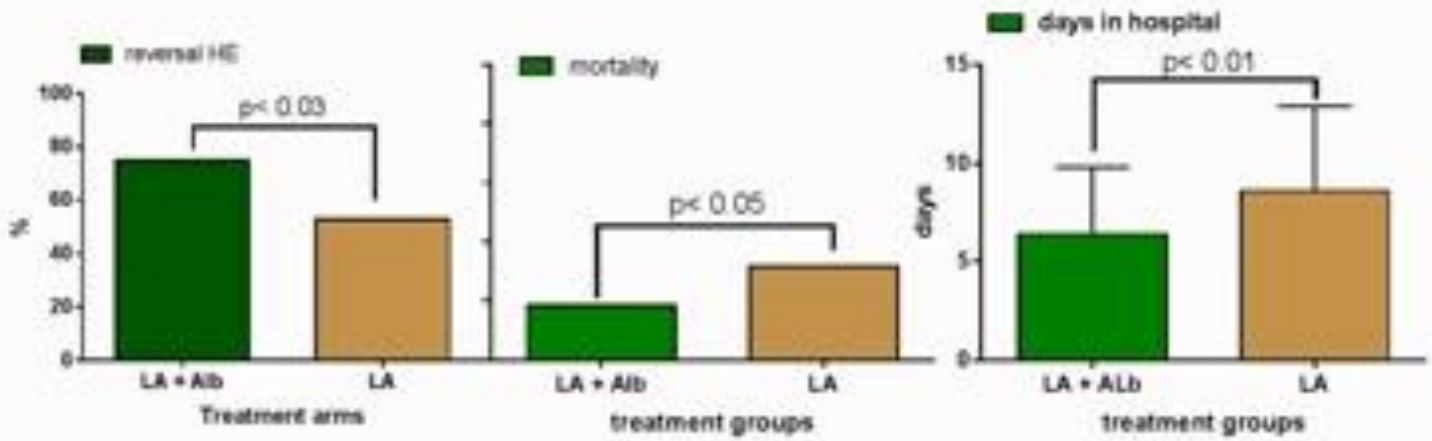
Abstract 247: A Randomized Controlled Trial Comparing Lactulose plus Albumin versus Lactulose alone for Treatment of Hepatic Encephalopathy

Barjesh C. Sharma et al, ILBS, New Delhi, India

Results:

- 120 patients (mean age 40 ± 9 years; M:F 100:20) were enrolled
- 30% patients CTP class B; 70% CTP Class C; mean CTP 9.8 ± 2.1; mean MELD 26.1 ± 5.3
- 22.5% had grade 2, 47.5% had grade 3, and 30% had grade 4 HE at admission
- Rate of complete reversal of HE was significantly higher with lactulose plus albumin (75%) vs. lactulose alone (53.3%) ($p=0.03$)
- Mortality was significantly lower with lactulose plus albumin (18.3%) vs. lactulose alone (31.6%), ($p<0.05$); significantly more deaths in group-B due to sepsis (6 vs. 14, $p=0.01$)
- There was a significant ($p<0.04$) decrease in arterial ammonia, IL-6, IL-18, TNF-alpha and endotoxin in both groups compared to baseline
  - Mean change in arterial ammonia was not different (p=NS) between the groups
  - However, significantly lower ($p<0.04$) levels of IL-6, IL-18, TNF-alpha and endotoxin were found in group A compared to group B after treatment
- Lactulose plus albumin group had shorter hospital stay compared to lactulose alone (6.4 ± 3.4 vs. 8.6 ± 4.3 days, $p=0.01$)

A randomized controlled trial comparing lactulose + albumin vs lactulose alone for hepatic encephalopathy



- Prospective, randomized controlled trial
- N= 120 (60 in each arm)
- Main difference was related to sepsis-related death

Abstract # 247. Sharma et al, ILBS and GB Pant Hospital, New Delhi

Abstract 247: A Randomized Controlled Trial Comparing Lactulose plus Albumin versus Lactulose alone for Treatment of Hepatic Encephalopathy

Barjesh C. Sharma et al, ILBS, New Delhi, India

Authors Conclusion:

- Combination of lactulose plus albumin is more effective than lactulose alone in treatment of overt HE

Abstract 248: Efficacy and Safety of Rifaximin Monotherapy vs. Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

Arun J. Sanyal et al. Virginia Commonwealth University, Richmond,VA

Background:

- Rifaximin + lactulose has demonstrated superiority to lactulose alone for the prevention of overt HE recurrence
- It is unknown if rifaximin alone is as efficacious as combination therapy

Aim:

- To conduct a noninferiority trial of rifaximin vs. rifaximin + lactulose in the prevention of overt HE recurrence

Abstract 248: Efficacy and Safety of Rifaximin Monotherapy vs. Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

Arun J. Sanyal et al. Virginia Commonwealth University, Richmond,VA

Methods:

- Adults with cirrhosis in remission (Conn score ≤1) after an overt HE episode in the past 6 months were randomized to open-label rifaximin 550 BID or rifaximin 550 mg BID + lactulose (titrated to 2-3 soft stools/d) daily for 6 months
- Monitored monthly for breakthrough HE (Conn score ≥2) and HE-related hospitalizations
- Time to onset of an overt HE episode (primary endpoint) and time to first HE-related hospitalization (secondary endpoint) were calculated using Cox regression stratified by analysis region
- Noninferiority was demonstrated if upper limit 2-sided, 95% confidence interval [CI] of hazard ratio (HR) of rifaximin to rifaximin + lactulose was <1.6
- Adverse events (AEs) were monitored throughout the study

Abstract 248: Efficacy and Safety of Rifaximin Monotherapy vs. Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

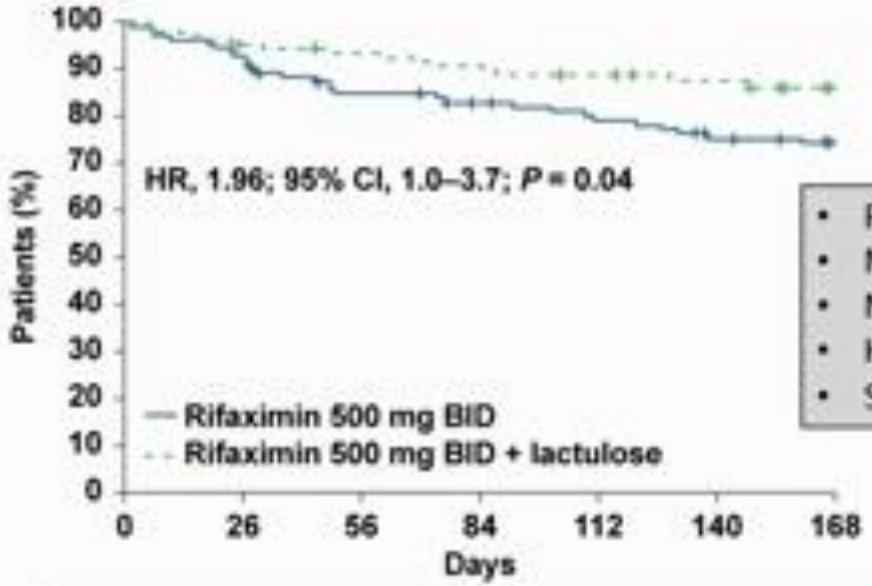
Arun J. Sanyal et al. Virginia Commonwealth University, Richmond,VA

Results:

- 221 patients randomized to rifaximin (n=113) vs. combination therapy (n=108)
- Most common etiology of cirrhosis was viral hepatitis (39.8% and 30.6%)
- Groups well matched for age (58.8 and 58.1 years), gender (61.1% and 64.8% male), mean MELD (11.9 and 11.8), and baseline Conn score (69% grade 0, 31% grade 1)
- Breakthrough HE reported in more patients with rifaximin (24.8%) vs. rifaximin + lactulose (13.9%); HR, 1.96; 95% CI: 1.0 - 3.7; log-rank test, *p=0.04)*
- HE-related hospitalizations observed in 13.6% in the rifaximin group and 22.6% in the rifaximin + lactulose group over 6 months (HR=1.7; 95% CI: 0.9 to 3.4; log-rank test, p=0.1)
- Higher discontinuation rates with rifaximin (38.9%) vs. rifaximin + lactulose (27.5%)
- The most common AEs were HE (19.5%) and peripheral edema (16.8%) with rifaximin, and insomnia and peripheral edema (13.9% for both) with rifaximin + lactulose
- Discontinuations due to AEs were similar [rifaximin (5.3%); rifaximin + lactulose (3.7%)]
- Two deaths were reported in each group

AASLD

Efficacy and Safety of Rifaximin Monotherapy Versus Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence



- Phase 4 open label 24 wk study
- Multi-center
- N= 222
- Hospitalization less in combo (ns)
- Safety profile similar

During 6 months breakthrough HE was reported in fewer patients treated with rifaximin + lactulose (13.9%) vs rifaximin alone (24.8%)

Abstract 248: Efficacy and Safety of Rifaximin Monotherapy vs. Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

Arun J. Sanyal et al. Virginia Commonwealth University, Richmond,VA

Authors Conclusions:

- Data suggest that rifaximin plus lactulose therapy is more efficacious than rifaximin alone for the prevention of HE recurrence
- Given the overall favorable safety profile of rifaximin, this combination appears to be well tolerated

Abstract 136: Hemodynamic Effects Of Carvedilol Plus Simvastatin In Cirrhosis With Portal Hypertension And No-Response To β-Blockers: A Double-Blind Randomized Trial

Edilmar Alvarado-Tapias et al. Barcelona, Spain

Background:

- In cirrhosis with portal hypertension, Carvedilol (CV) is more effective than traditional non-selective β-blockers (NSBB) to reduce the hepatic venous pressure gradient (HVPG)
- Statins also improve portal hypertension by reducing the intrahepatic vascular resistance
- However, whether the addition of statins may improve the hemodynamic effects of CV in cirrhosis with clinically significant portal hypertension (CSPH) has not been clarified

Aim:

- To evaluate whether the addition of simvastatin (SV) to CV can improve the hemodynamic effects of CV alone in cirrhosis with CSPH and without response to NSBB

Abstract 136: Hemodynamic Effects Of Carvedilol Plus Simvastatin In Cirrhosis With Portal Hypertension And No-Response To β-Blockers: A Double-Blind Randomized Trial

Edilmar Alvarado-Tapias et al. Barcelona, Spain

Methods:

- Patients with cirrhosis, CSPH and high-risk esophageal varices without previous bleeding were consecutively included
- HVPG was measured before and after IV propranolol (0.15 mg/kg)
- Acute responders (HVPG decrease ≥20% from baseline) were treated with nadolol (ND) and non-responders with CV
- Once NSBB (either ND or CV) had been titrated, patients were randomized to receive either placebo (PBO) or SV (40 mg/d) in double-blind conditions
- A second hemodynamic study was performed at 1 month to assess chronic response
- A standard liquid meal was then given and measurements repeated 30 minutes later (post-prandial)

Abstract 136: Hemodynamic Effects Of Carvedilol Plus Simvastatin In Cirrhosis With Portal Hypertension And No-Response To β-Blockers: A Double-Blind Randomized Trial

Edilmar Alvarado-Tapias et al. Barcelona, Spain

Results:

- 87 patients (70 CV, 17 ND) were randomized to either PBO (n=44) or SV (n=43)
- Baseline clinical and hemodynamic characteristics were similar between groups
- HVPG at 1 month decreased significantly in both groups; greater with NSBB+SV than with NSBB+PBO (15.2±13% vs. 10.4±9%, p= 0.05)
- More patients with SV achieved target response (HVPG decrease ≥20%): 37% vs. 18%, p= 0.05
- In acute non-responders, the HVPG decreased significantly both with CV+PBO (from 19.5±3 to 17.4±3 mmHg, p<0.001) and with CV+SV (from 20.0±3 mmHg to 16.8±4 mmHg, p< 0.001), with a trend toward slightly greater decrease with CV+SV than with CV+PBO (16.0±12% vs. 10.3±9%, p= 0.06)
- Postprandial increase of HVPG was markedly attenuated with SV: mean increase of 11.4±14% with CV+SV vs. 22.9±18% with CV+PBO (p= 0.03)

Abstract 136: Hemodynamic Effects Of Carvedilol Plus Simvastatin In Cirrhosis With Portal Hypertension And No-Response To β-Blockers: A Double-Blind Randomized Trial

Edilmar Alvarado-Tapias et al. Barcelona, Spain

Authors Conclusions:

- In high-risk patients with non-response to traditional NSBB, CV achieved a significant reduction in HVPG
- Such a reduction is significantly increased with the addition of SV
- Combined treatment with CV+SV achieved a marked and significant attenuation of the postprandial HVPG increase
- These results suggest that addition of SV may improve the clinical efficacy of CV alone

Abstract 250: Pilot study of Orphenadrine for Muscle Cramps in Patients with Liver Cirrhosis

Sherief Abd-Elsalam et al. Hepatology and gastroenterology, Tanta University, Tanta, Egypt

Background:

- Muscle cramps markedly affect the quality of life in cirrhotic patients with no available highly effective treatment

Aim:

- To assess the safety and efficacy of orphenadrine in treatment of muscle cramps in cirrhotic patients

Abstract 250: Pilot study of Orphenadrine for Muscle Cramps in Patients with Liver Cirrhosis

Sherief Abd-Elsalam et al. Hepatology and gastroenterology, Tanta University, Tanta, Egypt

Methods:

- Enrolled 30 patients with cirrhosis complaining of frequent muscle cramps (≥3 per week)
- Randomized to either orphenadrine 100 mg or Calcium carbonate twice daily for 1 month
- Severity, frequency and duration of muscle cramps were assessed before and after treatment as well as recurrence after washout of the drug for 1 month
- Side effects were recorded

Abstract 250: Pilot study of Orphenadrine for Muscle Cramps in Patients with Liver Cirrhosis

Sherief Abd-Elsalam et al. Hepatology and gastroenterology, Tanta University, Tanta, Egypt

Results:

- One month after treatment with orphenadrine:
  - Frequency of muscle cramps decreased significantly to 0.6 +/- 0.7 compared to 13.2 +/- 5.3 previously (p=0.000)
  - Duration of muscle cramps decreased from 9.2 +/- 20.6 to 0.1 +/- 0.2 minutes after treatment
  - Pain score improved significantly from 8 +/- 1.5 to 1.2 +/- 1.4 (p=0.000)
- Frequency of cramps and pain score were significantly lower with orphenadrine than with calcium (0.6 +/- 0.7 vs. 8.3 +/- 4.7) and (1.2 +/- 1.4 vs. 5.6 +/- 1.0) respectively (p=0.000)
- Time to relief was significantly shorter with orphenadrine than with calcium: (2.9 +/- 1.7 days vs. 11.7 +/- 8.4 days) (p=0.001)
- Following one month washout of the two treatments, the orphenadrine group had significantly less cramps and a lower pain score 2.2 +/- 1.1 vs. 9.2 +/- 5.0 and 4.1 +/- 1.3 vs. 7.1 +/- 0.8 respectively (p=0.000)
- Side effects were few and consisted of dry mouth, drowsiness, nausea and vomiting, with no significant difference between the two groups.

Abstract 250: Pilot study of Orphenadrine for Muscle Cramps in Patients with Liver Cirrhosis

Sherief Abd-Elsalam et al. Hepatology and gastroenterology, Tanta University, Tanta, Egypt

Authors Conclusion:

- Orphenadrine is safe and effective in the treatment of muscle cramps in cirrhotic patients

Abstract 58: Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients

Sabela Lens et al. Liver Unit, Hospital Clinic, Barcelona, Spain

Background:

- Data on hemodynamic changes induced by sustained virologic response (SVR) after all-oral HCV therapy in patients with clinical significant portal hypertension (CSPH, HVPG ≥ 10mmHg) are scarce
- Previous data suggest that patients with HCV and CSPH, despite achieving SVR, remain at risk of liver decompensation (LD)

Abstract 58: Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients

Sabela Lens et al. Liver Unit, Hospital Clinic, Barcelona, Spain

Methods:

- Multicenter prospective study of patients with HCV-related cirrhosis and CSPH before all-oral antiviral therapy (BL, baseline)
- Patients underwent HVPG, right-heart catheterization (RHC) and liver stiffness measurement (LSM) at BL and 24 weeks after treatment (FU, follow-up)
- Patients starting beta-blocker (BB) therapy between HVPG measurements were excluded

Abstract 58: Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients

Sabela Lens et al. Liver Unit, Hospital Clinic, Barcelona, Spain

Results:

- 118 cirrhotic patients with CSPH were included: 92% were CTP-A; 80% had esophageal varices (40% large) and 31% had at least one previous LD (14% variceal bleeding, 21% ascites); 44% were on BB at baseline
- Overall, HVPG decreased from 16.4 ± 4.5 to 14.5 ± 4.6 mmHg after SVR (mean change -1.9 ±3 mmHg; $p<0.01$)
- Clinically relevant decrease (≥10%) was observed in 65 (54%) patients (≥ 20% in 34%)
- After achieving SVR, CSPH (≥10 mmHg) persisted in 86% of patients
- Decrease in mean HVPG was similar in patients with (n=52) or without BB
- In 82 patients with paired LSM, BL-LSM was 31 ± 15 kPa with a mean reduction of -6 ± 12 kPa after SVR ($p <0.05$)
- Previously described cut-offs of 13.6 and 21 kPa presented high NPV (92%) and PPV (97%) for the presence of CSPH on follow-up, respectively
- Paired RHC (n= 82 patients) showed a significant rise in MAP due to increased systemic vascular resistance (+14% and +25%, $p<0.05$) with stable cardiac output
- Interestingly, mPAP and PVR also rose after therapy (+15% and +21%; $p<0.05$)
- Indeed, pulmonary hypertension (mPAP ≥25 mmHg) developed or exacerbated in 9 and 4 patients, respectively

Abstract 58: Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients

Sabela Lens et al. Liver Unit, Hospital Clinic, Barcelona, Spain

Authors Conclusions:

- Despite achieving SVR, CSPH persists 24 weeks after therapy in most patients (86%) with HCV-related cirrhosis successfully treated with antiviral therapy, indicating ongoing risk of decompensation
- Previously described LSM cut-offs to rule-in (21kPa) or rule-out (13.6kPa) CSPH are still useful after SVR
- Interestingly, improvement of systemic hemodynamics after SVR was associated with pulmonary hypertension in some patients, indicating the need for continued careful monitoring on long-term follow-up

Abstract 151: ^{13}C-Methacetin Breath Test to assess presence of clinically significant portal hypertension: A novel tool for the management of patient with compensated advanced chronic liver diseases

Juan Carlos Garcia-Pagan et al. Hospital Clinic, Barcelona, Spain

Background:

- In patients with compensated advanced chronic liver disease (cACLD), i.e. patients with advanced liver fibrosis/compensated cirrhosis, a Hepatic Venous Pressure Gradient (HVPG) ≥10mmHg is defined as Clinically Significant Portal Hypertension (CSPH) and is associated with an increased risk of varices, ascites, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma (HCC) and poor outcome after HCC resection
- However, HVPG is invasive, not universally available, inconvenient for serial use, and requires expertise and experience
- The ^{13}C-Methacetin Breath Test (MBT) using Exalenz BreathID system, is a non-invasive real-time molecular correlation spectroscopy system that measures the abundance of $^{13}CO2$ in expired breath exclusively produced by hepatic CYP450 metabolism of ingested non-radioactive ^{13}C-labeled Methacetin
- MBT has been shown to reflect degree of liver impairment

Aim:

- To investigate if MBT can assess CSPH in patients with cACLD

Abstract 151: ^{13}C-Methacetin Breath Test to assess presence of clinically significant portal hypertension: A novel tool for the management of patient with compensated advanced chronic liver diseases

Juan Carlos Garcia-Pagan et al. Hospital Clinic, Barcelona, Spain

Methods:

- MBT, HVPG and clinical variables (demographics, etiology, blood tests, and treatments) were collected from 200 patients with cACLD who had routine measurement of HVPG
- Patients with hepatic decompensation, portal vein thrombosis, variceal bleeding or HCC >3cm were excluded
- 22 patients were excluded from the final analysis due to protocol deviation or missing data
- The relationship between collected parameters and HVPG was analyzed by logistic regression modeling

Abstract 151: ^{13}C-Methacetin Breath Test to assess presence of clinically significant portal hypertension: A novel tool for the management of patient with compensated advanced chronic liver diseases

Juan Carlos Garcia-Pagan et al. Hospital Clinic, Barcelona, Spain

Results:

- Analysis was conducted on 178 patients (66% males) with 65% having CSPH
- Average age was 60 years (±9.6)
- Etiology of cACLD was 74% HCV, 7% NASH, 7% ASH, 3% HBV and 10% others, including HIV/HBV or HCV co-infections
- The developed model detected CSPH with an AUROC of 0.86, $p<.0001$
- A sub-analysis was conducted in 128 patients (CSPH in 61%) of all etiologies, excluding those that received direct anti-HCV therapy with recent SVR, resulting in an AUROC of 0.91, $p<.0001$
- Selecting two cutoff points in the model with at least 90% sensitivity and 90% specificity, CSPH could be ruled in or ruled out in 83.5% of these patients (with 93% PPV and 83% NPV)
- For the detection of portal hypertension (HVPG ≥6mmHg in 82%), the AUROC was 0.93, $p<.0001$

Abstract 151: ^{13}C-Methacetin Breath Test to assess presence of clinically significant portal hypertension: A novel tool for the management of patient with compensated advanced chronic liver diseases

Juan Carlos Garcia-Pagan et al. Hospital Clinic, Barcelona, Spain

Authors Conclusions:

- MBT non-invasively detects CSPH at point-of-care with high sensitivity and specificity.
- MBT may serve as a useful non-operator, non-etiology dependent tool in the clinical follow-up of patients with cACLD

Abstract 2079: Treatment of refractory ascites with the automated low flow ascites (alfa)pump: analysis of the surveillance database

Guido Stirnimann et al. University Hospital, Bern, Switzerland

Background:

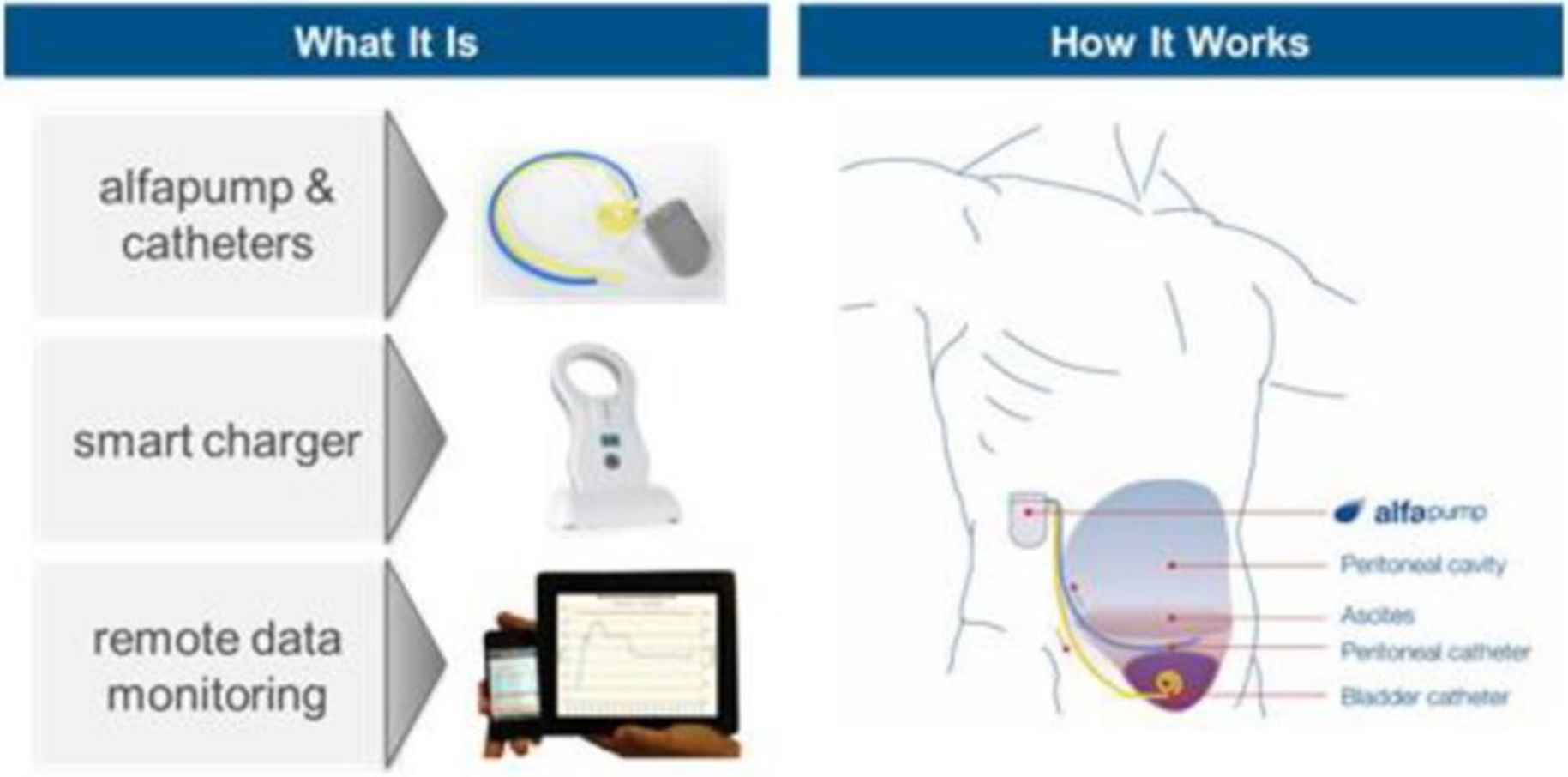
- Refractory ascites (RA) is a frequent complication of cirrhosis requiring repeat paracentesis or placement of a transjugular intrahepatic porto-systemic shunt (TIPS)
- The automated low flow ascites pump (alfapump system, Sequana Medical AG, Zurich) is an innovative treatment option for patients with RA

Aim:

- Here we report real world efficacy and safety surveillance data in the first cohort of patients treated with this device

Abstract 2079: Treatment of refractory ascites with the automated low flow ascites (alfa)pump: analysis of the surveillance database

Guido Stirnimann et al. University Hospital, Bern, Switzerland



Abstract 2079: Treatment of refractory ascites with the automated low flow ascites (alfa)pump: analysis of the surveillance database

Guido Stirnimann et al. University Hospital, Bern, Switzerland

Methods:

- Patients treated with the alfapump system prior to October 2014 in selected centers in Germany, Switzerland, the UK, and Spain were enrolled and prospectively followed for up to 24 months
- Adverse events, device deficiencies, number and volume of paracenteses, reinterventions, and patient clinical and laboratory data were recorded

Abstract 2079: Treatment of refractory ascites with the automated low flow ascites (alfa)pump: analysis of the surveillance database

Guido Stirnimann et al. University Hospital, Bern, Switzerland

Results:

- Fifty-six patients were included (43 males; mean age 62, range 50-78)
- Baseline mean MELD score was 13.6 (SD, 4.4) and Child-Pugh score was 8.9 (SD, 1.3) with 25% Child-Pugh Class C
- After alfapump system implantation, the median required paracentesis decreased from 2.2 (IQR, 1.5-4.3) to 0.2 (IQR, 0.0-0.4) L/month
- In 17 patients (30.4%), the pump was explanted
  - Due to an SAE (n=12): 5 with peritonitis, 5 with sepsis or suspected infection, 1 with UTI and 1 with a perforated diverticulum; or
  - Due to device deficiency (n=5): 2 with pump pocket infection, 2 with macroscopic hematuria and 1 clogged pump
- Minor pump-related re-interventions, most commonly associated with blocking of the peritoneal catheter, were required in 22 patients (39.3%)
- At 6 months, an increase in median plasma creatinine of 26.0 mmol/L (=0.29mg/dL) and decrease in median serum albumin of -1.3 g/L were noted. Serum bilirubin and INR were unchanged
- Subsequent slides report overall outcomes and causes of death

Table 1: Disposition at data cutoff

Total enrolled (ITT/safety population)	56
Still on core treatment	3 (5.4%)
Completed study (24 months follow-up)	3 (5.4%)
Received liver transplant	9 (16.1%)
alfapump system no longer required (spontaneous recovery)	1 (1.8%)
Withdrawn due to SAE*	17 (30.4)
Subsequent death§	7 (12.5)
Recovered	7 (12.5)
Outcome unknown	3 (5.4%)
Deceased on study	23 (41.1%)
Deceased overall	30 (53.6%)
Median follow-up, months (range, IQR)	5.8 (0.7-26.4, 3.4-12.9)
Mean follow up, months (SD)	8.31 (6.7)

**includes infection (all cause), suspicion of infection, macrohematuria, sepsis*

§complications linked to liver disease; persistent liver insufficiency; multi-organ failure

Table 2: Causes of death

	N	%
Progressive liver disease	15	50
Sepsis/infection	6	20
Renal failure	2	6.7
Post TIPS bleeding	1	3.3
Hepatocellular carcinoma	1	3.3
Stroke	1	3.3
Ischemic heart disease	1	3.3
Perforated diverticulum	1	3.3
Unknown/other	2	6.7
Total*	30	100

*Includes 7 deaths after subject withdrawal

Abstract 2079: Treatment of refractory ascites with the automated low flow ascites (alfa)pump: analysis of the surveillance database

Guido Stirnimann et al. University Hospital, Bern, Switzerland

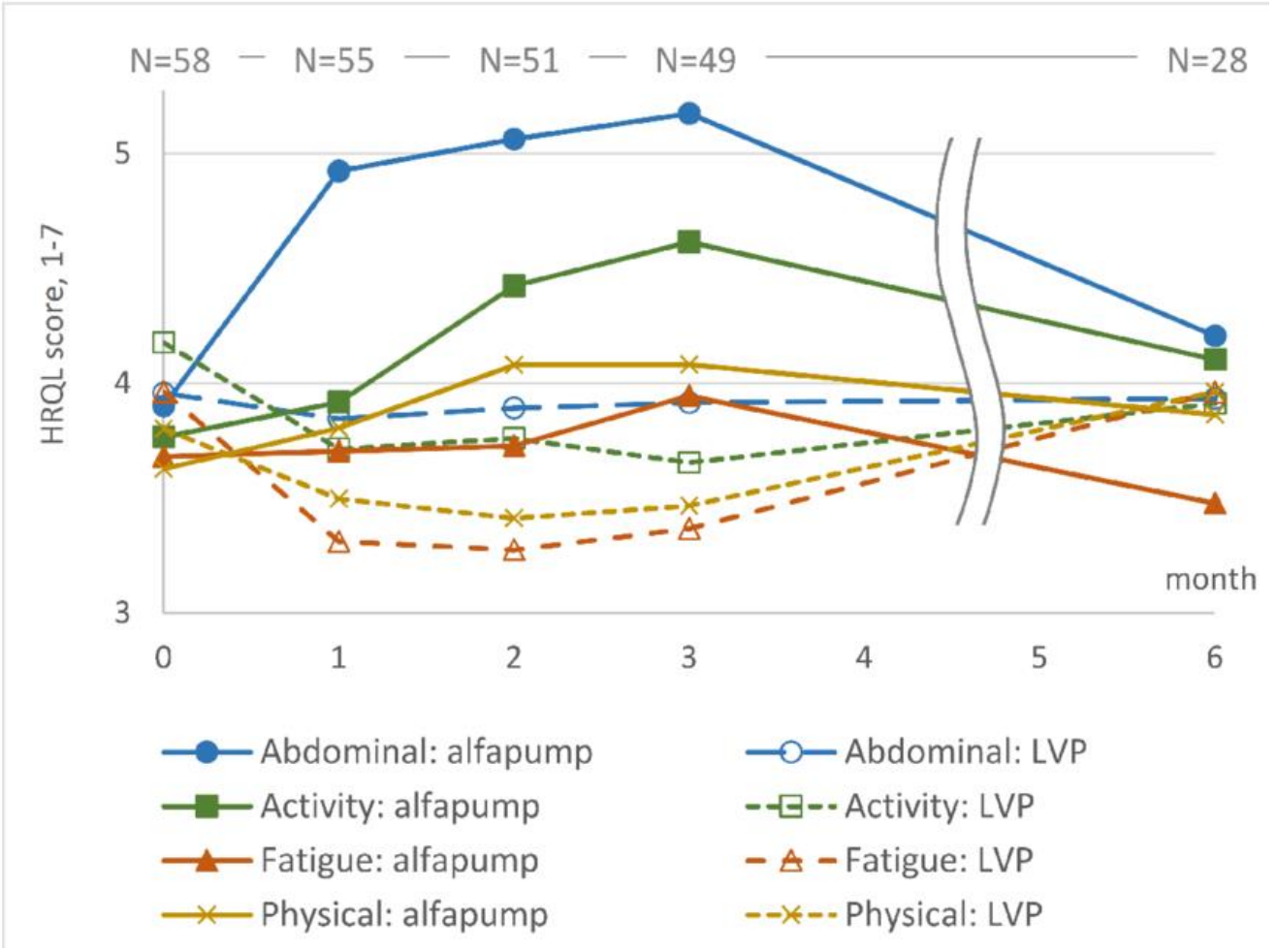
Authors Conclusions:

- Continuous drainage of ascites by the alfapump system led to a clinically meaningful drop in the need for paracentesis
- The alfapump system expands the therapeutic options for patients with refractory ascites caused by end stage liver disease
- Careful patient selection and close follow up are mandatory
- Remaining issues currently being explored in studies include the role of albumin replacement and its effect on relative volume status and comparison of alfapump to TIPS

Abstract 2077: Patients with Refractory Ascites Treated with alfapump® System (AP) have Better Health-related Quality of Life (HRQL) as Compared to those Treated with Large Volume Paracentesis (LVP): Results of a Multicenter Randomized Controlled Study

Zobair M. Younossi et al. Center For Liver Disease, Inova Fairfax Hospital, Falls Church, VA

Figure 1. Summary HRQL Scores in Patients with RA by the Treatment Arm



Note: Abdominal, Activity, Fatigue are parts of CLDQ, Physical is a summary score of SF-36.

Abstract 2064: Oral Rifaximin Soluble Solid Dispersion Immediate-Release 40mg Prevents Development of Cirrhosis-Related Complications: a Phase 2, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

Jasmohan S. Bajaj et al. Sponsored by Salix Pharmaceuticals

Background:

- Cirrhosis-related complications are a major healthcare burden
- Treatments that reduce further decompensation are needed
- This trial evaluated an investigational oral rifaximin formulation, soluble solid dispersion (SSD), administered as an immediate-release (IR) or sustained extended-release (SER) tablet

Abstract 2064: Oral Rifaximin Soluble Solid Dispersion Immediate-Release 40mg Prevents Development of Cirrhosis-Related Complications: a Phase 2, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

Jasmohan S. Bajaj et al. Sponsored by Salix Pharmaceuticals

Methods:

- Adults with cirrhosis and well-controlled ascites (grade 1), with no history of esophageal variceal bleeding or spontaneous bacterial peritonitis were randomized to 1 of 5 rifaximin SSD groups (IR 40 mg, IR 80 mg, SER 40 mg, SER 80 mg, IR 80 mg + SER 80 mg) or placebo once nightly for 24 weeks
- The primary endpoint was time to all-cause mortality or hospitalization for any cirrhosis-related complication at 24 weeks
- Safety was assessed through 26 weeks
- Study was powered for differences vs. placebo only

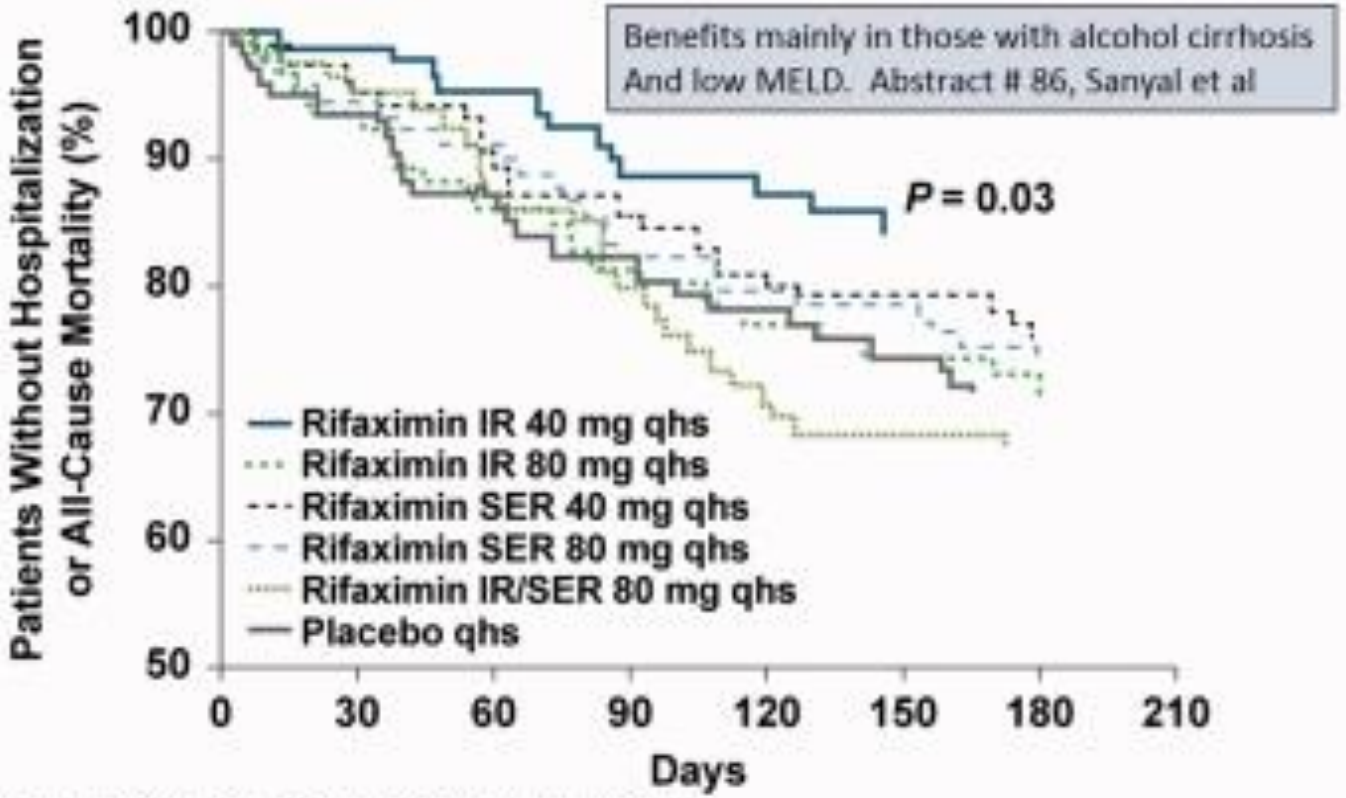
Abstract 2064: Oral Rifaximin Soluble Solid Dispersion Immediate-Release 40mg Prevents Development of Cirrhosis-Related Complications: a Phase 2, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

Jasmohan S. Bajaj et al. Sponsored by Salix Pharmaceuticals

Results:

- 518 patients were treated (78-94 patients per group)
- Mean age was 57.1, mean MELD score was 11.5, and 80.6% of patients were Child-Pugh B
- Mean exposure duration was 152.3 days overall
- A 52% reduction in risk of mortality or cirrhosis complication–related hospitalizations was observed with rifaximin SSD IR 40 mg vs. placebo (hazard ratio: 0.48; 95% CI [0.24–0.94]; log-rank test *p=0.03),* but not with other groups
- Significantly fewer patients treated with rifaximin SSD IR 40mg vs. placebo had a hepatic encephalopathy (HE) episode (2.6% vs. 12.8%; *P=0.01). No significant differences in all cause* mortality or HE-related hospitalizations were observed.
- More patients receiving IR 40 mg than placebo experienced adverse events (AEs) of insomnia (12.8% vs 7.4%) and headache (10.3% vs 6.4%)
- AEs of interest that were lower with IR 40 mg vs. placebo included pruritus (1.3% vs. 9.6%) and fatigue (1.3% vs. 11.7%)

Rifaximin IR 40 mg improved all cause mortality + hospitalization composite clinically meaningful benefit endpoint



Abstracts 2064: Bajaj et al, Salix Pharmaceuticals

Abstract 2064: Oral Rifaximin Soluble Solid Dispersion Immediate-Release 40mg Prevents Development of Cirrhosis-Related Complications: a Phase 2, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial

Jasmohan S. Bajaj et al. Sponsored by Salix Pharmaceuticals

Author's Conclusions:

- Rifaximin SSD IR 40 mg was well tolerated and prevented the development of further decompensation in patients with cirrhosis and well-controlled ascites

Abstract 2095: Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

Catherine T. Frenette et al. Scripps Clinic, La Jolla, CA

Background:

- Caspases play a central role in apoptosis and inflammation, contributing to progression of chronic liver disease
- Emricasan (EMR), an oral caspase inhibitor, decreases apoptotic and inflammatory markers in patients with chronic liver disease and improved MELD and Child-Pugh (CP) scores after 3 months (mo) vs. placebo (pbo) in cirrhosis patients with baseline MELD ≥15
- Final results from the 3-mo open-label EMR phase are reported here

Abstract 2095: Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

Catherine T. Frenette et al. Scripps Clinic, La Jolla, CA

Methods:

- In this 6-mo Phase 2 study at 26 U.S. sites, 86 subjects with cirrhosis (alcohol [N=33], HCV [N=25], NASH [N=20], other [N=8]) and MELD 11-18 were randomized to EMR 25 mg or pbo orally twice daily for 3 mo, followed by open-label EMR 25 mg for 3 mo

Abstract 2095: Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

Catherine T. Frenette et al. Scripps Clinic, La Jolla, CA

Results:

- 86 subjects were randomized (44 EMR, 42 pbo); 74 completed 3-mo randomized phase (40 EMR, 34 pbo); 69 completed 6 mo (36 EMR-EMR, 33 pbo-EMR)
- Mean age was 58 yrs, with 63% male, 88% Caucasian, mean (SD) MELD 12.8 (2.4) and CP 6.9 (1.2)
- EMR for 3 mo led to non-significant decreases vs. placebo in MELD (-0.1 vs. +0.1) and CP (-0.2 vs. +0.1).
- Further improvement in MELD and CP occurred after 6 mo EMR (both -0.3 vs. Day 1)
- In the pre-specified subgroup with MELD ≥15, there was a significant treatment effect of EMR vs. pbo on MELD (least squares [LS] adjusted mean difference -2.2) and CP (-1.3) with sustained improvements after 6-mo EMR (MELD -2.8 [Figure 1] and CP -0.7 vs. Day 1)
- Improvement was observed across etiologies (LS adjusted mean difference for MELD: -1.63 NASH [$p<0.05$], -0.60 HCV, -0.77 alcohol, -0.74 other; for CP: -0.96 NASH [$p<0.05$], -0.31 HCV, -0.78 alcohol [$p<0.05$], -0.95 other)
- EMR was well tolerated, with no clinically relevant difference vs. pbo in AEs, SAEs, routine labs, vitals, ECGs

Abstract 2095: Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

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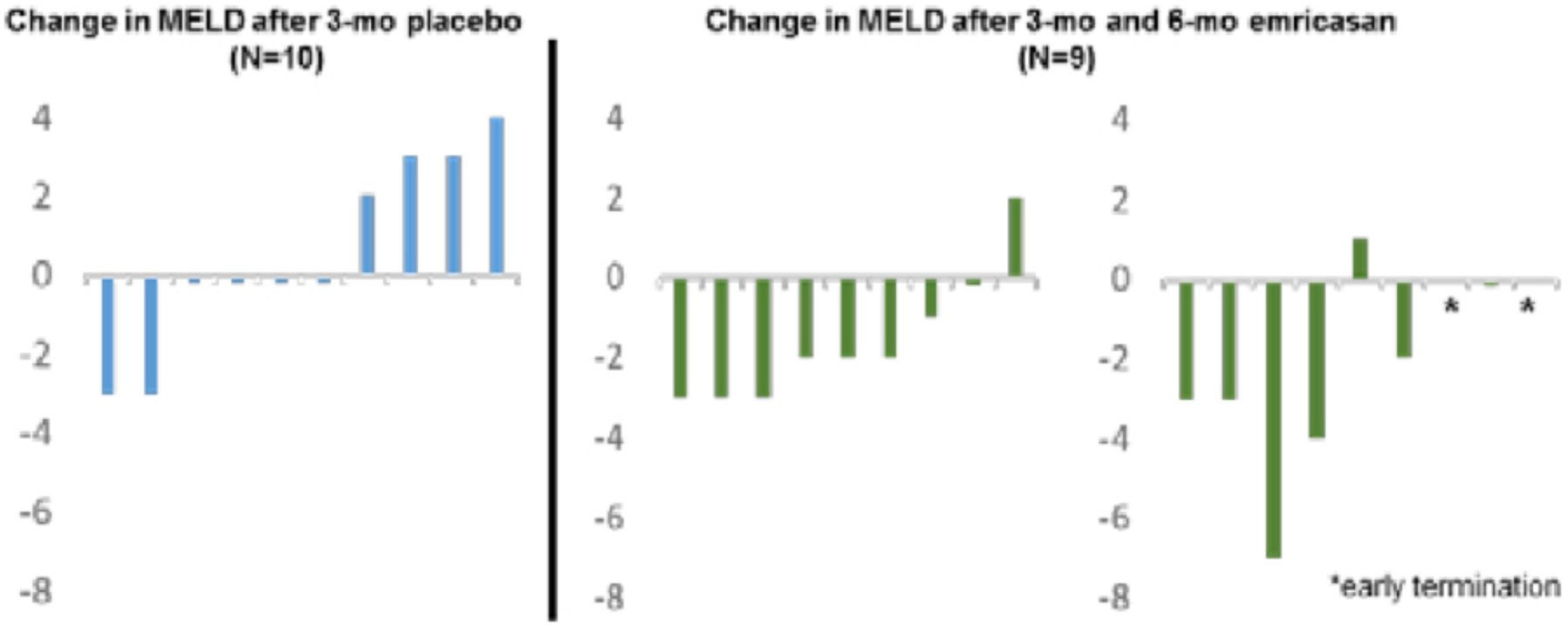
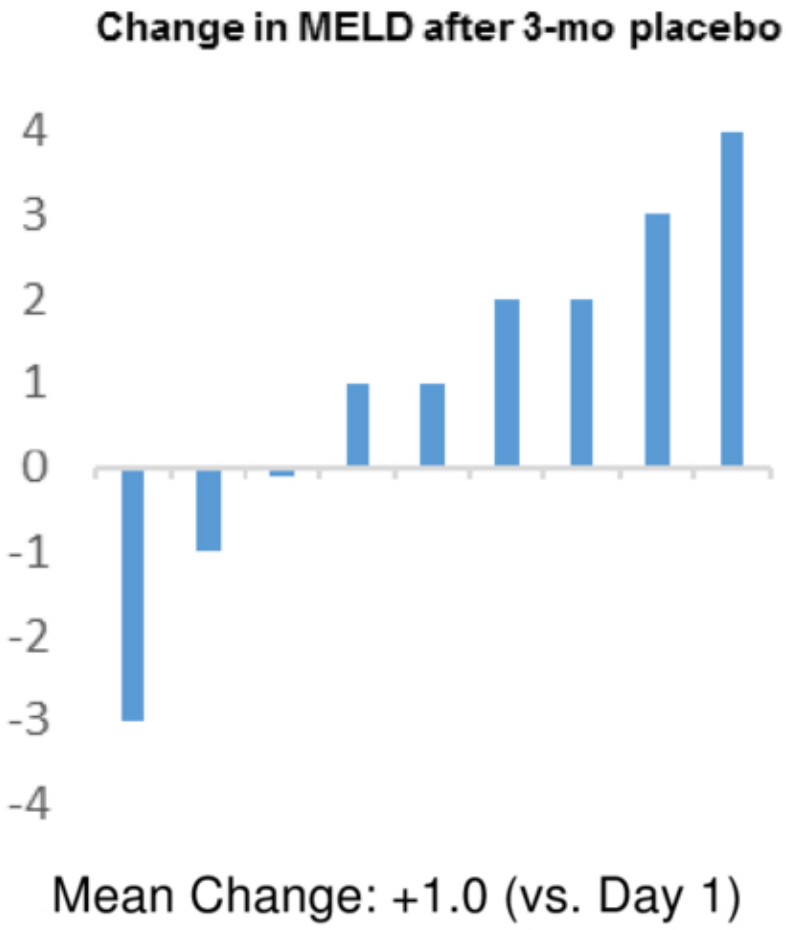
Figure 1. Change in MELD Score after 3-mo Placebo (N=10) and after 3-mo and 6-mo Emricasan (N=9) in Subjects with Baseline MELD Score ≥15

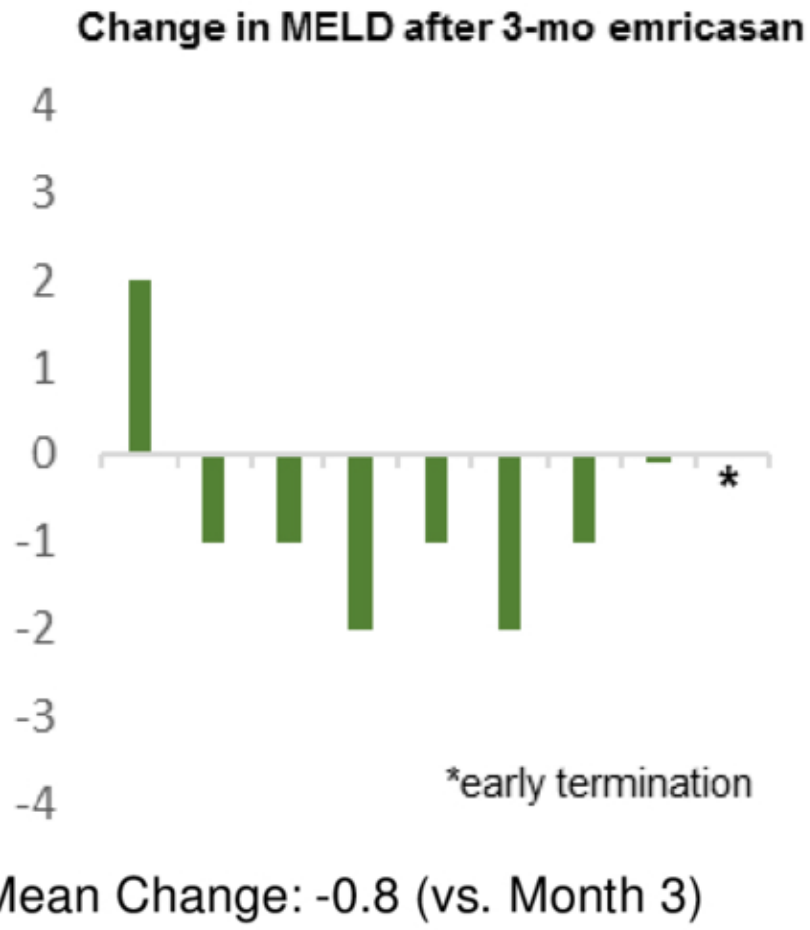


Abstract 2099: Emricasan (IDN-6556) Orally for 6 Months in Patients with Non-alcoholic Steatohepatitis (NASH) Cirrhosis Decreases the Progression of MELD score and Improves Liver Function

Catherine T. Frenette et al. Scripps Clinic, La Jolla, CA

Figure 2. Change in MELD Score after 3-mo Placebo followed by 3-mo Emricasan in NASH Cirrhosis Subjects (N=9)





Abstract 2095: Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

Catherine T. Frenette et al. Scripps Clinic, La Jolla, CA

Author's Conclusions:

- Emricasan had beneficial effects in improving MELD and CP scores in subjects with cirrhosis of various etiologies and mildly to moderately elevated MELD scores after 6 mo and was well tolerated
- Baseline MELD ≥15 and NASH etiology were the strongest predictors of response. The current data support the further study of emricasan in patients with cirrhosis and mild to moderate hepatic impairment