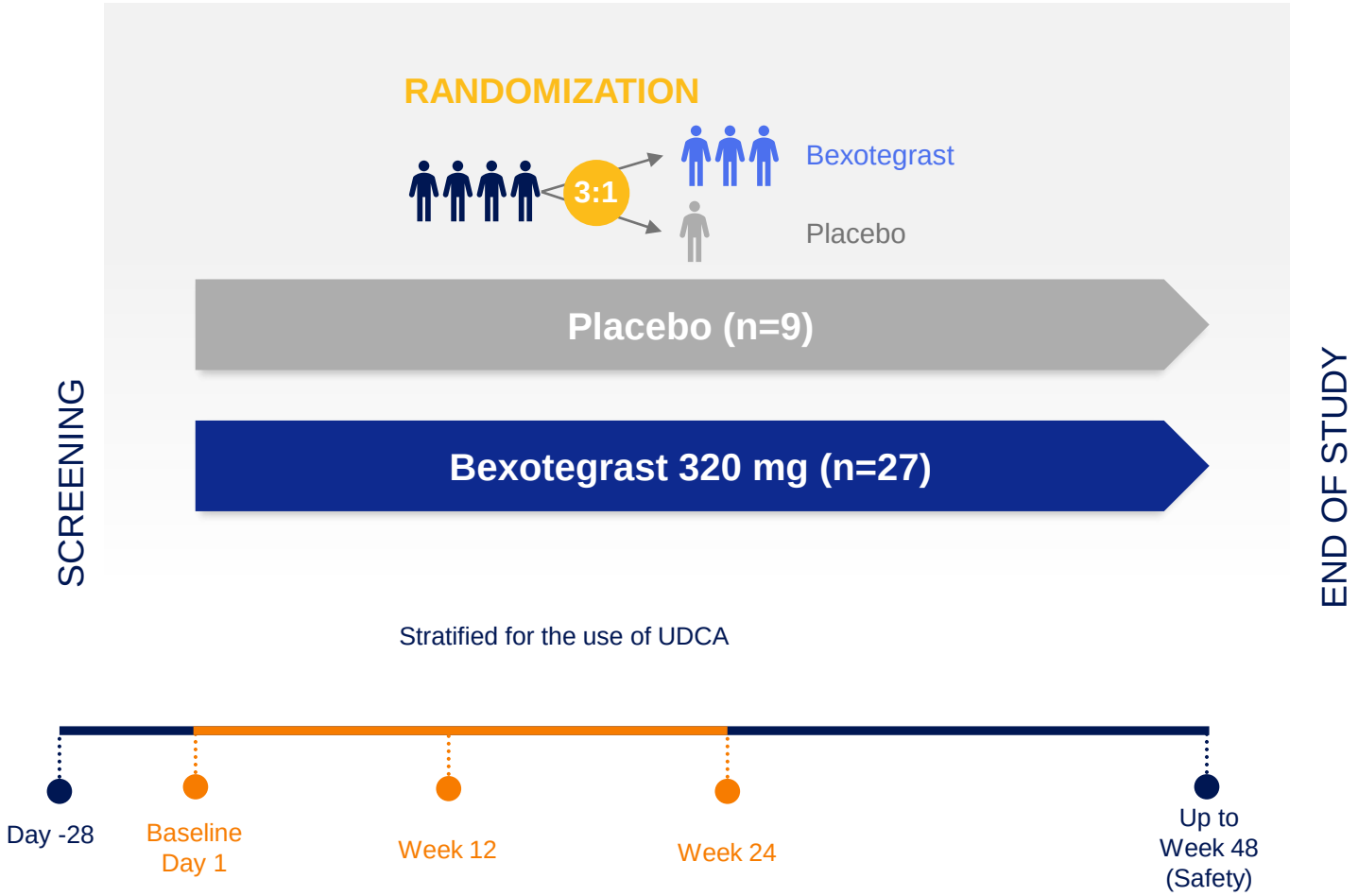
INTEGRIS-PSC Phase 2a Trial

Week 24 Analysis of Bexotegrast 320 mg Cohort

JULY 2024

INTEGRIS-PSC Part 3 Study Design and Objectives

First PSC Trial Enriched for Participants with Suspected Liver Fibrosis



Due to trial design and enrollment trajectory, longest treatment duration was 40 weeks

PRIMARY AND SECONDARY ENDPOINTS

- Safety, tolerability, PK

EXPLORATORY ENDPOINTS

- Changes in transient elastography at Week 24
- Changes in liver fibrosis markers, ELF score and PRO-C3
- Changes in liver imaging
- Changes in liver biochemistry

INCLUSION CRITERIA

- At-risk for moderate/severe fibrosis defined by at least one criterion:
  - ELF ≥ 7.7
  - TE ≥ 8 but ≤ 14.4 kPa
  - MRE ≥ 2.4 but ≤ 4.9 kPa
  - Historical biopsy

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UDCA = Ursodeoxycholic acid ; TE = Transient elastography; ELF = enhanced liver fibrosis

INTEGRIS-PSC – Key Findings at Week 24 for 320 mg Cohort

Bexotegrast 320 mg was well tolerated in participants with PSC over longer term dosing

- Favorable safety and tolerability profile maintained up to 40 weeks
- No treatment-related severe or serious adverse events on bexotegrast

Bexotegrast continued to demonstrate antifibrotic activity

- Improvement in liver stiffness compared to placebo by transient elastography at Week 24
- Reduction in ELF score at Week 24 observed relative to an increase on placebo in high-risk subpopulation
- Stable ELF score observed from Week 12 to 24 in the overall bexotegrast-treated population

Bexotegrast improved markers and symptoms of cholestasis

- Statistically significant improvement in ALP levels at Week 24 compared to placebo
- Contrast MRI suggests continued improvement in hepatocyte function and bile flow from Week 12 to 24
- Stable score on the Itch NRS compared to an increase on placebo over 24 weeks
- Pruritis and cholangitis AEs reported in lower proportions of bexotegrast treated patients than placebo

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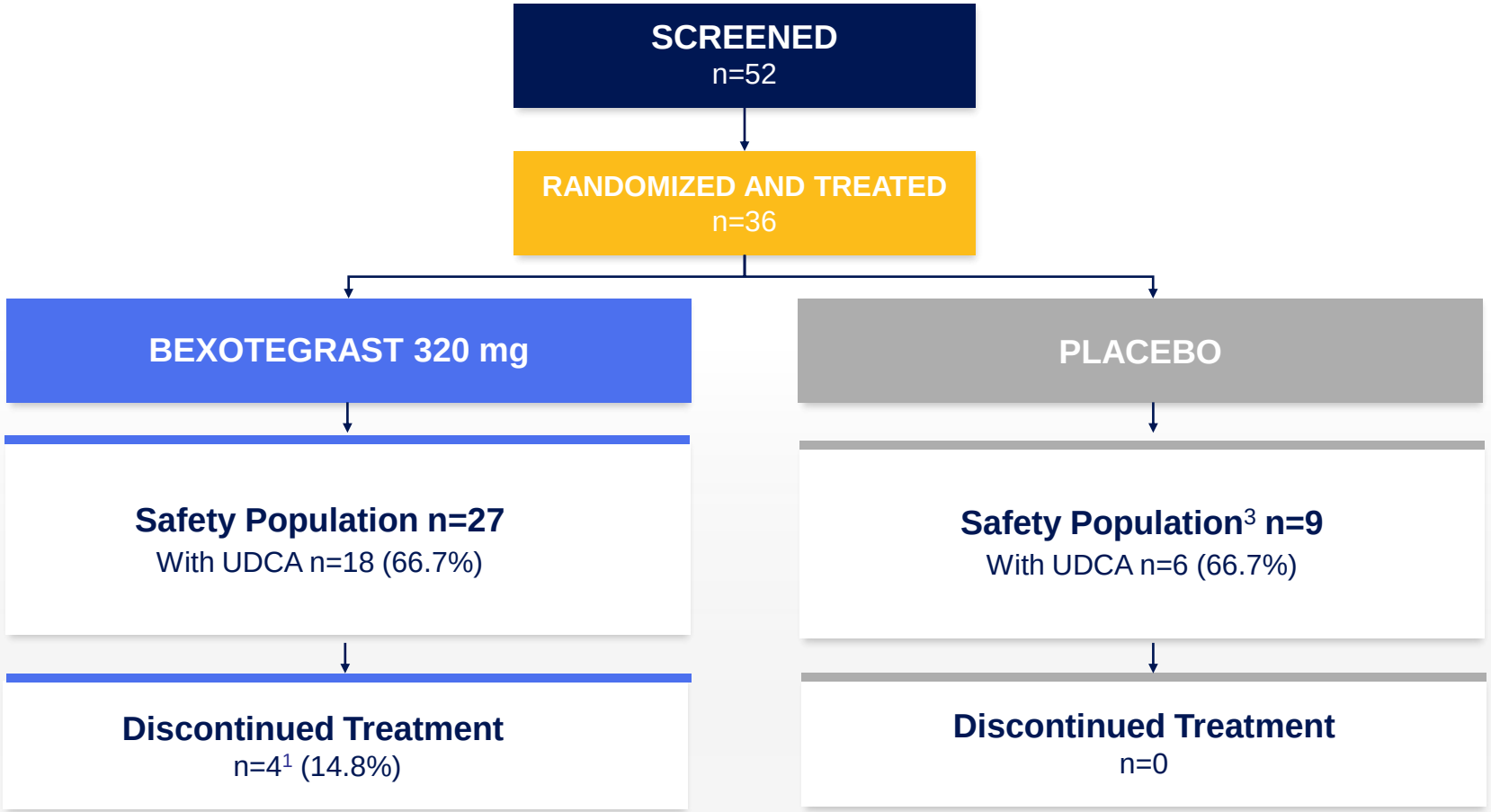
INTEGRIS-PSC – Participant Disposition – 320 mg Cohort



1 – Adverse Event (n=1), Withdrawal by subject (n=2) other (n=1); One discontinuation occurred post Week 12.

UDCA = Ursodeoxycholic acid

Baseline Demographics – 320 mg Cohort Participants

Characteristic	Bexotegrast 320mg (n=27)	Placebo (n=9)
Male sex, n (%)	13 (48.1)	7 (77.8)
Age (yr), mean (SD)	47.1 (14.47)	44.1 (10.04)
Race, n (%)		
White	26 (96.3)	7 (77.8)
Black	0	1 (11.1)
Asian	1 (3.7)	0
Other / Not Reported / Unknown	0	1 (11.1)
Time since diagnosis of PSC (yr), mean (SD)	9.4 (11.20)	6.7 (5.37)
Concomitant UDCA use, n (%)	18 (66.7)	6 (66.7)
IBD, n (%)	13 (48.1)	5 (55.6)
Ulcerative colitis	6 (22.2)	3 (33.3)
Crohn's disease	8 (29.6)	2 (40.0)
IBD Other	0	0
Partial Mayo Score, mean (SD)	0.8 (1.17)	0 (0)
Itch NRS, mean (SD)	0.9 (1.77)	0.9 (1.05)

Duration since diagnosis at screening is calculated from the first reported date for preferred terms of PSC.
Partial Mayo score only reported for those with active IBD at Baseline.
BMI = Body Mass Index; IBD= inflammatory bowel diseases; NRS= numerical Rating scale;
SD = Standard deviation

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Baseline Disease Activity Markers – 320 mg Cohort Participants

	Bexotegrast 320mg (n=27)	Placebo (n=9)
Liver Biochemistry, mean (SD)		
Alkaline phosphatase (ALP) (U/L)	190.6 (91.29)	318.6 (282.73)
> ULN, n (%)	22 (81.5)	6 (66.7)
Alanine aminotransferase (ALT) (U/L)	60.4 (37.76)	85.8 (70.79)
Aspartate aminotransferase (AST) (U/L)	44.6 (24.69)	58.2 (50.91)
Total Bilirubin (mg/dL)	0.53 (0.208)	0.76 (0.424)
Direct bilirubin (mg/dL)	0.16 (0.062)	0.33 (0.341)
Markers of Fibrosis, mean (SD)		
ELF Score	9.0 (0.84)	9.5 (0.93)
PRO-C3 (ng/mL)	46.48 (19.536)	60.18 (39.630)
Transient Elastography (kPa)	8.7 (3.14)	8.6 (2.85)

ELF: Enhanced Liver Fibrosis; PROC-C3: neo-epitope pro-peptide of type III collagen formation.
PRO-C3 quantified using Roche COBAS platform (assay reports approximately 2x higher concentrations than previous generation PRO-C3 ELISA)

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Safety and Tolerability Profile Maintained over Longer Term Dosing

Safety Population – 320 mg Cohort - TEAEs Week 12 to Week 40

AE, n (%) of Participants Reporting After Week 12	Bexotegrast 320mg (n=27)	Placebo (n=9)
TEAE	16 (59.3)	5 (55.6)
Related to study drug	**0**	**0)**
Serious TEAE	1 (3.7)[1]	1 (11.1)[2]
Related to study drug	**0**	**0**
TEAE of CTCAE Grade 3 or Higher	1 (3.7)[1]	1 (11.1)[2]
Related to study drug	**0**	**0**
TEAE Leading to Interruption of Study Drug	1 (3.7)[3]	1 (11.1)[2]
TEAE Leading to Withdrawal of Study Drug	1 (3.7)[4]	0
TEAE Leading to Early Termination from Study	0	0
TEAE Leading to Death	0	0

1 – Cholangitis/Enterobacter bacteremia (n=1); 2- Cholangitis (n=1); 3 - Syncope (n=1); 4 – Increased ALT/AST/ALP (n=1)

AE = Adverse Event; TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Events. Adverse events coded using MedDRA v. 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose.

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Most Frequent TEAEs Consistent with Previous Findings

Safety Population – 320 mg Cohort

TEAE, n (%) of Participants Reporting	Bexotegrast 320mg (n=27)	Placebo (n=9)
Most frequent TEAEs (≥ 10% in the 320 mg treatment group)		
COVID-19	5 (18.5)	1 (11.1)
Nasopharyngitis	5 (18.5)	1 (11.1)
Diarrhea	4 (14.8)	0
Colitis ulcerative	3 (11.1)	0
Fatigue	3 (11.1)	2 (22.2)
Headache	3 (11.1)	0
Pruritus	3 (11.1)	2 (22.2)

Cholangitis was reported in 3.7% of bexotegrast participants and 11.1% of placebo participants, consistent with previous findings

TEAE = Treatment Emergent Adverse Event; Adverse events coded using MedDRA version 24.0.
TEAE is defined as any AE starting (or worsening) on or after the date of first dose

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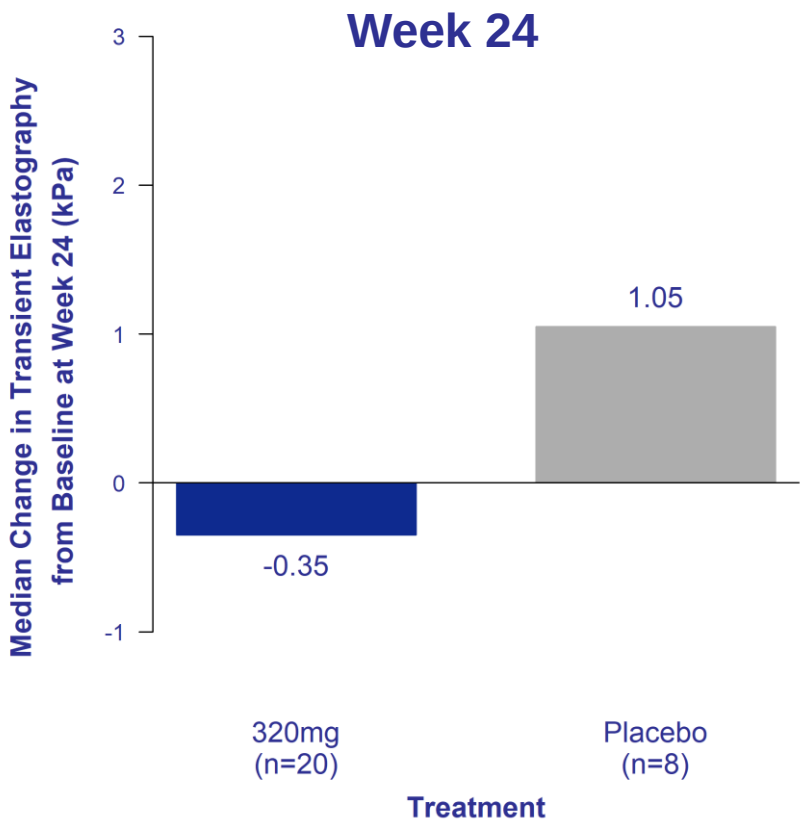
Improvement in Liver Stiffness with Bexotegrast Compared to Placebo

Safety Population – 320 mg Cohort

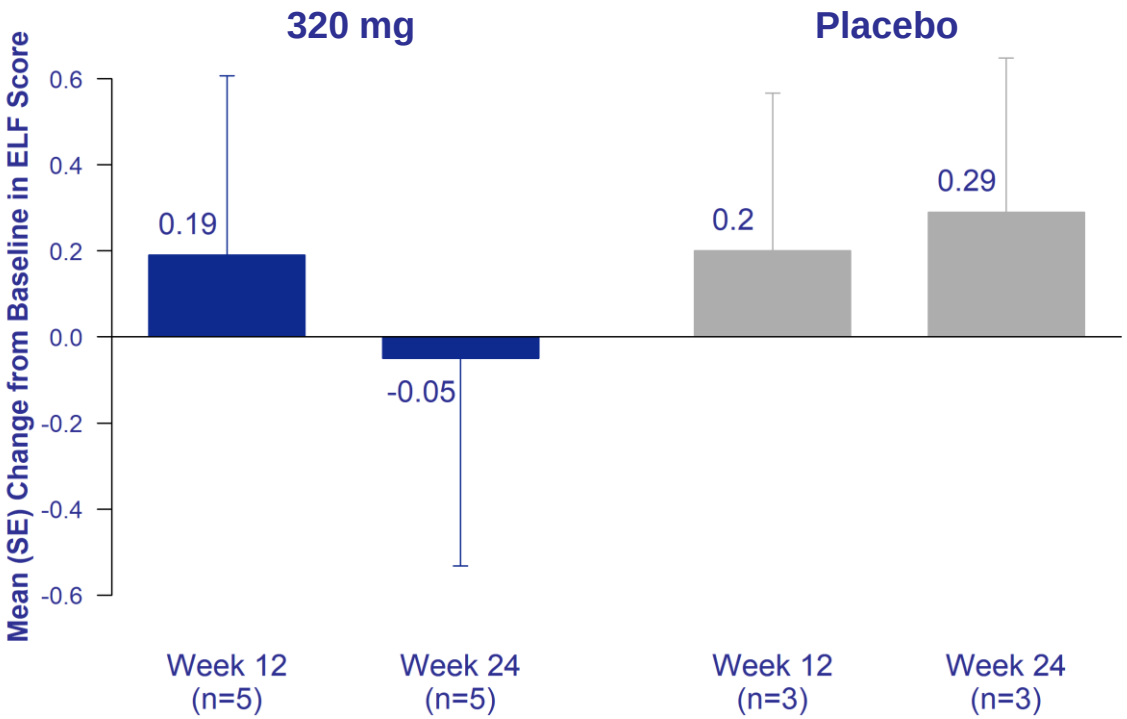


Reduced liver stiffness by transient elastography suggests stabilization of liver fibrosis

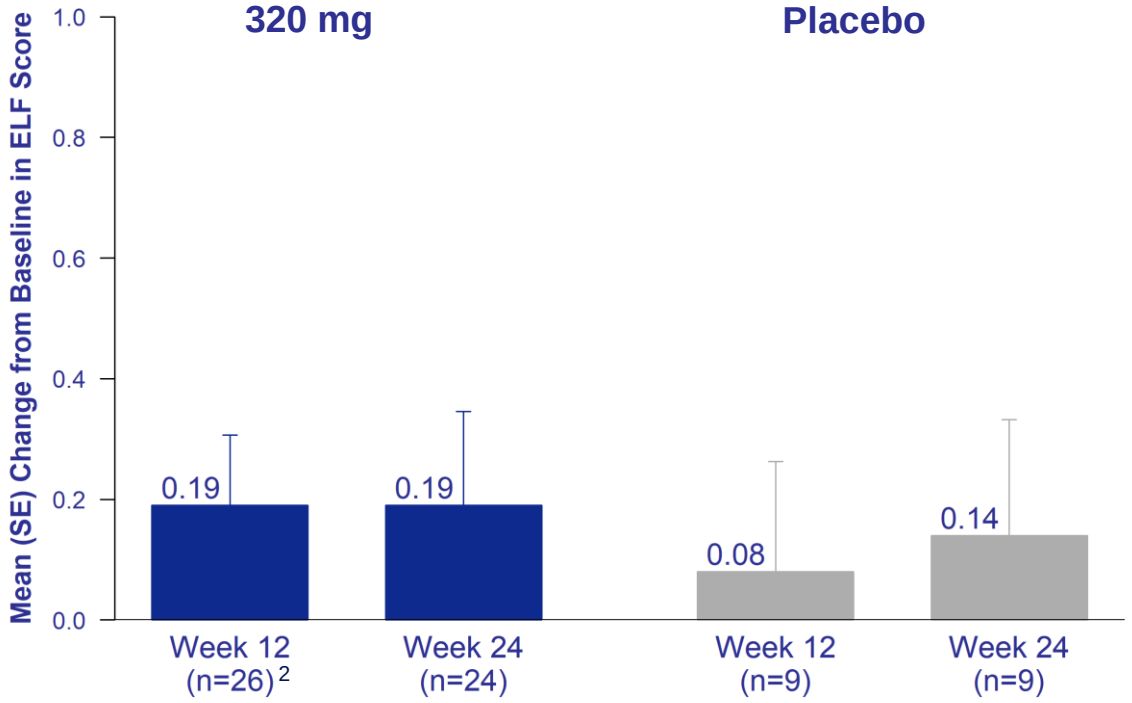
Reduction in ELF Observed with Bexotegrast in High-Risk Patients

Safety Population – 320 mg Cohort

Participants at High Risk of Progression[1]
(Baseline ELF > 9.8)



All Participants



Reduction in ELF score at Week 24 observed, compared to an increase on placebo in patients at high risk for disease progression

ELF: enhanced liver fibrosis.
1 – ELF score >9.8 is associated with increased risk for advanced liver fibrosis and disease progression.
2 – Includes one patient who was not included in 12-week interim analysis due to sample unavailability at the time of interim analysis.

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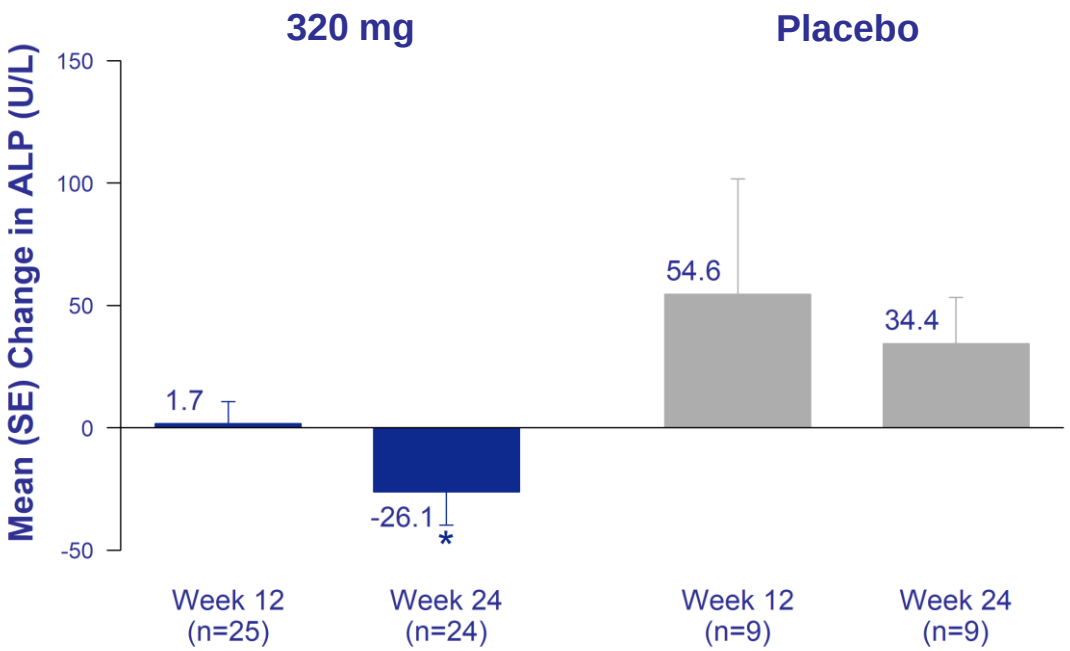
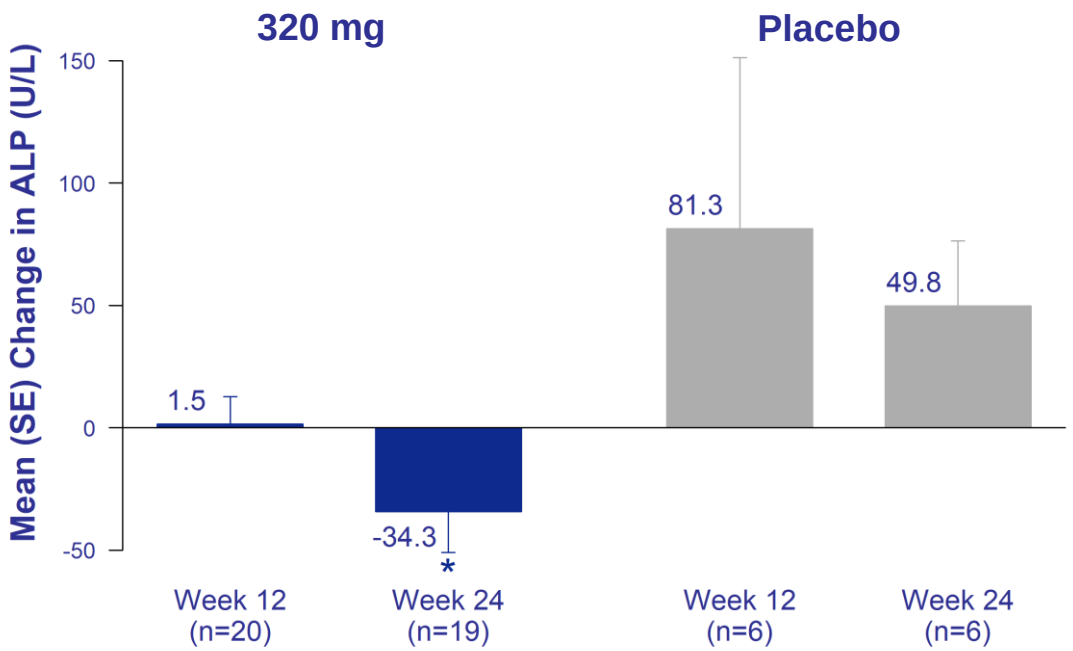
Bexotegrast Reduced ALP over 24 Weeks

Safety Population – 320 mg Cohort

All Participants



Elevated ALP at Baseline



Statistically significant ALP reductions observed in bexotegrast participants compared to increased ALP on placebo

ALP - alkaline phosphatase

* $p < 0.05$ vs placebo

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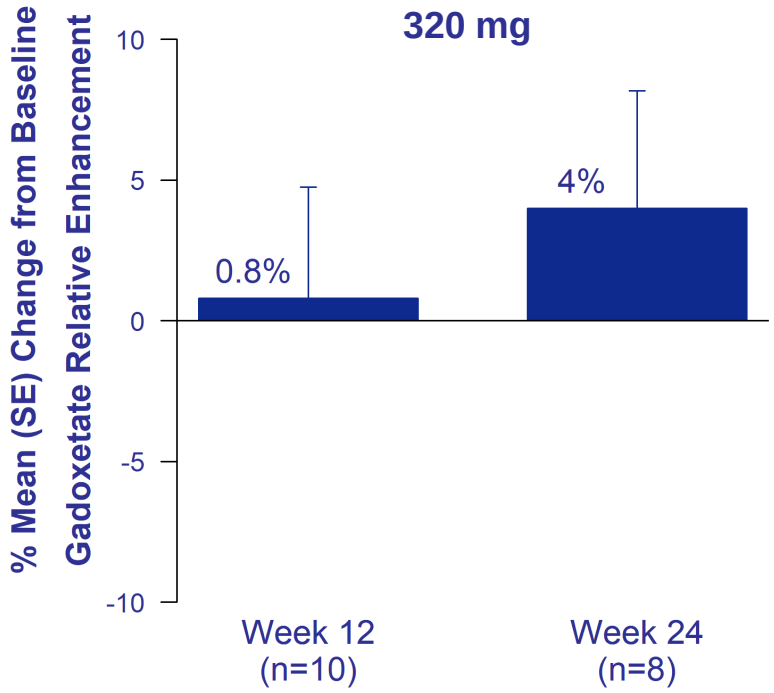
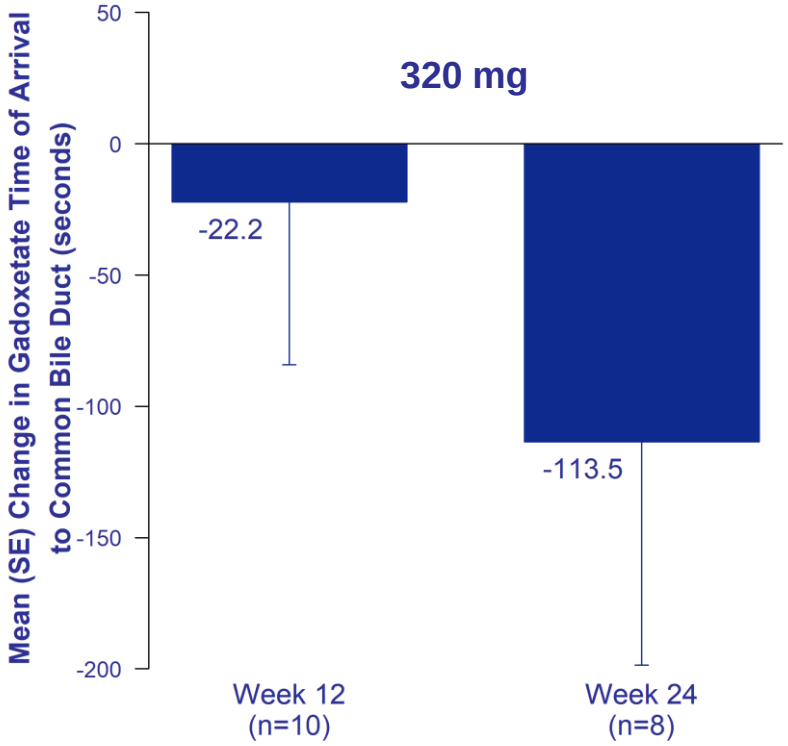
Continued Improvement in MRI Parameters Observed from Week 12 to 24

Safety Population – Sub Study - 320 mg Cohort

Relative Enhancement



Time to Arrival to Common Bile Duct



Relative Enhancement and time to arrival continued to improve at Week 24 suggesting further improvement in hepatocyte function and bile flow

Placebo not shown due to small n. n=1 placebo for relative enhancement; n=2 placebo for time to arrival to common bile duct.
Relative enhancement (RE), using the contrast agent gadoxetate, is a measure of hepatocyte function. Time of arrival of gadoxetate to bile duct is a measure of bile flow/excretory function.
MRI was an optional sub study to main study.

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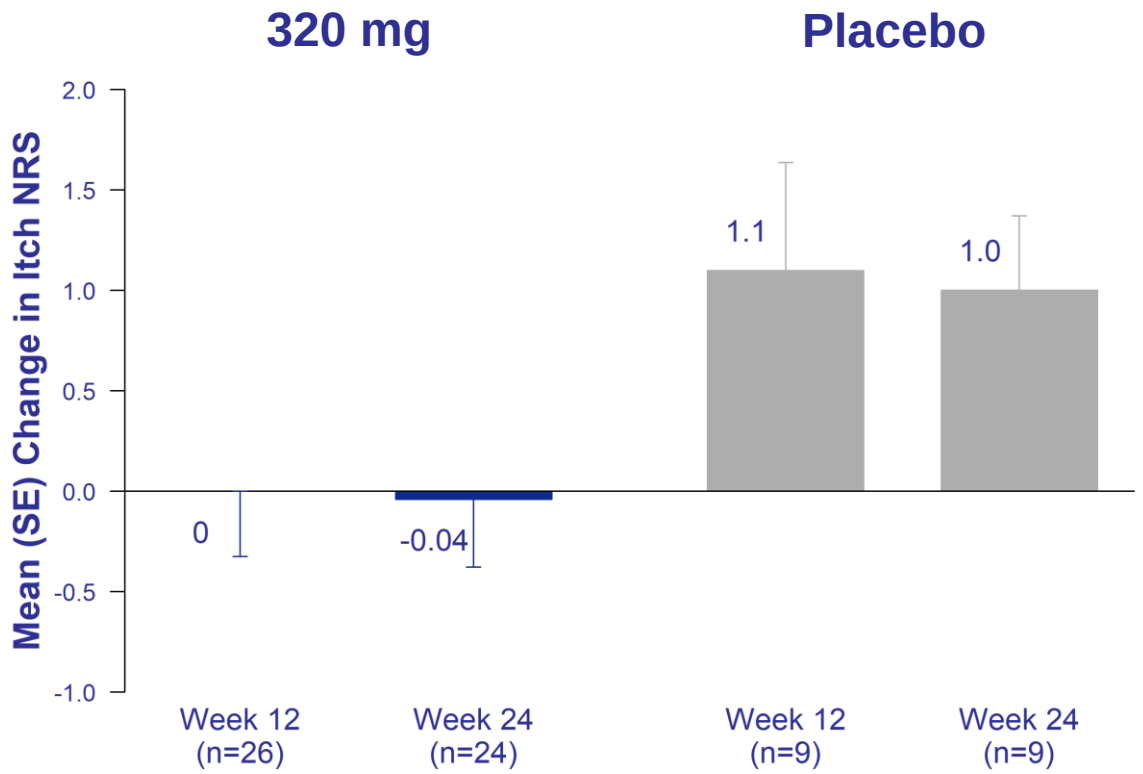
Stable Itch NRS Observed with Bexotegrast Compared to Increase on Placebo

Safety Population – 320 mg Cohort



Mean Itch NRS score did not increase over 24 weeks of treatment with bexotegrast compared to an increase on placebo

NRS: Numerical Rating scale; Itch NRS is a patient reported outcome which assesses severity of itch, over the last 24 hours, on a scale of 0 (no itch) to 10 (Worst imaginable itching)

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Bexotegrast – Conclusions and Next Steps

Bexotegrast continues to be well tolerated across multiple patient populations

- Well tolerated in over 700 trial participants treated with bexotegrast to date
- No treatment-related SAEs observed in patient studies to date

Bexotegrast continues to demonstrate broad antifibrotic activity across multiple indications

- Strong evidence for antifibrotic activity across pulmonary and hepatic fibrosis indications
- Evidence to date suggests potential disease modification in both IPF and PSC
- Totality of evidence provide strong confidence in ongoing BEACON-IPF Phase 2b/3 trial

Path forward for bexotegrast

- Pliant remains focused on execution of the ongoing BEACON-IPF
- Pliant will continue to evaluate the best path forward in PSC

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Thank You