Multicenter, Double-Blind, Randomized Trial of Emricasan in Subjects Post Liver Transplantation with Recurrent Hepatitis C Virus and Liver Fibrosis or Cirrhosis Despite Achieving Sustained Virologic Response: POLT

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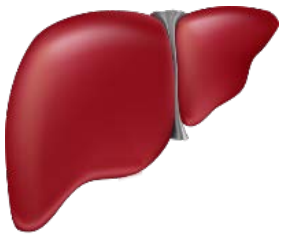
Background

- Direct acting antivirals (DAAs) are safe and highly effective in treating recurrent HCV infection post liver transplantation, as most patients achieve a sustained virologic response (SVR) [1-3]
- Despite achieving SVR, there remains a population of HCV patients post liver transplantation with residual and advanced fibrosis who may progress to cirrhosis

[1]Charlton M et al Gastroenterology. 2015;149(3):649-59
[2]Saxena V, Khungar V et al Hepatology. 2017;66(4):1090-1101
[3]Reau N Hepatology. 2018 Apr 19. doi: 10.1002/hep.30046.

Emricasan (IDN-6556):
Caspases in Liver Disease



Various Etiologies
- Obesity: NASH / NAFLD
- Infections: HCV / HBV
- Alcohol-related conditions
- Autoimmune disorders

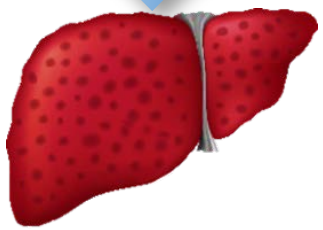
APOPTOTIC CASPASE ACTIVATION

ACTIVATED CASPASES

2 | 3 | 6 | 7 | 8 | 9 | 10

Biomarkers:
Caspase 3/7
cCK18 (M30)

Excessive Apoptosis and Inflammation



INFLAMMASOME PATHWAY

ACTIVATED CASPASES

1 | 4 | 5

Biomarkers:
Transaminases
flCK18 (M65)

[1]Guicciardi and Gores. Semin Liver Dis 2010; 30:402-10
[2]Shiffman et al. Aliment Pharmacol Ther 2010; 31:969-78
[3]Spada et al. Hepatology 2014; 60:1277A

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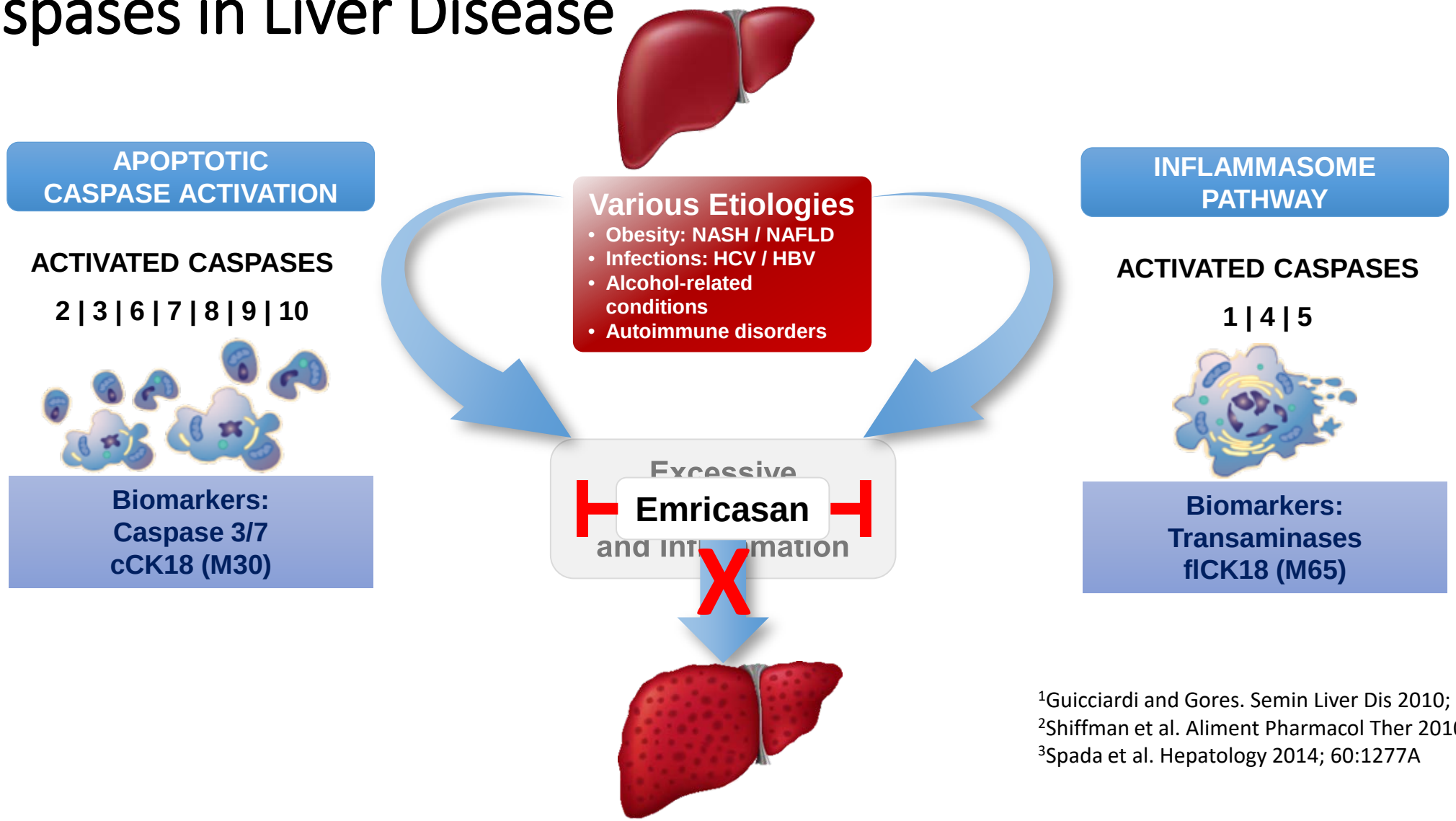

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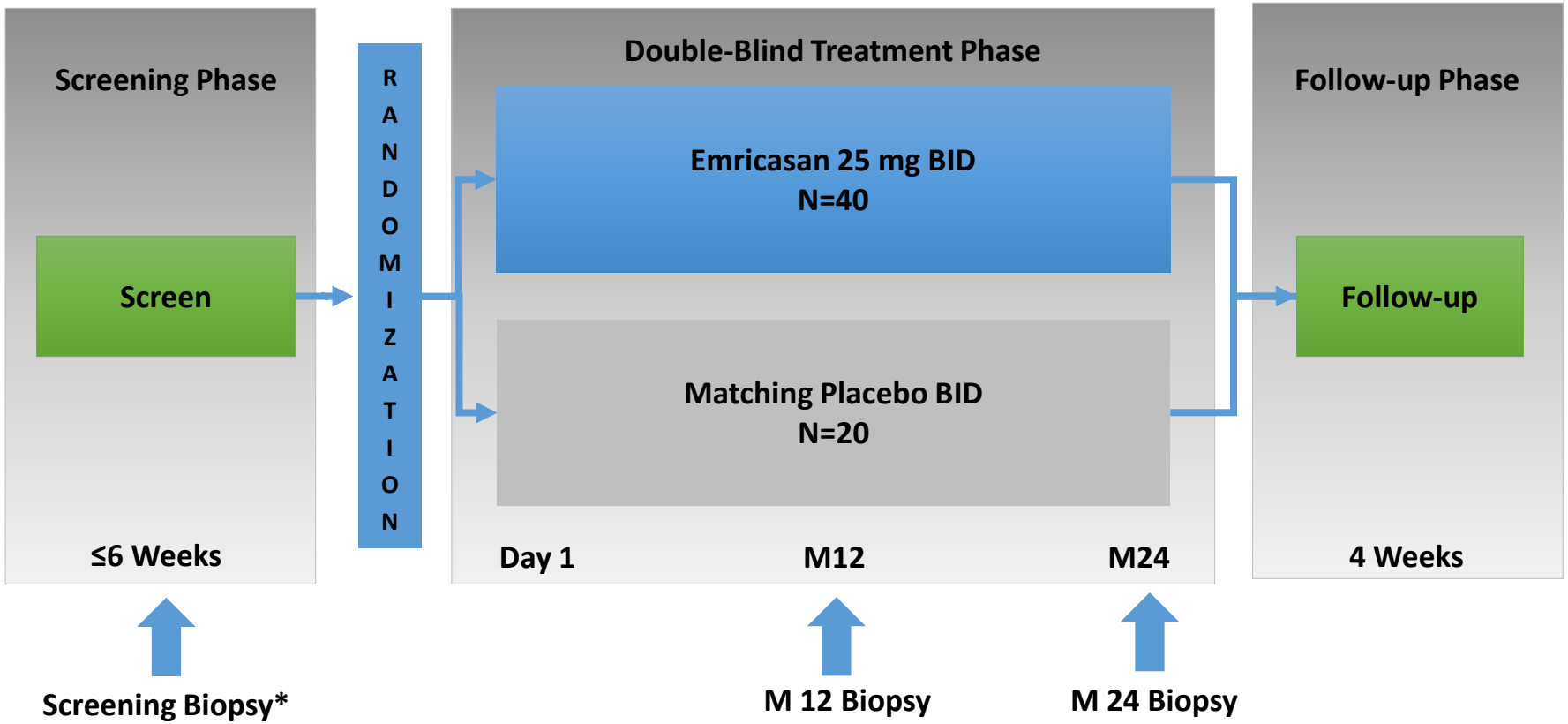
Study Aims

- To determine the safety and efficacy of emricasan in reducing or preventing progression of hepatic fibrosis in post transplant HCV recipients achieving SVR with anti-viral therapy
- To assess changes from baseline in ALT and caspases 3/7

POLT: Study Design



*A biopsy must be conducted if previous biopsy was >3 months prior to Day 1 or if tissue not available or insufficient quantity

Subjects were stratified according to Ishak fibrosis score at baseline:

- F2
- F3-F5
- F6

Study Endpoints

- The primary endpoint: improvement or stability in Ishak fibrosis stage between emricasan compared to placebo at month 24
  - Improvement defined as ≥1-stage decrease in fibrosis stage (all subjects)
  - Stability defined as no change in fibrosis stage (in baseline F2-F5 subjects)
- The secondary endpoints included
  - Change from baseline in ALT and caspases 3/7
  - Long-term assessment of safety and tolerability of emricasan over 24 months in subjects post liver transplantation
- Statistical considerations:
  - Primary endpoint used a multiple imputation technique for subjects with missing data
  - All other analyses were based on observed data

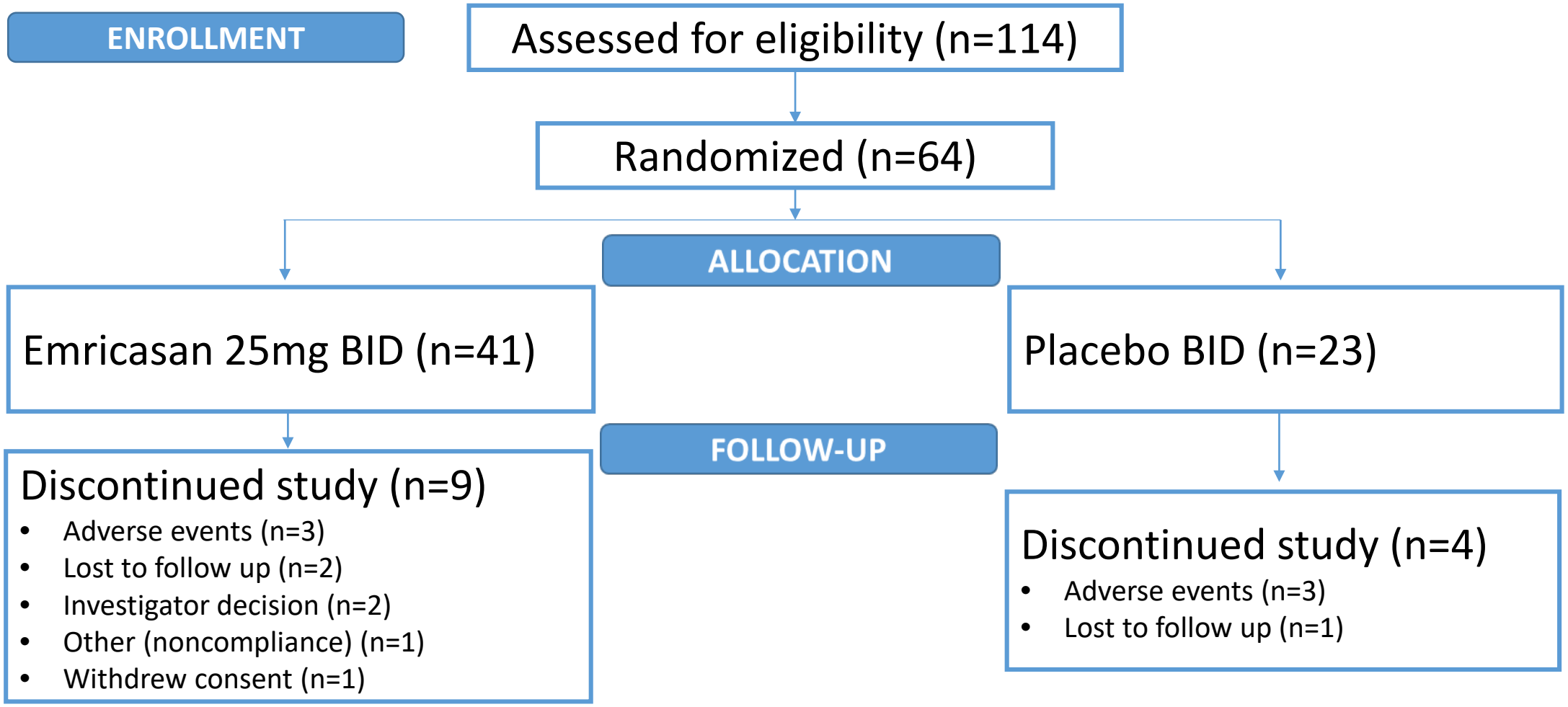
Key Inclusion Criteria

- History of liver transplant for HCV-induced liver disease and diagnosis of HCV infection post liver transplantation
- Documented SVR with anti-viral treatment within 18 months prior to Day 1
- Confirmed liver fibrosis or cirrhosis (Ishak F2 to F6) on biopsy, as read by central histopathologist within three months of Day 1

Key Exclusion Criteria

- Active HIV and/or HBV infection
- Autoimmune diseases
- Chronic liver disease of any other etiology
- Evidence of allograft rejection within three months of Day 1
- Decompensated liver disease
- HCC at entry into the study
- Renal transplant or severe renal impairment with eGFR <30mL/min/1.73m^2
- Concurrent sirolimus use

Subject Disposition



Subject Demographics

	Emricasan (N=41)	Placebo (N=23)
Age (yr)		
Median	61.6	61.1
Age group (yr) – n (%)		
18-39	2 (4.9)	0
40-64	27 (65.9)	17 (73.9)
≥65	12 (29.3)	6 (26.1)
Gender – n (%)		
Female	9 (22.0)	5 (21.7)
Male	32 (78.0)	18 (78.3)
Race – n (%)		
Black or African American	7 (17.1)	2 (8.7)
White	30 (73.2)	20 (87.0)
More than one race	1 (2.4)	0
Unknown or Not reported	3 (7.3)	1 (4.3)

Subject Baseline Characteristics

	Emricasan (N=41)	Placebo (N=23)
Ishak Fibrosis Stage (n%)		
F2	9 (22.0)	6 (26.1)
F3	20 (48.8)	7 (30.4)
F4	5 (12.2)	5 (21.7)
F5	2 (4.9)	2 (8.7)
F6	5 (12.2)	3 (13.0)
Median		
ALT (U/L)	18.0	21.0
AST (U/L)	22.0	26.0
Caspase 3/7 (raw RLU)*	1808.5	2057.0
cCK18 (IU/mL)**	199.0	235.0
fICK18 (IU/mL)***	342.0	420.0

Historical values in normal volunteers:

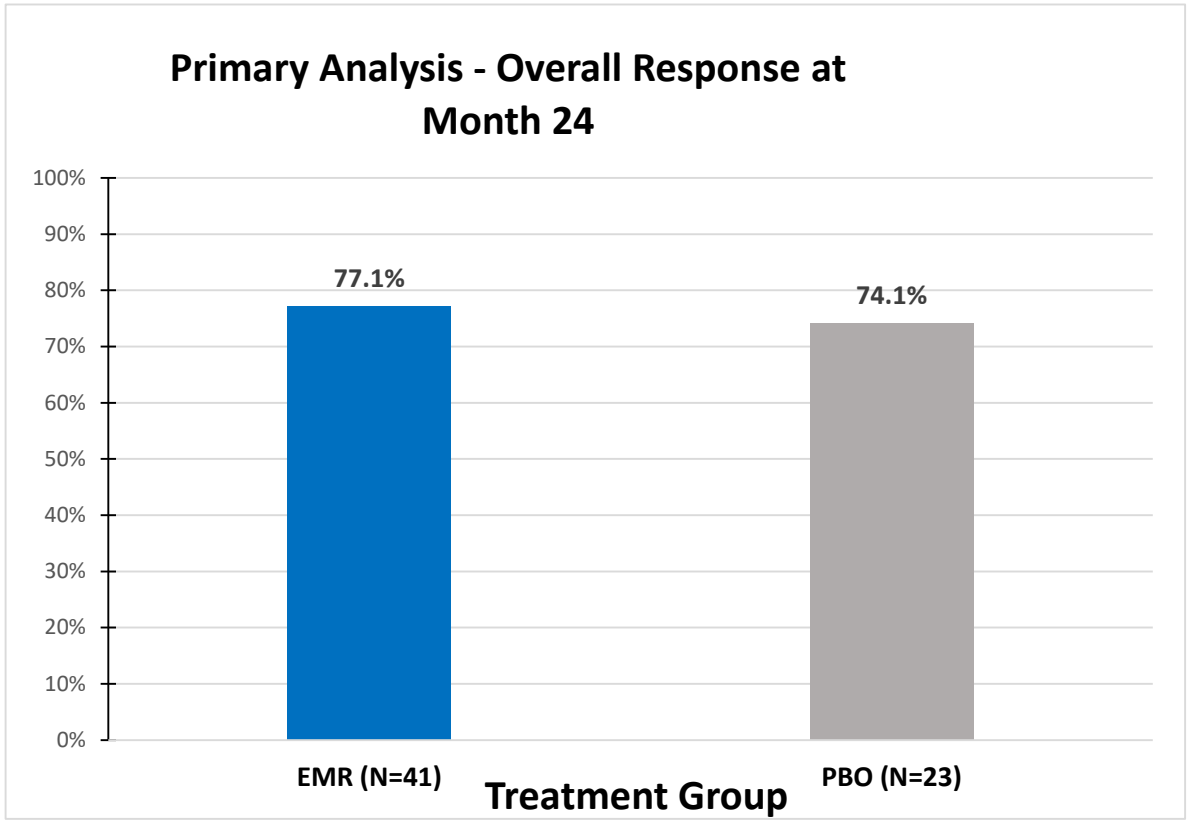
*Caspase 3/7: 919.5 (Study-05); 1173 (Study-08) **cCK18: 334.0 (Study-05); 332 (Study-08) ***fICK18: 240.0 (Study-05); 178 (Study-08)

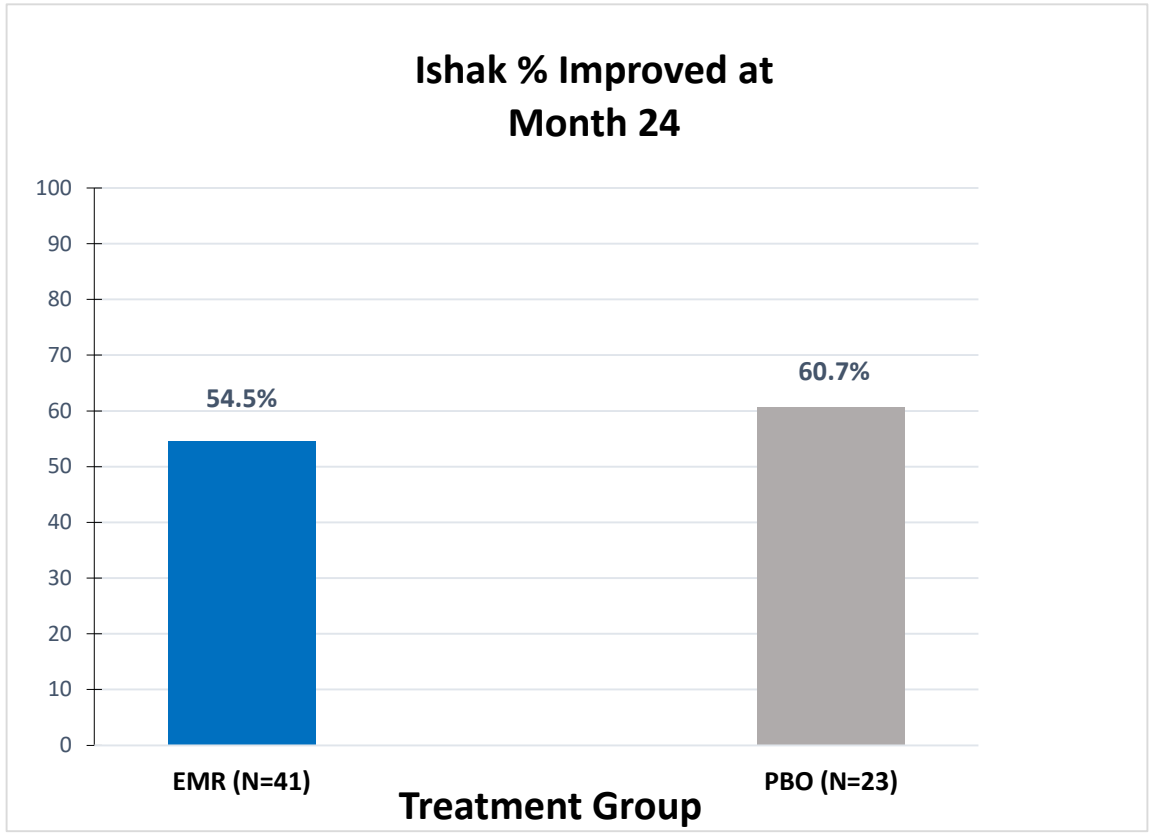
Liver Transplant History

	Emricasan (N=41)	Placebo (N=23)
Median number of years since transplant	5.87	6.55
Median time since SVR (days)	227.0	233.0
Immunosuppressant Therapy	n (%)	n (%)
tacrolimus +/-steroids	35 (85.4)	19 (82.6)
cyclosporine +/- steroids	5 (12.2)	4 (17.4)
Previous HCV treatment		
antiviral	33 (80.5)	19 (82.6)
antiviral-immunotherapy	8 (19.5)	4 (17.4)

Primary Endpoint: Response Rate F2-F6 Ishak Fibrosis Stages at Month 24*

- Response (stable or improved) showed no significant treatment difference (%)
- Improvement alone (≥ 1 stage) showed no significant treatment difference (%)





*Multiple imputations

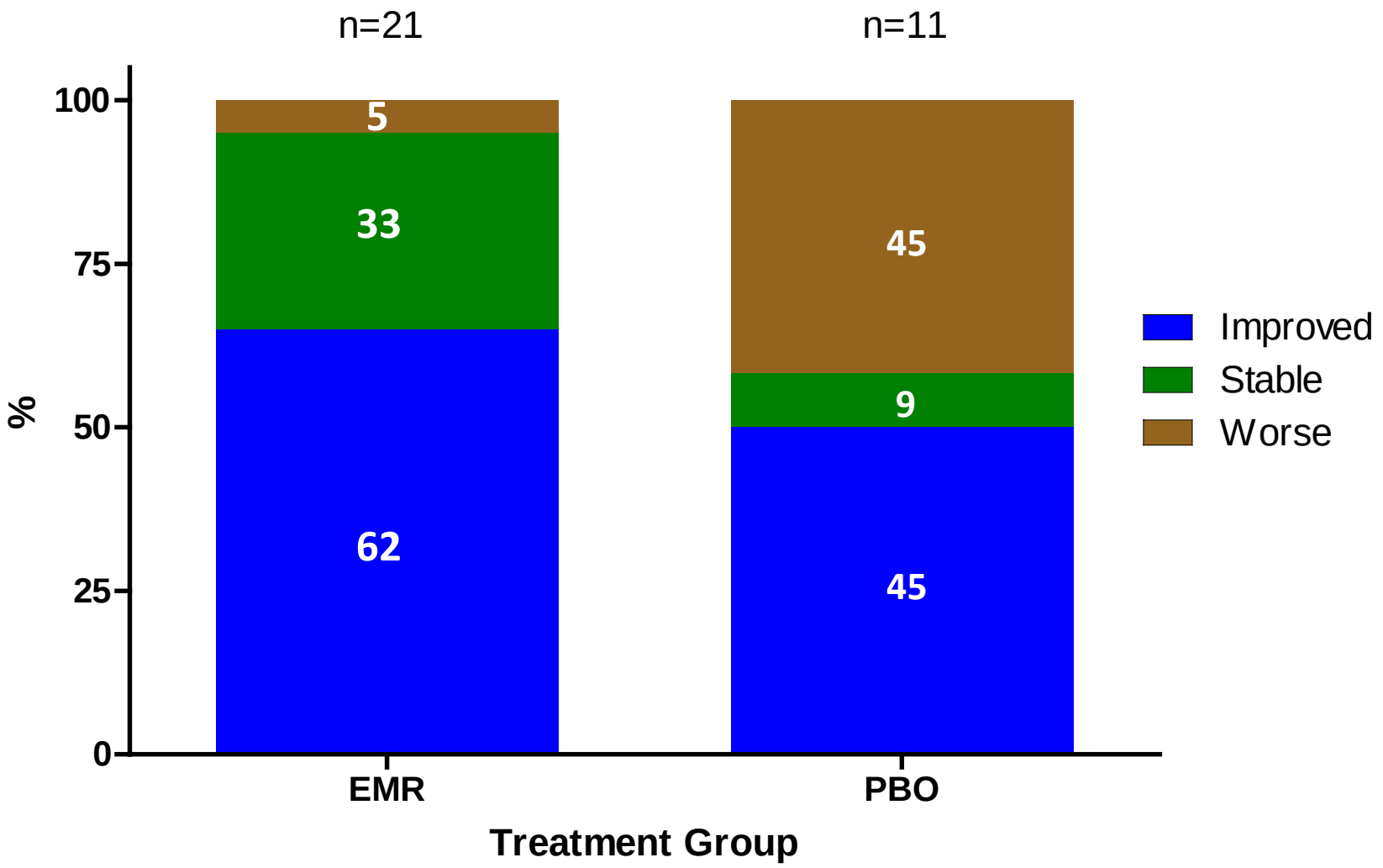
Responses by Pre-Specified Ishak Fibrosis Stages

Ishak Fibrosis Stage	Emricasan % (n)	Placebo % (n)	Difference %	p Value
Overall Population	78.1 (32)	73.7 (19)	4.4	0.718
F2*	83.3 (6)	100 (5)	-16.7	1.000
F3,4,5*	95.2 (21)	54.6 (11)	40.7	0.011
F6^	0 (5)	100 (3)	-100	0.018

*Pre-specified strata: response=stable or improvement in Ishak Fibrosis Stage Month 24 (observed data)

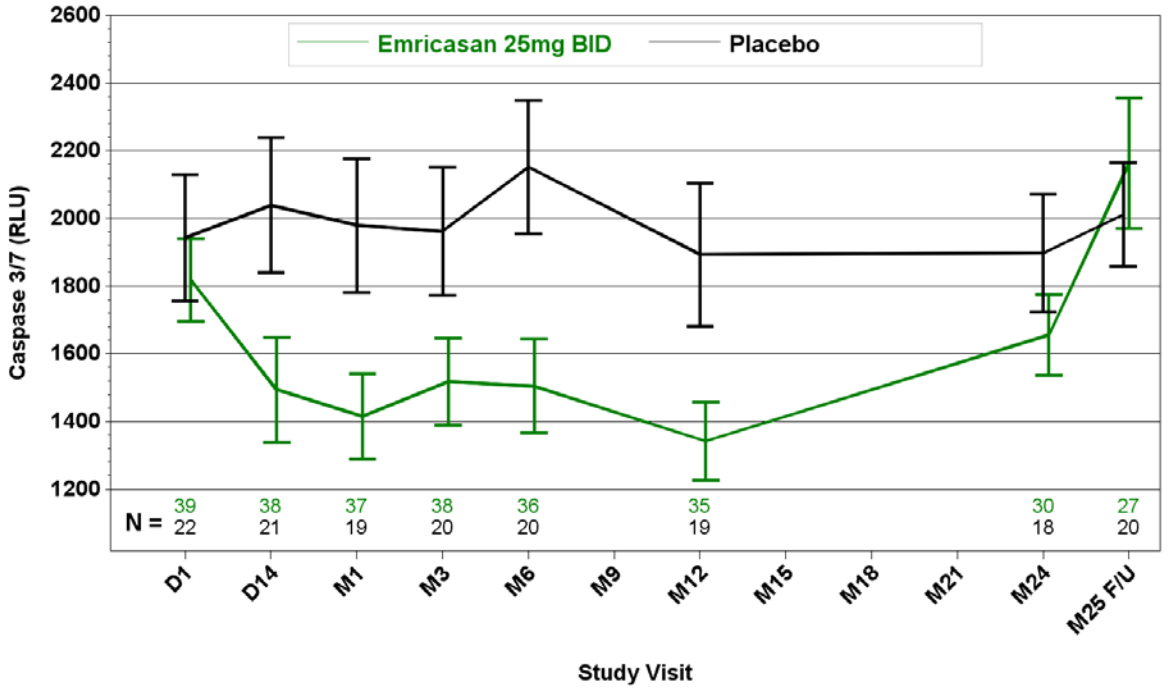
^Improvement only in Ishak Fibrosis Stage at Month 24

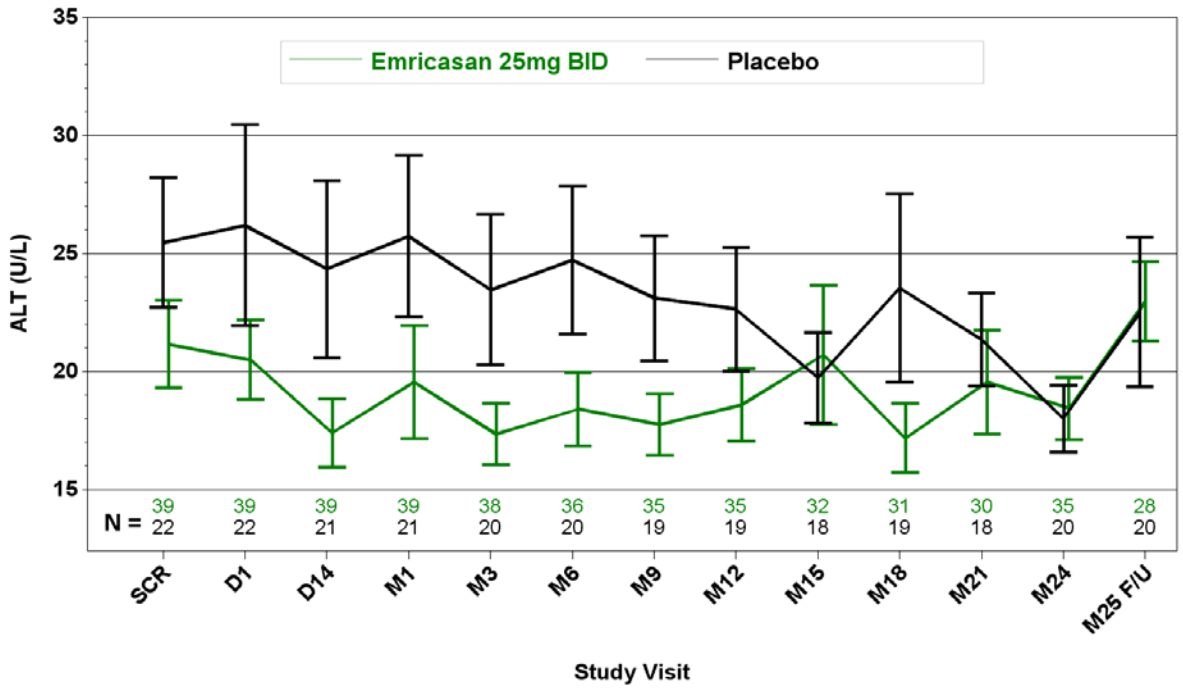
Prespecified F3-F5 Subgroup: Ishak Fibrosis Stage Response at Month 24



Serum Biomarkers

- Caspase 3/7 values were modestly elevated and showed a clear treatment effect through month 12
- ALT values were within the normal range at baseline and showed a small treatment effect through month 12





Treatment Emergent Adverse Events (TEAEs): Balanced Between Groups

	Emricasan (N=41)	Placebo (N=23)
Subjects with TEAE – n (%)	37 (90.2)	20 (87.0)
Subjects with serious TEAE – n (%)	14 (34.1)	7 (30.4)
Subjects with moderate TEAE – n (%)	26 (63.4)	16 (69.6)
Subjects with severe TEAE – n (%)	13 (31.7)	7 (30.4)
Subjects with TEAE leading to study discontinuation – n (%)	3 (7.3)	3 (13.0)

Adverse Events with Preferred Term Incidence of ≥10% in Either Treatment Group

	Emricasan (N=41)		Placebo (N=23)	
	n	%	n	%
Diarrhea	9	22	5	21.7
Nausea	7	17.1	4	17.4
Headache	7	17.1	7	30.4
Fatigue	7	17.1	6	26.1
Arthralgia	6	14.6	2	8.7
Hypertension	6	14.6	3	13.0
Dizziness	2	4.9	5	21.7
Rash	2	4.9	4	17.4
Upper respiratory tract infection	1	2.4	4	17.4
Muscle spasms	0	0	3	13.0

Treatment Emergent Adverse Events of Interest

System Organ Class Preferred term	Emricasan n (%)	Placebo n (%)
Infections & infestations	13 (31.7)	9 (39.1)
Neoplasms, malignant		
Hepatocellular CA*	2 (4.9)	0 (0)
Pancreatic CA	0 (0)	1 (4.3)
Prostate CA	1 (2.4)	0 (0)
Squamous cell CA, skin	0 (0)	1 (4.3)

*10 subjects in emricasan group & 2 subjects in placebo group had HCC prior to transplant

Summary

- In liver transplant recipients with recurrent HCV, fibrosis, and despite SVR:
  - The primary endpoint, subjects with improvement or stability in Ishak fibrosis stage, was similar between groups at 24 months (p=NS)
  - However, there was both significant improvement & stability in fibrosis stage in the F3-F5 subgroup vs. placebo (p=0.01)
  - Tolerability and safety profiles were similar in emricasan and placebo subjects
  - Emricasan safety profile was encouraging given use for 24 months in combination with immunosuppression

Acknowledgements : Co-investigators

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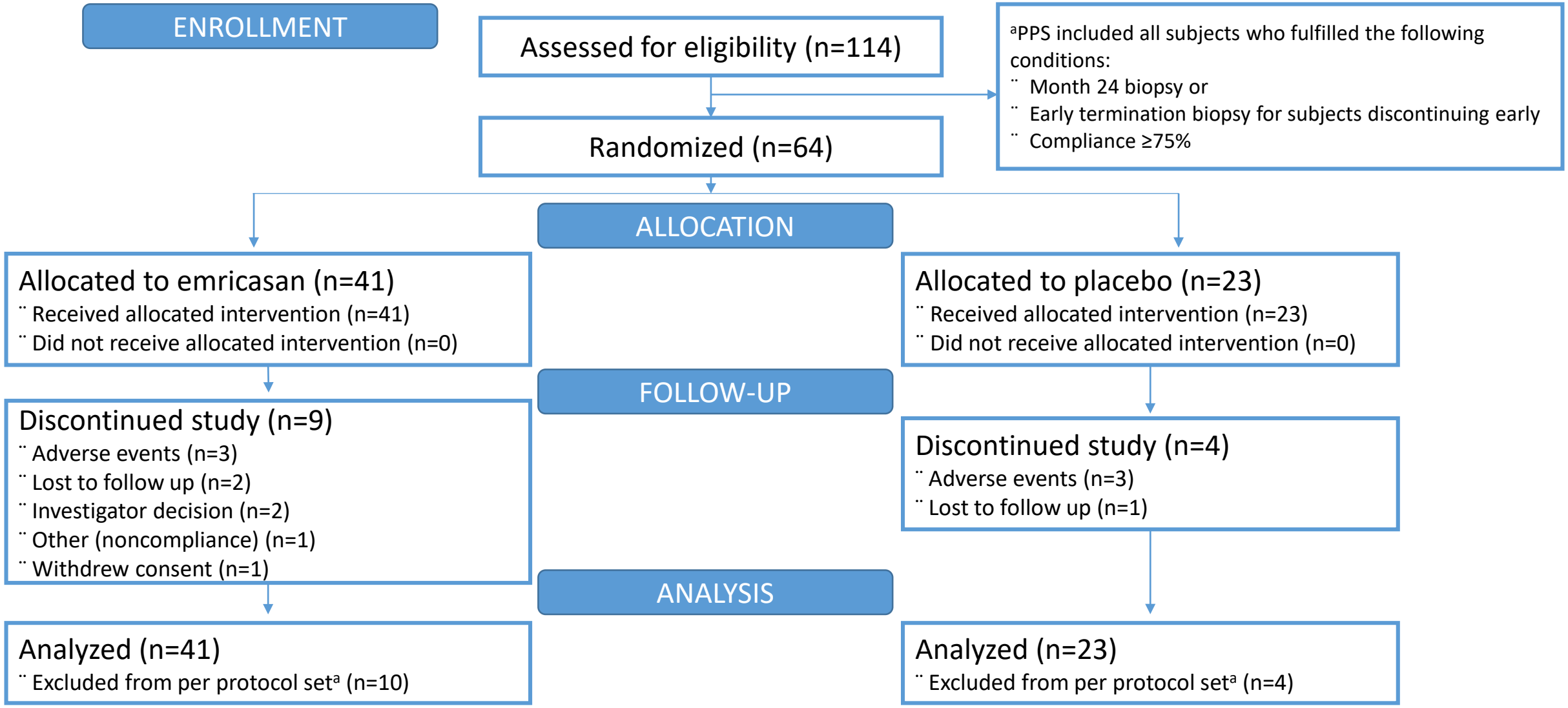
Back up/Supporting Slides

Subject Disposition



Baseline Disease Characteristics

	Emricasan 25 mg BID (N=41)	Placebo (N=23)	Total (N=64)
BMI (kg/m^2)			
n	40	23	63
Mean (SD)	28.10 (4.330)	30.51 (4.701)	28.98 (4.583)
Median	27.75	29.40	28.70
Min, Max	17.8, 38.0	23.0, 42.5	17.8, 42.5

Adverse and Serious Adverse Events: Neoplasms

	n (%)	Events	n (%)	Events	n (%)	Events
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**8 (19.5)**	**10**	**2 (8.7)**	**2**	**10 (15.6)**	**12**
	Emricasan 25 mg BID (N=41)		**Placebo (N=23)**		**Total (N=64)**	
Basal cell carcinoma	**3 (7.3)**	**4**	**0**	**0**	**3 (4.7)**	**4**
Hepatocellular carcinoma	**2 (4.9)**	**2**	**0**	**0**	**2 (3.1)**	**2**
Colon adenoma	**1 (2.4)**	**1**	**0**	**0**	**1 (1.6)**	**1**
Mycosis fungoides	**1 (2.4)**	**1**	**0**	**0**	**1 (1.6)**	**1**
Pancreatic carcinoma metastatic	**0**	**0**	**1 (4.3)**	**1**	**1 (1.6)**	**1**
Prostate cancer	**1 (2.4)**	**1**	**0**	**0**	**1 (1.6)**	**1**
Seborrhoic keratosis	**1 (2.4)**	**1**	**0**	**0**	**1 (1.6)**	**1**
Squamous cell carcinoma of skin	**0**	**0**	**1 (4.3)**	**1**	**1 (1.6)**	**1**

Serious Adverse Events: Infections

	Emricasan		Placebo		Total	
Infections and infestations	**4 (9.8)**	**6**	**1 (4.3)**	**2**	**5 (7.8)**	**8**
Biliary tract infection bacterial	1 (2.4)	1	0	0	1 (1.6)	1
Enterobacter bacteremia	1 (2.4)	1	0	0	1 (1.6)	1
Gastroenteritis cryptosporidial	1 (2.4)	1	0	0	1 (1.6)	1
Gastroenteritis viral	1 (2.4)	1	0	0	1 (1.6)	1
Influenza	0	0	1 (4.3)	1	1 (1.6)	1
Pneumonia	1 (2.4)	1	0	0	1 (1.6)	1
Pneumonia mycoplasma	1 (2.4)	1	0	0	1 (1.6)	1
Sepsis	0	0	1 (4.3)	1	1 (1.6)	1