

APACHE Studie – Albumin Plasmapherese

Primary Efficacy/Endpoints

- Primary: To evaluate the effect of standard medical treatment (SMT) plus PE-A 5% (SMT+PE-A 5%) on 90-day overall survival
- Secondary:
 - To evaluate the effect of SMT+PE-A 5% on 90-day transplant-free survival.
 - To evaluate the effect of SMT+PE-A 5% on 28-day overall survival
- Exploratory objectives focusing on survival parameters, organ failures, changes in various scores (CLIF-SOFA, CLIF-C, CPT and MELD), systemic inflammation markers, infections, albumin levels and time to discharge

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Main Inclusion criteria

- Male or female cirrhotic subjects between 18 and 79 years of age
- Subjects with **ACLF-1b, ACLF-2, or ACLF-3a** detected either at admission or during hospitalization (**must be ACLF-1b, -2, or -3a within the Screening Period [a maximum of 10 days]**)
- In case of HE, informed consent will be provided by a relative or a legally authorized representative (surrogate)

ACLF Grading

Illness Severity Scoring

- Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) will be used for ACLF Grading
- Number of organ failures determines the ACLF Grade
- Local lab results, where applicable, will be used to determine number organ failure as noted below

Organ/System	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <6.0	≥6.0 to <12.0	≥12.0
Kidney (creatinine, mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <3.5 or use of renal replacement therapy	≥3.5 to <5.0	≥5.0
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet count ≤20x10 ⁹ /L
Circulation (mean arterial pressure, mmHg)	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or E<0.1 or NE<0.1	Dopamine >15 or E<0.1 or NE<0.1
Lungs PaO ₂ /FiO ₂ or SpO ₂ /FiO ₂	>400 >512	>300 to ≤400 >357 to ≤512	>200 to ≤300 >214 to ≤357	>100 to ≤200 >89 to ≤214	≤100 ≤89

Shaded areas designate areas of organ failure

NOTE: The CLIF-SOFA score includes subscores ranging from 0 to 4 for each of 6 components (liver, kidney, brain, coagulation, circulation, and lungs), with higher scores indicating more severe organ impairment. Aggregate scores ranging from 0 to 24 and provide information on overall severity. The shaded areas indicate the diagnostic criteria for organ failures.
E, epinephrine; HE, hepatic (encephalopathy) impairment, INR, International Normalized Ratio; NE, norepinephrine; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; SpO₂, pulse oximetric saturation.

ACLF Grading

- Study population: subjects with cirrhosis and ACLF-1b, ACLF-2, or ACLF-3a

Table 2-1 Grades of ACLF

	Grades of ACLF	
Exclusion Grading At Screening	No ACLF	- No organ failure - One organ failure (liver failure, coagulation, circulatory or respiratory failure) with creatinine <1.5 mg/dL and no HE
	ACLF grade 1a	- Single kidney failure without mild or moderate HE
Inclusion Grading At Screening	ACLF grade 1b	- Single organ failure with serum creatinine ranging from 1.5 mg/dL to 1.9 mg/dL and/or mild-to-moderate HE
	ACLF grade 2	- Presence of 2 organ failures
	ACLF grade 3a	- Presence of 3 organ failures
	ACLF grade 3b	- Presence of ≥4 organ failures