

Administration of Zemaira®

ICD-10-PCS Coordination and Maintenance Committee
Fall Update

Disclaimer

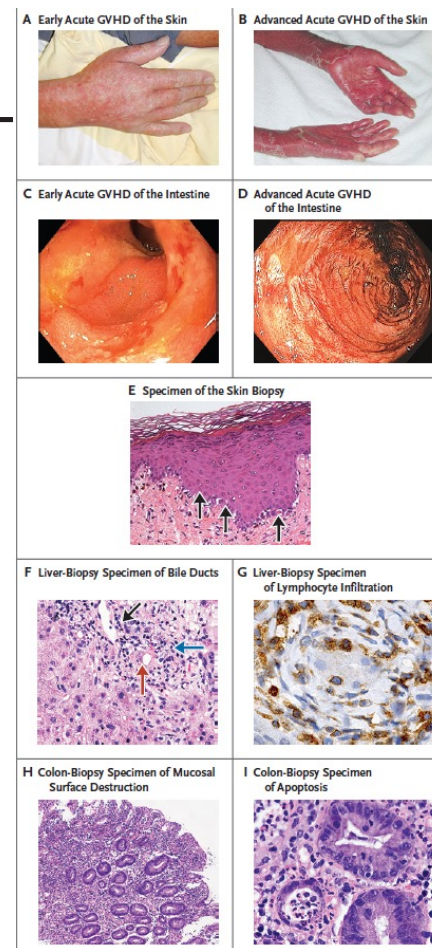
Zemaira® is an investigational therapy for acute graft-versus-host disease and has not been approved by the FDA for that indication.

Zemaira® Overview

- Zemaira® (CSL964) is a plasma-derived alpha1-proteinase inhibitor (A1-PI) used in combination with corticosteroids for first-line treatment of acute graft-versus-host disease (aGVHD) in adults
- Zemaira® is designed to impact the aGVHD disease pathology, e.g., reduction of pro-inflammatory cytokine secretion and activity; exertion of potential tissue protective effects via serine protease inhibition; and impact on immune cell populations to attenuate aGVHD pathophysiology, including T-regulatory (Tregs) to T-effector (Teff) cell ratio increase and inhibition of neutrophil migration to sites of inflammation

Addressing Acute Graft-versus-Host disease – an area of unmet medical need

- Rare and life-threatening condition occurring in patients undergoing allogeneic hematopoietic stem cell transplantation (HCT) caused by immune-competent donor T cells, developing in ~50% of patients
- One of the leading causes of death within 100 days after allo-HCT
- Mainly impacts skin, gastrointestinal tract and liver
- Clinically relevant risk of infectious disease complications due to underlying malignancy, immunosuppressive cancer therapies and aGVHD itself
- No FDA-approved first line treatment available – current standard of care is high-dose corticosteroids, which is ineffective in ~50% of patients (steroid-refractory aGVHD)

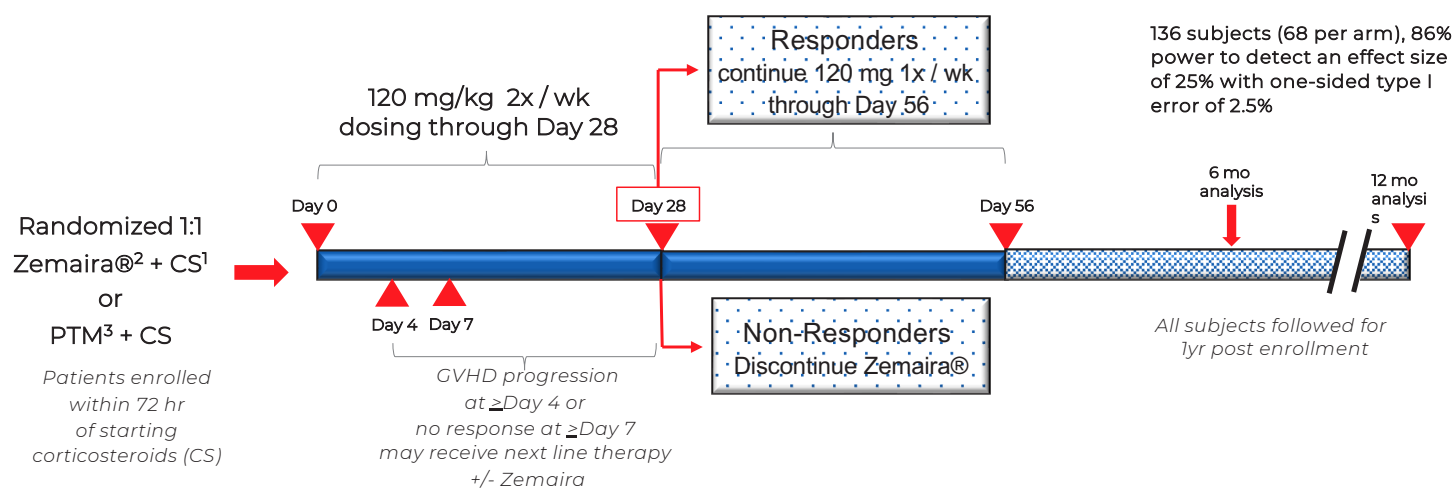


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CSL964_5001: Study in collaboration with



The **primary objective** was to compare the rate of **complete response (CR)** and **partial response (PR)** on **Day 28** post-randomization between Zemaira® + CS versus placebo + CS in patients with high-risk acute GVHD



Interim analysis was conducted when 76 subjects became evaluable for the primary endpoint

¹ Methylprednisolone starting dose equivalent to prednisone 2 mg/kg/day. (Taper at discretion of treating physician)

² Zemaira® dose of 120 mg/kg 2x weekly based on PK modeling (goal: ≥ 350 mg/ml)

³ PTM = Placebo to match, 5% albumin (diluted)

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Study Definitions

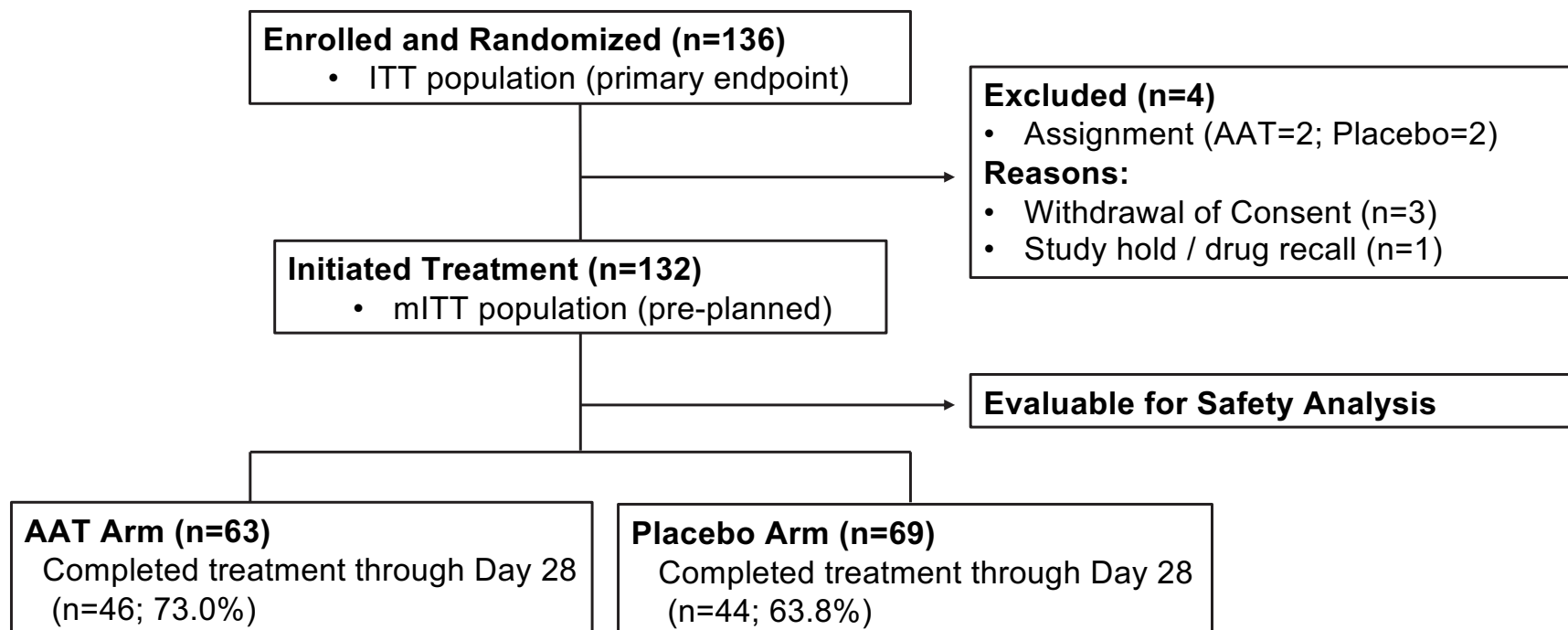
- **Primary Response Definition:**

- Overall (complete or partial) response at Day 28 post-randomization compared to max GVHD organ staging within 72 hours prior to enrollment
- Next-line systemic GVHD therapy or escalation of steroids to ≥ 2.5 mg/kg/day of prednisone or higher or death prior to Day 28 classified as No Response.
- No Response, Mixed Response, and progression were treated as a failure for the primary endpoint.

- Primary endpoint assessed by intention to treat (ITT) - all randomized patients

- Pre-planned modified ITT (mITT) – patients initiating randomized treatment

Enrollment and Analysis Populations



Patient Characteristics

Characteristics	AAT (N=65)	Placebo (N=71)	Total (N=136)
Gender, n (%)			
Male	45 (69.2)	39 (54.9)	84 (61.8)
Female	20 (30.8)	32 (45.1)	52 (38.2)
Age (years)			
Median (range)	59 (22-76)	59 (20-75)	59 (20-76)
Acute GVHD Eligibility, n (%)			
Refined Minnesota High Risk	49 (75.4)	52 (73.2)	101 (74.3)
Isolated Stage 2 lower GI	8 (12.3)	12 (16.9)	20 (14.7)
Stage 1 lower GI ± upper GI + skin	8 (12.3)	7 (9.9)	15 (11.0)

Patient Characteristics: Organ Involvement and GVHD Biomarkers

Characteristics	AAT (N=65)	Placebo (N=71)	Total (N=136)
High Stage Organ Involvement, n (%)			
Stage 3-4 Lower GI + Skin			
MAGIC Biomarker Risk Score, n (%)			
	3 (4.6)	16 (22.5)	19 (14.0)

Primary Endpoint (ITT & Supplemental mITT)

Variable	n	#CR+PR (%)	Odds	95% CI	P-value
Treatment Arm (ITT)					
AAT	65	39 (60.0)	1.92	0.954, 3.866	0.034 ¹
Placebo	71	32 (45.1)	1.00	-	-
Treatment Arm (mITT)					
AAT	63	40 (63.5)	2.22	1.072, 4.578	0.016 ¹
Placebo	69	32 (46.4)	1.00	-	-

¹One-sided Wald test of at a 0.025 significance level

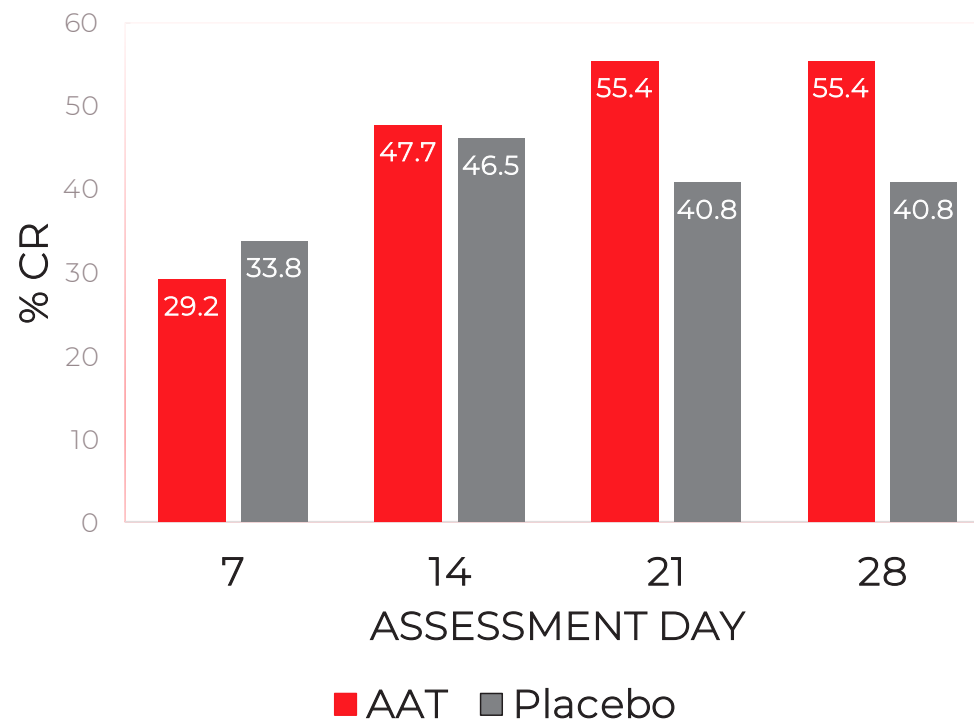
mITT Definition: a pre-specified analysis that excluded patients who did not receive treatment, and utilized pre-treatment aGVHD staging (vs pre-randomization)

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Higher Complete Response (CR) Rates with AAT Treatment



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Treatment Response in Lower GI Tract GVHD, Steroid dose & need for Next Line Therapy

Endpoint	N	%, change	P-value
Response in lower GI tract GVHD prior to D28			
AAT	63	65.1%	0.053
Placebo	67	47.8%	
Reduction in steroids prior to D28 (mg/kg/day)			
AAT	60	-1.72	0.048
Placebo	63	-1.54	
Subjects initiating next line therapy prior to D28			
AAT	65	24.6%	--
Placebo	71	43.7%	

Zemaira® offers a positive benefit risk profile in aGVHD

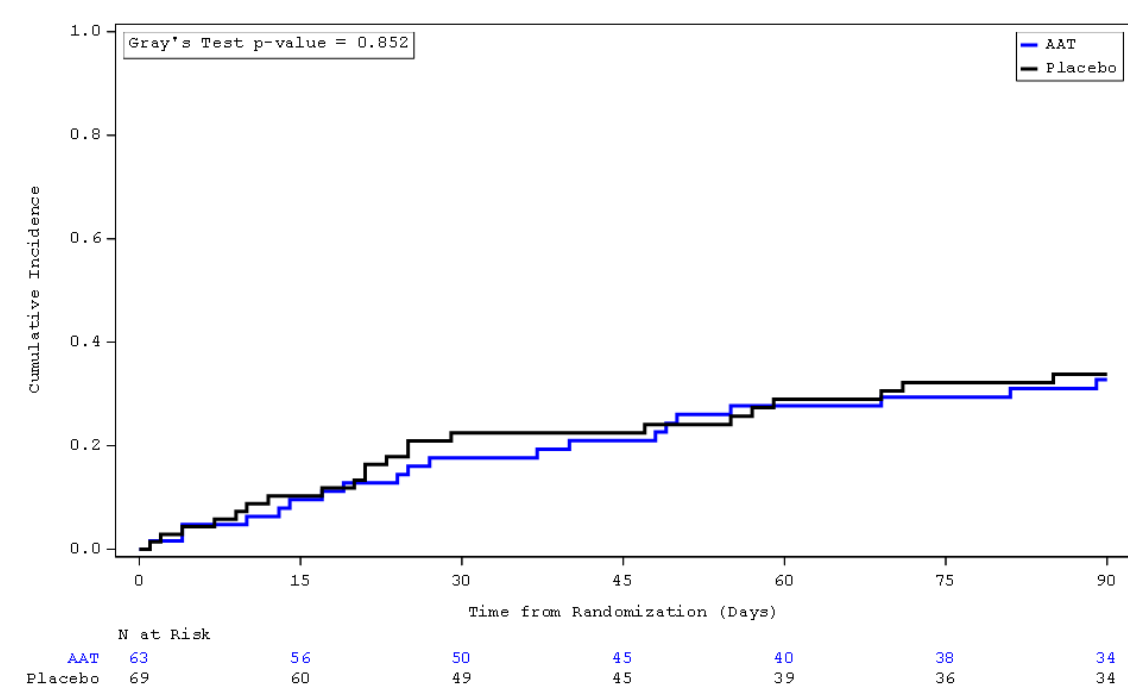
At Day 56, more Zemaira® recipients were alive and free of acute or chronic GVHD and they experienced fewer Grade 3-5 TEAEs through Day 86

	Zemaira <i>no./total no (%)</i>	Placebo <i>no./total no (%)</i>	Odds Ratio (95% CI)	P value
GVHD-free survival at Day 56 (ITT)	29/65 (44.6)	25/71 (35.2)	1.51 (0.75, 3.04)	0.247
Grade 3-5 TEAEs through 30 days post last dose (safety population)	29/63 (46.0)	45/69 (65.2)	(-----N/A-----)	0.029 ¹

¹Two-sided Barnard's exact test based on % subjects impacted

- Zemaira® does not add to the immunosuppressive burden of CS treatment
- There was no increased risk of developing infections in the Zemaira® arm vs the placebo arm indicating Zemaira® does not add to the immunosuppressive burden of CS treatment

No increase in Grade 2-3 Systemic Infections with AAT



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Secondary Endpoints

Endpoint†	6 months‡		12 months‡	
	AAT (N=65)	Placebo (N=71)	AAT (N=65)	Placebo (N=71)
Non-Relapse Mortality	20.0%	21.1%	21.7%	21.1%
Chronic GVHD	22.3%	13.8%	34.8%	21.8%
Relapse	23.4%	21.1%	25.1%	22.7%
Overall Survival	73.0%	72.4%	66.1%	64.2%
Progression-free survival	58.3%	57.7%	54.9%	56.1%

† Data are the cumulative incidences

‡ Time from Randomization

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Summary

Efficacy

- **Clinically meaningful increase in ORR at Day 28** compared with placebo that was consistent across primary and pre-specified supplementary analyses and driven by a higher proportion of CR
- **Fewer subjects initiating next-line therapy at Day 28** compared with placebo
- **Greater and faster reduction in CS dose at Day 28** compared with placebo
- **Higher GVHD-free survival at Day 56** compared with placebo

Safety

- **Better tolerability of Zemaïra® treatment** than placebo as demonstrated by fewer overall treatment-emergent adverse events (TEAEs) up to 30 days post last study treatment dose
- **No increased risk for infection development** as demonstrated by similar systemic infection occurrence

Documentation

There are no additional terms to describe Zemaïra®. The administration of Zemaïra® will be documented in the medication administration record, the physician's progress notes, the nurse's notes, and the electronic medical record.

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