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ORAL ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: Phase 3 Long-Term Data

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Background

C5 inhibitors eculizumab (Ecu) and ravulizumab (Rav) have transformed the natural history of paroxysmal nocturnal hemoglobinuria (PNH). Ecu resulted in patient (pt) survival comparable to that of the general population over 20 y of follow-up under real-world conditions. Overall survival rate at 6 years for pts treated with Rav was 98.4%. Where available, Rav is the standard of care for PNH, inhibiting terminal complement activation to prevent intravascular hemolysis (IVH) and thrombosis. Of pts with PNH treated with Rav/Ecu, 10-20% experience clinically significant extravascular hemolysis (cs-EVH). Efficacy and safety of the first-in-class oral factor D inhibitor danicopan (Dan; ALXN2040) as add-on treatment to Rav or Ecu for pts with PNH and cs-EVH were assessed in a phase 3, randomized, double-blind, placebo (Pbo)-controlled superiority clinical trial (ALPHA, NCT04469465). 12-wk data (double-blind treatment period [TP] 1) showing superiority of Dan vs Pbo on primary and key secondary endpoints were previously reported and represent the final analysis set for the trial. Open-label 24-wk (TP2) and ongoing long-term extension (LTE) data are presented.

Methods

Pts (≥18 y) with PNH and cs-EVH (hemoglobin [Hgb] ≤9.5 g/dL; absolute reticulocyte count [ARC] ≥120×10 ^{9}/L) on Rav/Ecu >6 mos were randomized double-blind 2:1 to Dan or Pbo add-on therapy for 12 wks (TP1). At wk 12, Pbo arm pts switched to Dan (Pbo-Dan) and Dan arm pts continued Dan (Dan-Dan) for another 12 wks (TP2), followed by a 1-y LTE in which all pts received Dan add-on therapy. The initial Dan dose of 150 mg 3 times daily (TID) could be escalated to 200 mg TID based on clinical response at investigator discretion. Primary endpoint was change from baseline (CFB) at wk 12 in Hgb. Other secondary endpoints: proportions of pts with Hgb increase ≥2 g/dL in absence of transfusion and with transfusion avoidance through wk 24; CFB in Hgb at wk 24; and CFB in ARC, lactate dehydrogenase (LDH), and C3 fragment deposition on PNH red blood cells at wks 12 and 24. Safety assessments included treatment-emergent adverse events (TEAEs) and laboratory abnormalities throughout the study.

Results

As of 20 September 2022, 86 pts were randomized; 60 completed TP2 (Dan n=40; Pbo n=20). Baseline characteristics were similar between arms (**Table**). At wk 24 (**Fig**), mean Hgb level was maintained in the Dan-Dan arm and increased from wk 12 in Pbo-Dan arm. ARC (**Fig**) and other secondary endpoints were maintained in the Dan-Dan arm and improved in Pbo-Dan arm (**Table**) at wk 24. The proportion of pts with Hgb increase of ≥2 g/dL in the absence of transfusion was maintained in the Dan-Dan arm and improved in the Pbo-Dan arm from wk 12 (Dan, 59.5%; Pbo, 0%) to wk 24 (Dan-Dan 46.3%; Pbo-Dan, 35.0%). Transfusion avoidance was maintained in the Dan-Dan arm and increased in Dan-Pbo arm from wk 12 (Dan, 83.3%; Pbo, 38.1%) to wk 24 (Dan-Dan 78.0%; Pbo-Dan, 90.0%). Mean LDH levels were maintained from wk 12 to 24 (**Table**) and were near normal (<1.5×ULN) in both arms. Transfusions decreased in the Pbo-Dan arm from wk 12 (Pbo; mean [SD], 2.2 [2.3]) through 24 wks (Pbo-Dan; mean [SD], 0.1 [0.5]).

The safety analysis included the n=80 pts exposed to Dan during the trial. At wk 24, study drug compliance was 98.8% (10.35) in the Dan-Dan arm and 98.3% (3.95) in Pbo-Dan arm. Escalation to 200 mg TID occurred for 41/57 (71.9%) pts in the Dan-Dan arm and 14/23 (60.9%) in Pbo-Dan arm. There were no deaths, meningococcal infections, or discontinuations due to hemolysis.

Through data cut-off, 90% (72/80; 464 events) of pts had ≥1 TEAE after exposure to Dan. Serious AEs related to Dan were reported by 2 pts (gastrointestinal disorders/increased blood bilirubin; headache). 6 events in 4 pts led to withdrawal of study drug. 4 events were reported as breakthrough hemolysis (BTH) based on investigator discretion. Only 1 AE was associated with LDH >2×ULN (actual value 2.2×ULN) and potentially met the BTH definition used in other clinical studies. This AE was related to a complement-amplifying condition, COVID-19. This pt continued the study and BTH was resolved.

Conclusions

Danicopan as add-on to Rav or Ecu significantly improves Hgb and ARC levels and reduces the need for transfusion by addressing cs-EVH while maintaining control of IVH through 48 wks of treatment. Danicopan demonstrated a favorable benefit-risk profile with no deaths, meningococcal infections, or discontinuations due to hemolysis.

Disclosures Kulasekararaj: *F. Hoffmann-La Roche Ltd:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Akari Therapeutics:* Consultancy; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Achillion:* Consultancy; *Celgene/BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Samsung:* Consultancy; *BioCryst:* Consultancy. **Griffin:** *Regeneron Pharmaceuticals:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sobi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Amgen:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Biocryst:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Apellis:* Other: educational grant support . **Piatek:** *Alexion, AstraZeneca Rare Disease:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Rigel:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Annexon Biosciences:* Membership on an entity's Board of Directors or advisory committees; *Osotec:* Research Funding; *Incyte:* Research Funding; *Celgene:* Research Funding; *Argenx:* Research Funding; *Apellis:* Membership on an entity's Board of Directors or advisory committees; *Sobi:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sanofi:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Shammo:** *sanofi Aventis:* Consultancy, Honoraria, Speakers Bureau; *MJH:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *NS bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Apellis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Alexion:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Protagonist:* Research Funding; *Astra Zeneca:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Research Funding; *Incyte:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *CTI BioPharma Corp., a Sobi company:* Consultancy, Honoraria, Research Funding; *AbbVie:* Current equity holder in publicly-traded company, Research Funding; *Blueprint:* Honoraria, Speakers Bureau; *otsuka:* Research Funding. **Nishimura:** *Roche:* Membership on an entity's Board of Directors or advisory committees; *Chugai Pharmaceutical Co., Ltd:* Membership on an entity's Board of Directors or advisory committees; *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Patriquin:** *Takeda:* Consultancy, Honoraria, Speakers Bureau; *Regeneron:* Other: clinical site investigator; *Apellis:* Consultancy, Honoraria, Other: clinical site investigator, Speakers Bureau; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Other: clinical site investigator, Speakers Bureau; *BioCryst:* Consultancy, Honoraria, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Speakers Bureau. **Schrezenmeier:** *Novartis:* Honoraria, Other: travel support, Research Funding; *Sobi:* Honoraria, Other: travel support, Research Funding; *Roche:* Other: honoraria (to University of Ulm) ; *Alexion, AstraZeneca Rare Disease:* Honoraria, Other: travel support, Research Funding; *Apellis:* Other: honoraria (to University of Ulm) ; *Sanofi:* Other: honoraria (to University of Ulm). **Gaya:** *Alexion, AstraZeneca Rare Disease:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sobi:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Patel:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Liu:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Filippov:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Sicre De Fontbrune:** *Novartis:* Honoraria, Research Funding;

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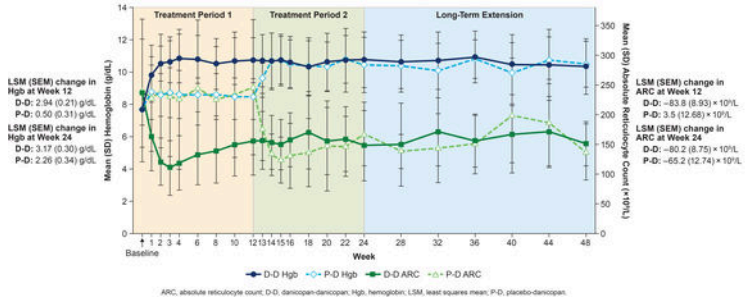
Table. Summary of Study Disposition, Baseline Demographics and Characteristics, and Secondary Endpoints

Study Disposition		Danicopan (N = 57) n (%)			Placebo (N = 29) n (%)		
Randomized		57			29		
Received ≥1 dose of danicopan or placebo (safety set)		57 (100)			29 (100)		
Treatment Period 1							
Completed		48 (84.2)			23 (79.3)		
Discontinued		2 (3.5)			2 (6.9)		
Adverse event		2 (3.5)			1 (3.4)		
Withdrawal by patient		0			1 (3.4)		
Ongoing		7 (12.3)			4 (13.8)		
Treatment Period 2							
Entered		48 (84.2)			23 (79.3)		
Completed		40 (70.2)			20 (69.0)		
Discontinued		1 (1.8)			0		
Adverse event		1 (1.8)			0		
Ongoing		7 (12.3)			3 (10.3)		
LTE							
Entered		40 (70.2)			20 (69.0)		
Ongoing		36 (63.2)			19 (65.5)		
Discontinued		4 (7.0)			1 (3.4)		
Adverse event		0			1 (3.4)		
Noncompliance		1 (1.8)			0		
Physician decision		1 (1.8)			0		
Withdrawal by patient		2 (3.5)			0		
Baseline Demographic/ Characteristic	**Statistics/category**	**Danicopan (N = 57)**			**Placebo (N = 29)**		
Age, years	Mean (Min, Max)	52.8 (20, 82)			52.9 (29, 77)		
Sex, n (%)	Female	34 (59.6)			20 (69.0)		
Race/ethnicity, n (%)	American Indian/Alaska Native	1 (1.8)			0		
	Asian	22 (38.6)			10 (34.5)		
	Black or African American	2 (3.5)			0		
	Caucasian	28 (49.1)			14 (48.3)		
	Other	1 (1.8)			0		
	Not Reported	3 (5.3)			4 (13.8)		
	Unknown	0			1 (3.4)		
Hgb (g/dL)	Mean (SD)	7.67 (0.95)			7.89 (1.01)		
ARC (x10⁹/L)	Mean (SD)	248 (97)			223 (115)		
LDH (U/L)	Mean (SD)	304.00 (123.60)			286.40 (93.14)		
Transfusion instances 6 months prior to screening	Median	2			2		
	Min, Max	0, 10			0, 8		
C5 inhibitor , n (%)	Ravulizumab	36 (63.2)			15 (51.7)		
	Eculizumab	21 (36.8)			14 (48.3)		
Endpoint	**Statistic**	**Danicopan-Danicopan**			**Placebo-Danicopan**		
		Baseline	Week12	Week24	Baseline	Week12	Week24
Change from baseline in LDH (U/L)	Mean (SD)	298.73 (105.71)	268.24 (61.38)	279.21 (88.64)	278.25 (68.40)	328.38 (224.31)	277.55 (64.78)
Hgb increase of ≥2 g/dL in the absence of transfusion*	N	-	42	41	-	21	20
	n (%)	-	25 (59.5)	19 (46.3)	-	0	7 (35.0)
Transfusion avoidance† to Week 12 and from Week 12–24	N	42	42	41	21	21	20
	n (%)	13‡ (31.0)	35 (83.3)	32 (78.0)	6‡ (28.6)	8 (38.1)	18 (90.0)
C3 Fragment Deposition on PNH RBCs	N	42	42	42	21	21	21
	n	24	33	26	11	12	12
	Median, %	26.60	4.60	6.70	21.30	37.20	5.15

All pts received either Rav or Ecu in addition to study drug. Reasons for treatment withdrawal included gastrointestinal disorders, hepatobiliary disorders, COVID-19, and increased alanine aminotransferase, aspartate aminotransferase, blood bilirubin, and hepatic enzyme levels. AE, adverse event; ARC, absolute reticulocyte count; Ecu, eculizumab; Hgb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; Rav, ravulizumab; RBCs, red blood cells.

*Data for placebo-danicopan arm only for 12 weeks of danicopan exposure during treatment period 2; 0 participants had Hgb increase ≥2 g/dL in treatment period 1. †Defined as pts who remain transfusion-free and did not require a transfusion per protocol-specified guidelines. ‡Pts who were RBC transfusion-free during the 12 wks prior to first dose.

Fig. Change in Hemoglobin and Absolute Reticulocyte Count During 48 Weeks of Treatment



ARC, absolute reticulocyte count; D-D, danicopan-danicopan; Hgb, hemoglobin; LSM, least squares mean; P-D, placebo-danicopan.

Figure 1

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