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OP0290

EMAPALUMAB (ANTI-INTERFERON-GAMMA MONOCLONAL ANTIBODY) IN PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME (MAS) COMPLICATING SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

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Background: MAS is a severe complication of rheumatic diseases and occurs most frequently in patients with sJIA. Data from animal models and from observational studies in patients suggest that interferon gamma (IFN γ) is a driver of the hyperinflammation and hypercytokinemia observed in MAS.

Objectives: To assess the pharmacokinetics, efficacy, and safety of intravenous (IV) infusions of emapalumab, a fully human anti-IFN γ monoclonal antibody, in patients with MAS in the context of sJIA.

Methods: This ongoing, pilot, open-label, single-arm study (NCT03311854) includes patients with MAS (2016 ACR/EULAR criteria) on a background of confirmed, or high presumption of, sJIA, and with inadequate response to high-dose IV glucocorticoids. Emapalumab is initiated at 6mg/kg (1 dose) and continued at 3mg/kg twice weekly for a total of 4 weeks, or less upon achievement of complete response (CR). CR is defined as an absence of MAS clinical signs plus white blood cell and platelet counts above the lower limit of normal, LDH, AST and ALT <1.5 x upper limit of normal, fibrinogen >100mg/dL, and ferritin decreased by $\geq 80\%$ or to <2,000 ng/mL.

Results: We report preliminary data from the first 9 patients (median age [range] 11.6 [2.1-25.3] years) enrolled (7 in Europe and 2 in the USA). All patients had failed high-dose methylprednisolone, of which there were prior treatment failures from cyclosporin A (n=4) and from anakinra (n=4). Treatment with emapalumab resulted in rapid IFN γ neutralization, as demonstrated by the decrease in CXCL9 levels (Figure 1), and subsequent deactivation of T cells, as indicated by the decrease in sIL-2R levels. CR was achieved in all patients after a median of 23 (12-56) days. A progressive improvement in all clinical and laboratory parameters of MAS was observed (Table 1 and Figure 2). Glucocorticoids were tapered in all patients (median % tapering -92%; range -45% to -98% at Week 8). Emapalumab infusions were well tolerated by all patients, with no discontinuation. CMV reactivation was reported in 1 patient as a serious event possibly related to emapalumab and resolved with antiviral treatment.

Table 1. Time to response for key clinical and laboratory parameters.

Parameters	Median baseline value (range)	Median days of treatment (range)
D-dimers to <1000 mg/L	12,480 (550-89,552)	15 (1-49)
sIL-2R to <2000 ng/L	4596 (1664-20,954)	21 (6-37)
Ferritin <500 mg/L	29,240 (716-192,584)	21 (9-42)
Physician visual analog scale of MAS activity ≤ 1	9.0 (2-10)	19 (9-56)
All MAS laboratory parameters within range of CR	NA	21 (15-55)
All MAS parameters within range of CR	NA	23 (12-56)
Glucocorticoid tapering at ≤ 1 mg/kg prednisolone equivalent*	NA	42 (16-50)

*Data incomplete for 1 patient

Figure 1. Rapid neutralization of IFN γ . Each line represents an individual patient (n=9).

Figure 2. Ferritin levels and platelet counts over time.

Conclusion: Emapalumab administration led to rapid neutralization of IFN γ and was efficacious in controlling MAS with a favorable safety profile. These results support the pathogenic role of IFN γ in MAS/sJIA and the therapeutic value of IFN γ neutralization in MAS patients who have failed standard of care.

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OP0291

TOFACITINIB FOR THE TREATMENT OF POLYARTICULAR COURSE JUVENILE IDIOPATHIC ARTHRITIS: RESULTS OF A PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED WITHDRAWAL STUDY

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Background: Tofacitinib is an oral JAK inhibitor that is being investigated for JIA.

Objectives: To assess tofacitinib efficacy and safety in JIA patients (pts).

Methods: This was a Phase 3, randomised, double-blind (DB), placebo (PBO)-controlled withdrawal study in pts aged 2–<18 years with polyarticular course JIA (pcJIA), PsA or ERA (NCT02592434). In the 18-week open-label Part 1, pts received weight-based tofacitinib doses (5 mg BID or lower). Pts with $\geq$ JIA ACR30 response at Week (W)18 were randomised 1:1 in the DB Part 2 (W18–44) to continue tofacitinib or switch to PBO. Primary endpoint: disease flare rate by W44. Key secondary endpoints: JIA ACR50/30/70 response rates; change from Part 2 baseline (Δ) in CHAQ-DI at W44. Other efficacy endpoints: time to disease flare in Part 2; JADAS27-CRP in Parts 1 and 2. PsA/ERA pts were excluded from these efficacy analyses. Safety was evaluated in all pts up to W44.

Results: 225 enrolled pts with pcJIA (n=184), PsA (n=20) or ERA (n=21) received tofacitinib in Part 1. At W18, 173/225 (76.9%) pts entered Part 2 (pcJIA n=142, PsA n=15, ERA n=16). In pcJIA pts, disease flare rate in Part 2 was significantly lower with tofacitinib vs PBO by W44 (p=0.0031; Fig 1a). JIA ACR50/30/70 response rates (Fig 1b) and Δ CHAQ-DI (Fig 1c) at W44, and time to disease flare in Part 2 (Fig 2a), were improved with tofacitinib vs PBO. Tofacitinib reduced JADAS27-CRP in Part 1; this effect was sustained in Part 2 (Fig 2b). Overall, safety was similar with tofacitinib or PBO (Table): 77.3% and 74.1% had adverse events (AEs); 1.1% and 2.4% had serious AEs. In Part 1, 2 pts had herpes zoster (non-serious) and 3 pts had serious infections (SIs). In Part 2, SIs occurred in 1 tofacitinib pt and 1 PBO pt. No pts died.

Conclusion: In pcJIA pts, tofacitinib vs PBO resulted in significantly fewer disease flares, and improved time to flare, disease activity and physical functioning. Tofacitinib safety was consistent with that in RA pts.

Fig 1. Efficacy of tofacitinib vs PBO in 142 pts with pcJIA in Part 2: a) occurrence of disease flare^a by W44^b; b) JIA ACR50/30/70 response rates at W44^c; c) Δ CHAQ-DI at W44^d

These data are for pts with pcJIA; pts with PsA or ERA are not included and were analysed separately.
^aFlare is defined as a worsening of $\geq$ 30% in all of the 5 variables of the JIA core set, with $\geq$ 1 variable improving by $\geq$ 30% (Brunner et al. J Rheumatol 2022; 29: 1058-1064).
^bFigure 1a: one-sided hypothesis test was used to compare the occurrence of disease flare by W44 primary endpoint; JIA ACR50/30/70 response rates at W44; Δ CHAQ-DI at W44. Using this gatekeeping approach, statistical significance could be claimed for the next endpoint only if the prior endpoint in the sequence met the requirements for significance (p<0.05).
^cThe JIA ACR50/30/70 response criteria are: 50/30/70% joint swelling improvement by $\geq$ 50%, $\geq$ 30% and $\geq$ 70%, respectively, with $\geq$ 1 variable worsening by $\geq$ 30% (Giancane et al. Arthritis Rheum 1997; 40: 1320-1330).
^dFor systemic JIA, the absence of a flare was related to systemic JIA is also required.
^e5 mg BID or equivalent weight-based lower dose in pts $\leq$ 40 kg.
^fChange from Part 2 baseline (baseline: ACR, American College of Rheumatology; BID, twice daily; CHAQ-DI, Childhood Health Assessment Questionnaire - Disability Index; CI, confidence interval; ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; LI, lower limb; mean, least squares mean; PBO, placebo; pcJIA, polyarticular course JIA; PsA, psoriatic arthritis; pts, patients; SE, standard error; W, week).

Fig 2. Efficacy of tofacitinib vs PBO in pts with pcJIA: a) Kaplan-Meier plot of time to flare^a in Part 2; b) JADAS27-CRP over time in Part 1 and Part 2

These data are for pts with pcJIA; pts with PsA or ERA are not included and were analysed separately.
^aFlare is defined as a worsening of $\geq$ 30% in all of the 5 variables of the JIA core set, with $\geq$ 1 variable improving by $\geq$ 30% (Brunner et al. J Rheumatol 2022; 29: 1058-1064).
^b5 mg BID or equivalent weight-based lower dose in pts $\leq$ 40 kg.
^cConsistent A et al. Pediatr Rheumatol Online J 2016; 14: 23.
^dBID, twice daily; CI, confidence interval; ERA, enthesitis-related arthritis; HRI, hazard ratio; JADAS27-CRP, Juvenile Arthritis Disease Activity Score based on C-reactive protein, JIA, juvenile idiopathic arthritis; PBO, placebo; pcJIA, polyarticular course JIA; PsA, psoriatic arthritis; pts, patients; SE, standard error; W, week.

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Table. Safety in all pts

	Part 1	Part 2	
	Tofacitinib ^a N=225	Tofacitinib ^a N=88	PBO N=85
Pts with events, n (%)			
AEs	153 (68.0)	68 (77.3)	63 (74.1)
SAEs	7 (3.1)	1 (1.1)	2 (2.4)
Permanent discontinuations due to AEs	26 (11.6)	16 (18.2)	29 (34.1)
AEs of special interest			
Death	0	0	0
Gastrointestinal perforation ^b	0	0	0
Hepatic event ^b	3 (1.3)	0	0
Herpes zoster (non-serious and serious)	2 (0.9) ^c	0	0
Interstitial lung disease ^b	0	0	0
Major adverse cardiovascular events ^b	0	0	0
Malignancy (including non-melanoma skin cancer) ^b	0	0	0
Macrophage activation syndrome ^b	0	0	0
Opportunistic infection ^b	0	0	0
SI	3 (1.3)	1 (1.1) ^d	1 (1.2)
Thrombotic event (deep vein thrombosis, pulmonary embolism ^b or arterial thromboembolism)	0	0	0
Tuberculosis ^b	0	0	0

^a5 mg BID or equivalent weight-based lower dose in pts <40 kg

^bAdjudicated events

^cBoth non-serious

^dOne SAE of pilonidal cyst repair was coded to surgical procedures instead of infections, and was inadvertently not identified as an SI. Following adjudication, the SAE did not meet opportunistic infection criteria; it is also included in the table as an SI

AE, adverse event; BID, twice daily; PBO, placebo; pts, patients; SAE, serious AE; SI, serious infection

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OP0292

HIGH EFFICACY OF CANAKINUMAB IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA) ACROSS AGE GROUPS: COMPARISON OF CHILDREN, ADOLESCENTS AND YOUNG ADULTS BASED ON POOLED CLINICAL TRIAL RESULTS

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