A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Test the Efficacy and Safety of Mavrilimumab in Giant Cell Arteritis: Study Design and Methodology

Lara Pupim[1], Sebastian H. Unizony[2*], Maria C. Cid [3*], Lucas M. Pilipski[1], Rohan Gandhi[1], Joe Pirrello[1], Ai Ren[1], Fang Fang[1], John F. Paolini[1]

[1] Kiniksa Pharmaceuticals Corp., Lexington, MA; [2] Vasculitis and Glomerulonephritis Center, Department of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, Massachusetts; [3]Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

BACKGROUND

Giant Cell Arteritis (GCA)

- GCA is an inflammatory disease of medium and large arteries, with infiltration of monocytes, macrophages, and accumulation of giant cells[1,2]
- If untreated, GCA can cause blindness and arterial damage, including aortic aneurysm and arterial stenosis and occlusion[3]
- Need for diverse treatment options in GCA still exists; corticosteroids (CS) remain the mainstay of treatment for GCA despite the recent approval of tocilizumab
  - Relapses are seen in up to 80% of prednisone-treated patients[2]
  - Relapses are seen in up to 40% of tocilizumab-treated patients[4,5]
  - Increased CS exposure and toxicity are a concern[1,6]
- Therapeutics targeting different disease mediators are needed to address the unmet medical need

Granulocyte-macrophage colony stimulating factor (GM-CSF)

- GM-CSF is a pleiotropic inflammatory mediator that may contribute to key aspects of GCA pathogenesis (**Figure 1**)
- Emerging data highlight increased GM-CSF production in GCA vascular lesions (**Figure 2**)
  - Elevated GM-CSF and GM-CSF receptor alpha (GM-CSFRα) expression by inflammatory cells in all 3 layers of the artery (adventitia, media, and intima) in GCA(+) biopsies compared to controls[5]

Mavrilimumab

- Mavrilimumab (KPL-301; Kiniksa Pharmaceuticals, Ltd.), a fully human monoclonal antibody, binds to the GM-CSFRα subunit and blocks GM-CSF activity
  - Previously reported Phase 2b trials in >500 patients with rheumatoid arthritis (RA) met the primary efficacy endpoints and was well-tolerated[6-7]
- We hypothesize that mavrilimumab will maintain disease remission in new-onset and relapsing/refractory GCA patients during CS tapering and thus have initiated a Phase 2 study in those patient populations

Figure 1: Role of GM-CSF in GCA

GM-CSF and GM-CSFRα are overexpressed in GCA lesions

- Both the GM-CSF[5] and the receptor[8] are expressed in the lesion versus normal healthy controls

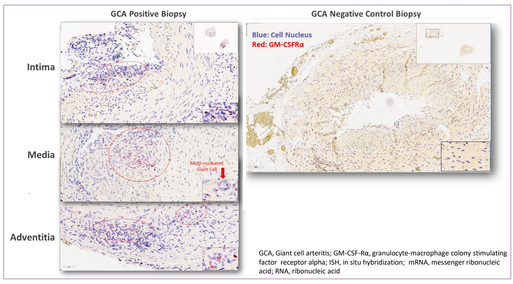
GCA Lesions are heavily comprised of giant cells & non-classical macrophages

- GM-CSF signaling plays a role in generation and maturation of giant cells[9] and non-classical macrophages (CD16+)[10]
- GM-CSF has been shown to induce endothelial cell migration and proliferation[11]
- Inhibition of GM-CSF signaling by mavrilimumab could reduce the number and/or activity of these cells in the vessel wall

Multiple key cytokines driving GCA are downstream of GM-CSF signaling

- Relevant downstream cytokines in GCA are IL-6, IFNγ and IL-17/2[12]
- Inhibiting GM-CSF signaling with mavrilimumab could reduce the relevant pathways involved in both new-onset disease and refractory disease maintenance
- Mavrilimumab reduced both IL-6 and CRP in Phase 2b in RA patients[6-7]

Figure 2: Elevated GM-CSF-Rα mRNA expression via RNAscope (ISH) in GCA(+) biopsies



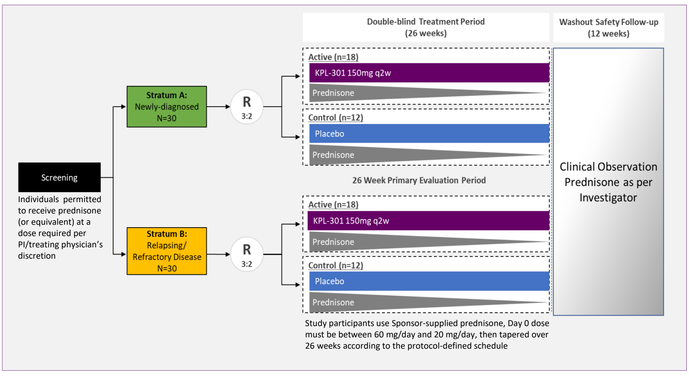
GCA, Giant cell arteritis; GM-CSF-Rα, granulocyte-macrophage colony stimulating factor receptor alpha; ISH, in situ hybridization; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid

METHODS

Study Design

- Phase 2, randomized, double-blind, placebo-controlled, global study to evaluate the efficacy and safety of mavrilimumab (KPL-301) in GCA (**Figure 3**; **Figure 4;** Clinical Trial Identifier: NCT03827018)
  - 60 participants (**Table 1**) with active disease (**Table 2**) randomized 3:2 to mavrilimumab (KPL-301) 150 mg or placebo administered subcutaneously (SC) every two weeks (q2wk) co-administered with a 26-week prednisone taper
  - Participants randomized into two strata:
    - Stratum A: new-onset (n=30)
    - Stratum B: Relapsing/refractory (n=30)

Figure 3: Mavrilimumab (KPL-301) Phase 2 Study Design in Giant Cell Arteritis (GCA)



Study participants use Sponsor-supplied prednisone, Day 0 dose must be between 60 mg/day and 20 mg/day, then tapered over 26 weeks according to the protocol-defined schedule

Endpoints

- Primary efficacy endpoint: Time to GCA flare by Week (Wk) 26 (**Table 3**)
- Secondary efficacy endpoints: Cumulative CS dose, quality-of-life, and pharmacokinetics
- Incidence of adverse events, clinical laboratory parameters, and pulmonary monitoring will be assessed

Adjudication of Primary Efficacy Endpoint

- A Clinical Endpoint Committee (CEC) will evaluate and adjudicate all suspected GCA flares occurring while on treatment during the 26-week treatment period
- Only CEC-confirmed GCA flares prior to Wk 26 will contribute to the primary efficacy endpoint
- Participants not experiencing a CEC-confirmed flare prior to Wk 26 will be censored for the primary endpoint at the Wk 26 visit
- Participants who withdraw or who are lost to follow-up prior to Wk 26 will be censored at the time of their last available visit

Patient Management: Post-Flare

- Participants who experience a flare or who cannot adhere to the protocol-defined CS taper due to a flare will be discontinued from blinded study drug and will receive escape therapy according to local standard of care
- Participants who discontinue study drug will continue on-study until the end of the Washout Safety Follow-up Period, unless they withdraw consent
- Both the participant and investigator will remain blinded to prior treatment assignment during follow-up

Table 1: Key Eligibility Criteria

Inclusion Criteria

- Age ≥ 50 to 85 years
- Diagnosis of new-onset or relapsing GCA (**Table 2**)
- Remission of GCA at or before Day 0 (resolution of symptoms and CRP <1.0 mg/dL or ESR < 20 mm in first hour), such that patient can safely participate in the study (including initiation of prednisone taper)
- Receiving / able to receive prednisone ≤60 mg/day PO at Day 0 for treatment of GCA
- Methotrexate (MTX; oral or parenteral, up to 25 mg/week) permitted in screening if started > 6 weeks prior to Day 0, but tapered to zero by Day 0
- Willing to receive antiplatelet therapy and treatment for prevention of corticosteroid induced osteopenia/ osteoporosis per Investigators discretion
- Willingness to undergo appropriate contraception prevention for both male and female participants

Exclusion Criteria

- Major surgery within 8 weeks prior to Screening or planned major surgery within 12 months after randomization
- Transplanted organs (except corneal transplant performed more than 3 months prior to randomization)
- Major ischemic even unrelated to GCA within 12 weeks of Screening

Table 2: Disease Definitions

New-Onset GCA

- ESR > 30 mm/hr or CRP > 1 mg/dL
- At least one of the following:
  - Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery pain or tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)
  - Unequivocal extracranial symptoms of GCA such as claudication of the extremities
  - Symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness
- At least one of the following:
  - TAB or ultrasound revealing features of GCA
  - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRI, CT/CTA or PET-CT of the aorta or other large vessels

Relapsing/Refractory GCA

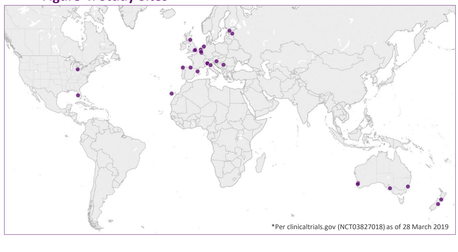
Relapsing:

- Diagnosis of GCA > 6 wks before Day 0 -and-
- Active GCA within 6 wks of Day 0 defined as clinical signs/symptom(s) and Westergren ESR > 30 mm/hr or CRP > 1 mg/dL (as defined above)

Refractory nonremitting:

- Diagnosis of GCA > 6 wks before Day 0 -and-
- Relapse or no remission since diagnosis, i.e. active GCA within 6 wks of Day 0 defined as clinical signs/symptoms and Westergren ESR > 30 mm/hr or CRP > 1 mg/dL (as defined above)

Figure 4: Study Sites*



*Per clinicaltrials.gov (NCT03827018) as of 28 March 2019

Table 3: Definition of On-Study GCA Flare (Primary Efficacy Endpoint)

- Re-increase of CRP from normal to ≥1mg/dL and/or of ESR from <20 mm to ≥30mm
  -and-
- **At least one** of the following signs/symptoms attributed by the Investigator to be new, worsening, or recurrent GCA:

1. Cranial symptoms
- New or recurrent headache or pain or tenderness of the scalp or the temporal artery
- Visual signs/symptoms such as ischemic retinopathy, optic neuropathy, diplopia, amaurosis fugax, etc.
- New or recurrent claudication of the tongue, masseter muscle, or worsening temporal artery signs and symptoms
- Transient ischemic attack or stroke related to GCA in the opinion of the Investigator

2. Extracranial symptoms
- Classic Polymyalgia rheumatica PMR-like symptoms, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness
- New or recurrent claudication in the peripheral circulation

3. Imaging
- New or worsening angiographic abnormalities detected via MRI, CT/CTA, or
- PET-CT of the aorta or other great vessels or via ultrasound of the temporal arteries

- **Supportive findings:** Other symptoms that are, in the opinion of the Investigator, related to worsening GCA, such as sustained daily recurrent fever with a temperature over 38°C for more than 1 week, chronic anemia, or unexplained weight loss

CONCLUSIONS

- Novel CS-sparing treatment options are needed for the treatment of GCA
- Mavrilimumab inhibits GM-CSFRα, which may have upstream and downstream roles in GCA pathogenesis
- This Phase 2 study will assess the efficacy and safety of mavrilimumab (KPL-301) in GCA and is currently enrolling / dosing patients

REFERENCES

1. Dejaco C, et al. Nat Rev Rheumatol. 2017; 13(10):578-592; 2. Roberts J & Clifford A. Ther Adv Chronic Dis 2017; 8(4-5): 69-79; 3. Weyand CM & Goronzy JJ. Nat Rev Rheumatol 2013; 9: 731-740; 4. Strand V, et al Arthritis Res Ther 2019;21(1):64; 5. Khanna D, et al. Arthritis Rheumatol. 2018; 70 (suppl 10); 6. Muratore F, et al. Clin Exp Rheumatol 2013; 31(S78): S86-S92; 7. Kiniksa, Data on File 2019; 8. Burmester GR, et al. Ann Rheum Dis. 2017 Jun;76(6):1020-1030; 9. Weinblatt ME et al. Arthritis Rheumatol. 2018 Jan;70(1):49-59; 10. Weyand CM, et al. Ann Intern Med 1994; 121: 484-491; 11. Yoshihara K, et al. J Vet Med Sci 2004; 66(9): 1065-1069; 12. van Sleen Y, et al. Sci Rep 2017;7(1):6553; 13. Bussolino F, et al. Nature 1989; 337: 471-473; 14. Samson M, et al. Autoimmunity Reviews 2017; 16: 833–844.

DISCLOSURES

*Co-Principal Investigators who contributed equally to this work. Study sponsored by Kiniksa Pharmaceuticals, Ltd. Presenting author, L. Pupim, is an employee of Kiniksa Pharmaceuticals Corp.