SUPPLEMENTARY APPENDIX

Canakinumab Treatment for Patients With Active Recurrent or Chronic TNF-Receptor Associated Periodic Syndrome (TRAPS): An Open-Label, Phase 2 Study

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METHODS

Patients

Male or female patients aged 4 years and older were eligible if they had a clinical diagnosis of active recurrent or chronic TRAPS with a confirmed mutation of the *TNFRSF1A* gene. For a diagnosis of recurrent TRAPS, patients must have experienced >6 episodes per year prior to receiving an effective biologic, with each episode lasting ≥8 days. Eligible patients exhibited clinical signs and symptoms of active TRAPS, as evidenced by a physician's global assessment (PGA) of TRAPS activity score ≥2 (described below) and an elevated C-reactive protein (CRP) >10 mg/L and/or serum amyloid A protein (SAA) >10 mg/L at time of first canakinumab treatment. Patients previously treated with anakinra must have demonstrated a partial or complete clinical response with an associated decrease in CRP and SAA. All patients, or for children, their parents/legal guardians, provided written informed consent.

Exclusion criteria were: history of immunocompromised status including a positive HIV test; positive tuberculosis screen; live vaccination within 3 months prior to the start of the trial, during the trial, and 3 months following the last dose; history of recurrent and/or active bacterial, fungal, or viral infection; or malignancy other than localized basal cell carcinoma of the skin within the past 5 years. Pregnant or nursing women were excluded; those of child-bearing potential used effective contraception during the study. The following medications were prohibited prior to

the baseline visit: corticosteroids >0.2 mg/kg/day (or >15 mg/day for children >60 kg) within 1 week, anakinra within 24 hours, rilonacept within 1 week, tocilizumab within 3 weeks, etanercept within 4 weeks, rituximab within 26 weeks, conventional disease-modifying antirheumatic drugs within 4–12 weeks, any investigational biologic within 8 weeks, or any other investigational agent within 30 days or 5 half-lives whichever was longer. Prior treatment with canakinumab within 3 months of the baseline visit was not allowed. Patients with chronic TRAPS who required corticosteroid at the time of enrollment must have been on a stable dose of corticosteroid (≤0.2 mg/kg/d prednisone or equivalent) for at least 1 week prior to baseline and were not to change the dose unless instructed by the investigator.

Pharmacokinetic Assessments

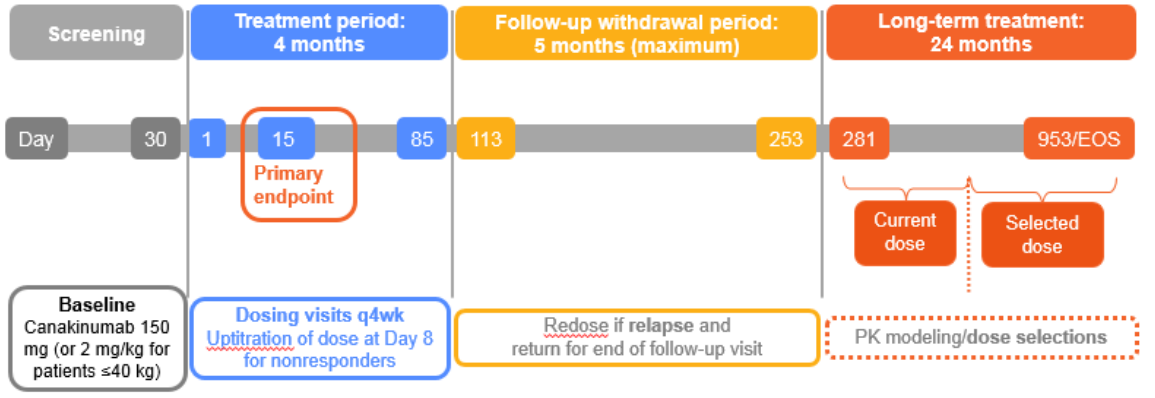
Blood samples for assessment of canakinumab concentrations were taken by direct venipuncture (2 mL from adults and 1 mL from patients <16 years of age) at Days 1, 3, 8, 15, 29, 57, 85, and 113. Canakinumab concentrations in serum were measured using a validated competitive enzymatic linked immunosorbent assay (ELISA) with a lower limit of quantification at 100 ng/mL.

Safety Assessments

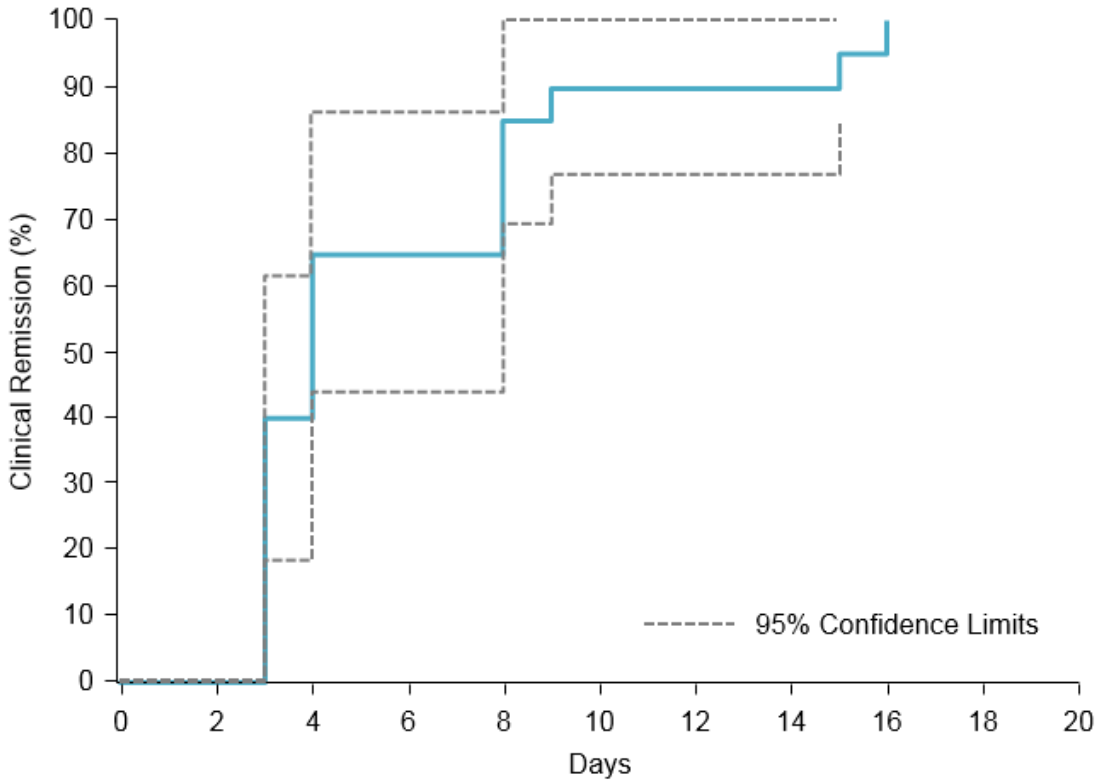
Adverse events and vital signs were monitored at all visits. Hematology, blood chemistry, and urinalysis were measured at all visits at which study treatment was administered. A physical examination was required at visits when acute TRAPS attacks were suspected. Blood samples for detection of anti-canakinumab

antibodies were collected on Days 1, 29, 113, and every 6 months during the long-term treatment period.

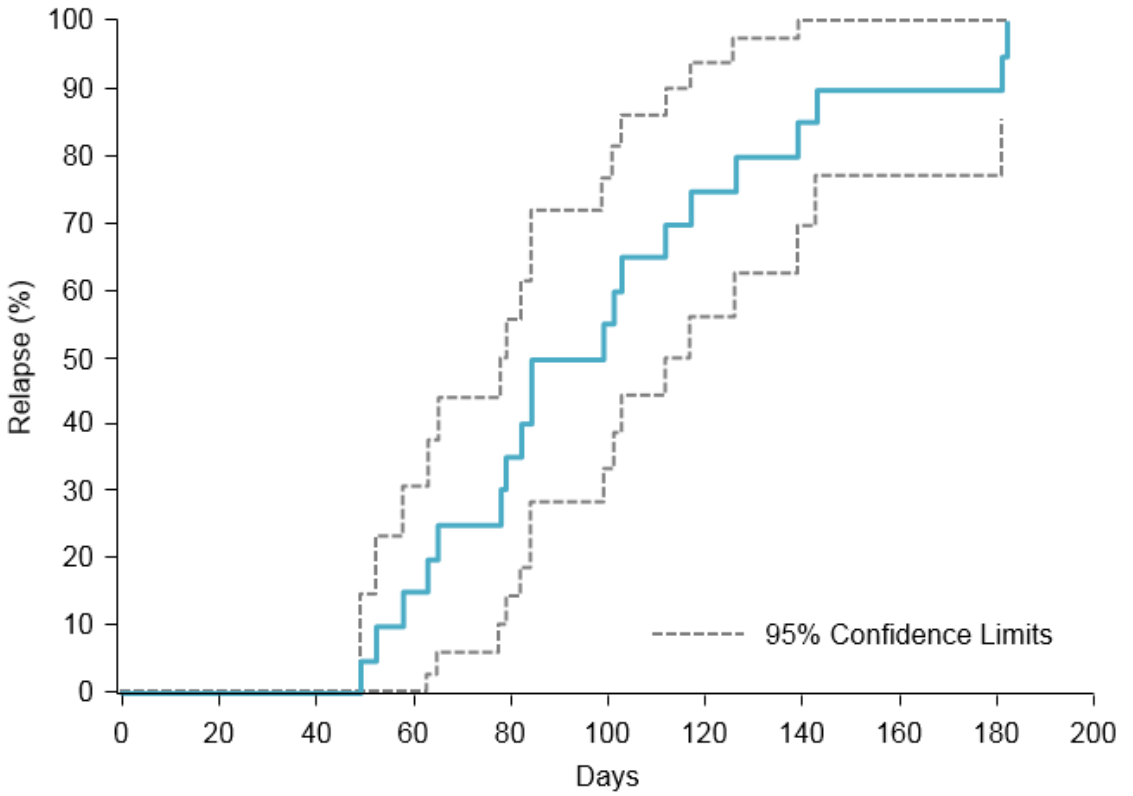
Supplementary Figure 1. Study design.



Supplementary Figure 2. Kaplan-Meier plot of time to investigator assessed clinical remission of TRAPS activity (PGA score ≤1).



Supplementary Figure 3. Kaplan-Meier plot of time to relapse after last dose of canakinumab in 4-month treatment period. Relapse = PGA ≥2 AND represents an increase ≥1 point from Day 15 AND CRP and/or SAA ≥30 mg/L without other explanation for cause AND represents a 30% increase from Day 15.



Supplementary Table 1. Investigator's Assessment of the Severity of Key Signs and Symptoms of TRAPS

Sign/Symptom	N	Absent	Minimal	Mild	Moderate	Severe
Skin disease						
Baseline	20	9 (45)	4 (20)	4 (20)	3 (15)	0
Day 15	20	19 (95)	1 (5)	0	0	0
End of follow-up	20	19 (95)	0	0	1 (5)	0
End of study	18	18 (100)	0	0	0	0
Extremity musculoskeletal pain						
Baseline	20	2 (10)	0	13 (65)	4 (20)	1 (5)
Day 15	20	19 (95)	0	1 (5)	0	0
End of follow-up	20	17 (85)	2 (10)	1 (5)	0	0
End of study	18	17 (94)	0	1 (6)	0	0
Abdominal pain						
Baseline	20	9 (45)	2 (10)	8 (40)	1 (5)	0
Day 15	20	18 (90)	2 (10)	0	0	0
End of follow-up	20	15 (75)	4 (20)	1 (5)	0	0
End of study	18	17 (94)	1 (6)	0	0	0
Eye manifestations						
Baseline	20	5 (25)	7 (35)	4 (20)	4 (20)	0
Day 15	20	19 (95)	0	1 (5)	0	0
End of follow-up	20	19 (95)	1 (5)	0	0	0
End of study	18	16 (89)	2 (11)	0	0	0

Supplementary Table 2. Changes in Median CRP and SAA Levels During Follow-up and Long-Term Treatment

	CRP		SAA	
	N	Median (range), mg/L*	N	Median (range), mg/L*
Withdrawl/follow-up (f/u) period				
Day 113	20	4.8 (0.6–186)	20	2.2 (0.8–259)
Day 141	19	8.6 (0.8–310)	19	4.6 (1.0–1030)
Day 169	13	10 (2.0–583)	13	5.2 (0.8–952)
Day 197	11	70 (2.0–498)	11	68.9 (1.3–1700)
Day 225	4	14 (2.0–131)	4	40 (4.0–699)
End of f/u	20	8.4 (0.6–186)	20	4.8 (0.8–609)
Long-term treatment period				
Day 281	20	6.8 (2.0–87)	20	5.2 (1.2–96)
Day 309	20	5.9 (2.0–246)	20	3.9 (0.8–795)
Day 337	20	5.8 (2.0–140)	20	3.5 (0.8–762)
Day 365	19	5.0 (2.0–23)	19	2.5 (0.8–25)
Day 393	17	5.8 (2.0–14)	17	3.4 (0.8–19)
Day 421	18	8.0 (2.0–105)	18	4.4 (0.8–302)
Day 449	18	4.5 (1.8–16)	17	2.5 (0.8–20)
Day 477	19	5.8 (1.2–56)	19	4.0 (0.8–120)
Day 505	18	5.9 (1.8-31)	18	4.9 (0.8–73)
Day 533	19	3.8 (1.2–14)	19	3.4 (0.8–12.2)
Day 561	19	3.8 (1.1–18)	19	3.6 (1.0–32)
Day 589	12	3.8 (1.6–10)	12	2.2 (1.1–7.5)
Day 617	17	3.8 (0.9–38)	17	3.6 (0.8–17)
Day 673	18	5.9 (1.2–410)	18	3.5 (0.9–1510)
Day 729	18	8.4 (1.2–264)	18	4.8 (0.8–807)
Day 785	17	8.0 (1.2–290)	18	4.0 (0.8–864)
Day 841	18	9.2 (2.0–214)	18	4.8 (0.8–556)
Day 897	18	7.0 (1.8–388)	18	6.1 (0.8–895)
End of study	16	4.0 (1.8–112)	18	4.9 (1.2–221)

*Normal CRP and SAA level defined as ≤0−10 mg/L.

Supplementary Table 3. Trough (pre-dose) concentrations at week 16 (day 113, 4 weeks post last dose) from the 17 patients receiving 150-mg dose q4wk

	Canakinumab Concentration (µg/mL)
Mean	14.7
SD	5.23
CV%	35.3

CV, coefficient of variation; SD, standard deviation.

Supplementary Table 4. Description of Serious Adverse Events (SAE)

Patient (age, gender)	SAE (Day of diagnosis)	Relevant history	Description of SAE	Drug related	Canakinumab continued	Treatment of SAE (outcome)
17F	Upper respiratory tract infection (Day 3)	Fever presented 5 days before first dose of study drug	Culture positive for *S. pneumoniae* and *H. influenzae* on Day 1	No	Yes	Augmentin, ceftriaxone (resolved on Day 11)
41M	Pericarditis (Day 245)	Chest pain, gout	Fever, left-sided chest pain, and joint pain on Day 242; EEG showed normal sinus rhythm with ST elevation, and echocardiography showed small global pericardial effusion	No	Yes	Ibuprofen (resolved by Day 267)
	Pregnancy-related condition		Wife became pregnant after patient had received study drug for approximately 1 year	No	Yes	Delivered normal female neonate by caesarean section at week 40 of pregnancy
77F	Foot deformity (approx. Day 725)	Cutaneous vasculitis, retroperitoneal fibrosis, and fibrosis	Osteoporosis diagnosed on Day 147 and treated with alendronic acid, calcium, and vitamin D; developed hammer toes on right foot	No	Yes	Underwent repair of contracted toes; osteoporosis ongoing at day 996
49M	Hypertriglyceridemia (Day 351)	Fungal skin infection	Triglyceride levels increased from 1.16	No	Yes	Omega-3 acid ethyl ester; serum

			mmol/L at baseline to 17.6 mmol/L on Day 351			triglycerides declined to 4.14 mmol/L by Day 437; event considered ongoing at last visit
54M	Abdominal pain (Day 665)	Duodenal ulcer, hypertension, amyloidosis, anxiety, chronic renal failure, chronic obstructive pulmonary disease	CT scan showed bowel dilation and air fluid levels suggesting subocclusion resulting in hospitalization	No	Yes	Fluid replacement, prednisone, and analgesics; resolved on Day 669
	Hyperkalemia (Day 1069)		Moderate hyperkalemia with metabolic acidosis resulting in hospitalization	No	Yes	Hemodialysis, allopurinol, and omega-3 triglycerides; resolved on Day 1070
37M	Abdominal pain with intestinal obstruction (Days 489 and 694); vomiting and diarrhea (Day 694)	Arthralgia, asthma, osteoporosis, headache	Abdominal X-ray showed air fluid levels with severe intestinal obstruction resulting in hospitalization	No	Yes	Fluid replacement for episode 1; paracetamol, hyoscine butylbromide, and prednisone also used for episode 2; resolved on Days 492 and 698, respectively
	Meniscus injury (Day 770)		Knee trauma while playing football; MRI showed lesion at meniscus	No	Yes	Surgery; resolved on Day 800

39M	TRAPS flare (Day 158)	None	Severe TRAPS symptoms resulting in hospitalization	No	Yes	Electrolyte replacement, omeprazole, paracetamol, sodium chloride, methylprednisolone, and tramadol; resolved on Day 161