patients (75%), presented by polyarthritis in 7/9 (77.8%), and oligoarthritis in 2/9 (22.2%). Two patients (16.7%) had cataract, one (8.3%) had bilateral uveitis, and one (8.3%) had optic atrophy. Sensorineural hearing loss was observed only in 3/12 (25%). Hydrocephalus was detected in 3/12 (25%). Delayed mental and psycho-speech development was observed in 6/12 (50%) patients. In 3/12 (25%), the development of MAS was recorded.

All patients had nucleotide variants in *NLRP3* gene. According to NGS results and clinical characteristics, 8/12 (66.7%) patients were diagnosed with MWS and 4/12 (33.3%) had CINCA/NOMID syndrome. In children with MWS, heterozygous variant c.2113C>A in *NLRP3* gene was the most common (5/8 (62.5%) patients). One of 8 (12.5%) patients with novel heterozygous variant c.2861C>T was detected; also one child (12.5%) have heterozygous variant c.598G>A and one (12.5%) – heterozygous variant c.943A>G. Four patients with CINCA/NOMID syndrome also had heterozygous variants in *NLRP3* gene: c.598G>A, c.2173C>A, c.1991T>C and c.796C>T.

Prior to genetic testing, 12/12 (100%) patients received NSAIDs; 6/12 (50%) were treated with oral glucocorticoids (GC), 3/12 (25%) – with intravenous GC, 2/12 (22.2%) – with methotrexate. Biologics treatment included: 5/12 (41.7%) CAN, 4/12 (33.3%) tocilizumab, and 1/12 (8.3%) etanercept. After genetic testing, 7/12 (58.3%) patients were successfully switched to CAN. Only 1/12 (8.3%) child with MWS developed secondary inefficiency on CAN treatment.

Conclusion: Systemic manifestations were detected in 91.6% of children, while active arthritis was observed in 75% of patients, which can cause difficulties in the diagnosis and treatment of CAPS. The effectiveness of canakinumab therapy was estimated in 91.6% of patients. The most frequent variant of the *NLRP3* gene in MWS was c.2113C>A. In patients with CINCA/NOMID syndrome all nucleotide variants were individual.

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FRI0465 TOFACITINIB POPULATION PHARMACOKINETICS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS: A POOLED ANALYSIS OF DATA FROM THREE CLINICAL STUDIES

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Background: Tofacitinib is an oral JAK inhibitor that is being investigated for juvenile idiopathic arthritis (JIA).

Objectives: To describe tofacitinib pharmacokinetics (PK) in patients with JIA, identify potential covariates accounting for variability in exposure, assess the formulation effect of oral solution vs tablet and propose a simplified dosing regimen.

Methods: This was a pooled analysis of data from 3 tofacitinib clinical studies in patients with JIA aged 2–<18 years: a Phase 1, open-label (OL), non-randomised study (NCT01513902); a Phase 3, randomised, double-blind, placebo-controlled, withdrawal study (NCT02592434); and an OL long-term extension study (NCT01500551). Tofacitinib was dosed at 5 mg twice daily (BID) in patients ≥40 kg or at body weight (BW)-based lower doses BID in patients <40 kg, to achieve average concentrations (C_{avg}) comparable with those in patients receiving 5 mg BID. A sparse PK sampling scheme was applied, and the plasma samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (lower limit of quantification = 0.100 ng/mL). A nonlinear mixed-effects modelling approach was used for the population PK model, and population parameter variability was assumed to be log-normally distributed. Covariates relating to patient demographics, disease characteristics, concomitant medications and formulation (oral solution vs tablet) were selected using a stepwise covariate modelling approach, and parameter-covariate relationships were evaluated using stepwise forward-inclusion ($p < 0.05$) backward-deletion ($p < 0.001$) procedures. The effect of time-varying BW on oral clearance (CL/F) and apparent volume of distribution (V/F) was characterised using an allometric model. Final model quality was assessed by Visual Predictive Checks (VPCs).

Results: Of 246 patients in the analysis, 74.0% were female; 87.8% were white, 2% were black, 10.2% were 'other' races and no patients were Asian. Median (range)

BW was 46.3 (11.1–121.8) kg. Initially, 100 patients received oral solution and 146 patients received tablets; 11 patients switched formulations during the studies. A one compartment disposition model with first-order absorption and a lag time sufficiently described the data. Final estimates for CL/F, V/F and the first-order absorption rate constant (k_a) for tablets were 26.1 L/hr, 89.2 L and 2.78 hr⁻¹, respectively. The only statistically significant covariate was a formulation effect on k_a . All parameters were estimated adequately. Estimated allometric exponents were 0.310 for CL/F and 0.537 for V/F. Absorption was described with an estimated lag time of 0.186 hr, and the oral solution had a 1.64-fold faster absorption rate vs the tablet. VPCs sufficiently described the observed data over time, across BWs and ages. Given the PK characterisation and variability in patients with JIA, a simplified dosing scheme was proposed, targeting C_{avg} values equivalent to those in patients receiving 5 mg BID: 3.2 mg BID solution in patients 10–<20 kg; 4 mg BID solution in patients 20–<40 kg; and 5 mg BID tablet or solution in patients ≥40 kg.

Conclusion: Tofacitinib population PK in patients with JIA were adequately described by a one compartment model parameterised in terms of CL/F, V/F and first-order absorption with a lag time. Drug absorption from the oral solution was faster than from the tablet. Tofacitinib does not require dose modification or restrictions for any covariates, except BW, to account for differences in C_{avg} . Based on the results of this analysis, a simplified BW-based dosing regimen was proposed.

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NO DISEASE PROGRESSION AFTER 36 MONTHS FOLLOW UP IN THE JUVENILE SYSTEMIC SCLERODERMA INCEPTION COHORT

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Background: Juvenile systemic sclerosis (JSSc) is an orphan disease with a prevalence of 3 in 1 000 000 children. There is rare longitudinal prospective follow up data of patients with JSSc. In the international juvenile systemic sclerosis cohort (JSScC) patients with a standardized assessment prospectively.

Objectives: To assess the changes regarding organ involvement pattern and patients related outcomes after 36 months follow up in the JSScC.

Methods: Patients diagnosed according to the ACR 2013 criteria for systemic sclerosis were included, if they developed the first non-Raynaud symptom before the age of 16 and were under the age of 18 at the time of inclusion. Patients were followed prospectively every 6 months with a standardized assessment.

Results: 39 patients in the JSScC had 36 months follow up. 80% had a diffuse subtype. 95% of the patients were Caucasian origin. 31 of the patients were female (80%). Mean disease duration at time of inclusion was 3.5 years. Mean age onset of Raynaud's was 8.8 years and mean age of onset at the first non-Raynaud's was 9.5 years. Around 30% of the patients were anti-Scl70 positive and none of them anti-centromere positive. The MRSS dropped from the time point of the inclusion into the cohort from 13.9 to 11.8 after 36 months. Pattern of organ involvement did not show any significant change, beside the increase of the nailfold capillary changes from 49% to 73% ($p = 0.037$). No renal crisis occurred. No mortality was observed.

They were positive significant changes in the patient related outcomes. The physician global disease activity decreased from 40.0 to 22.1 assessed on a VAS scale of 0 to 100 ($p < 0.001$).

Patients global disease activity decreased from 43.3 to 20.4 and patients global disease damage from 45.0 to 21.7 both assessed on a VAS scale of 0 to 100 ($p < 0.001$).

Conclusion: After 36 months follow up, we could observe a significant improvement of patient related outcomes and only one significant change in organ pattern involvement. In a mostly diffuse subset patient population this is a very promising result regarding outcome.

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