Conclusion: Response criteria are more discriminative than status criteria. ASDAS-CII and ASDAS-MI showed the best discrimination between treatment/placebo arms. Using the ASDAS-CII as primary outcome in future RCTs can reduce the number of patients needed to be included while keeping the same statistical power.

Table. Discriminative performances of response and status criteria in RCTs of biological and targeted synthetic DMARDs in axial spondyloarthritis

Minimum set of outcomes	Set 1: ASAS20,- 40,-PR, BASDAI50	Set 2: ASAS20,-40,- 5/6,-PR BASDAI50	Set 3: ASAS20,-40,- 5/6,-PR BASDAI50 ASDAS-CII, -MI, -ID	Set 4: All
N° of RCTs Total=16*	16	11	8	3
Descending X ² order	X ²	X ²	X ²	X ²
1	ASAS40 339	ASAS5/6 334	ASDAS-CII 309	ASDAS-CII 124
2	ASAS20 316	ASAS40 266	ASDAS-MI 253	ASDAS-MI 65
3	BASDAI50 297	ASAS20 254	ASAS40 169	ASAS5/6 48
4	ASAS-PR 146	BASDAI50 248	BASDAI50 163	BASDAI50 39
5	-	ASAS-PR 119	ASDAS-ID 117	ASAS40 34
6	-	-	ASAS20 98	ASDAS-LDA 27
7	-	-	ASAS-PR 80	ASAS-PR 22
8	-	-	-	ASAS20 21
9	-	-	-	ASDAS-ID 7

Legend. *total of 16 RCTs analysed, with different sets of RCTs within the 16 analysed based on the availability of response criteria; X²=Chi-square; RCTs=randomized controlled trials; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; ASAS= Assessment in SpondyloArthritis International Society; PR= partial remission; CII= clinically important improvement; MI= major improvement; LDA= low disease activity; ID= inactive disease

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New perspectives on therapeutic immune tolerance.

OP0316 EMERGING BEST-IN-CLASS IL-2 VARIANT HIGHLIGHTS TREG-DIRECTED THERAPY FOR AUTOIMMUNE DISEASE

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Background: Impairment or deficiency of regulatory T cells (Treg) is associated with chronic inflammation and autoimmune diseases. Interleukin 2 (IL-2) is a cytokine indispensable for Treg expansion and immunosuppressive function. However, expansion of cytotoxic effector T (Teff) and NK cells and the associated vascular leakage side effect limit the use of IL-2 in autoimmune diseases [1].

Objectives: Cugene developed a long-acting IL-2 variant with high Treg specificity and low toxicity to restore immune homeostasis and self-tolerance, and potentially cure autoimmune and inflammatory diseases.

Methods: IL-2 variants were generated based on the quaternary structure of IL-2 and IL-2Rαβ (alpha, beta, gamma) complex. Biological activity was determined by examining differential signaling activity in induction of STAT5 phosphorylation in defined lymphocyte populations of human PBMC using flow cytometry. Binding activity was evaluated by ELISA. Pharmacokinetics, pharmacodynamics, safety and tolerability were assessed in mice and cynomolgus monkeys. Treg suppressive function was determined *in vivo/ex vivo*, and anti-inflammatory and anti-antibody production efficacy were determined in delayed-type hypersensitivity (DTH) and T-cell-dependent antibody response (TDAR) models.

Results: Structure-based rational design and activity-guided fine-tuning generated an optimized IL-2 variant, CUG252. It demonstrated a strong and near wild-type IL-2 ability to stimulate STAT5 phosphorylation in IL-2Rαβ dominant Treg cells but abolished activities in IL-2Rβγ dominant effector CD4, CD8 and NK cells. This was a result of biased binding activity to IL-2Rα while dramatically

attenuated binding to IL-2Rβγ complex. In mice and monkeys, administration of CUG252 resulted in dose-dependent increases in Treg proliferation and expansion by more than 10- and 30-fold, respectively, with largely abolished activities in CD4+ T conventional, cytotoxic CD8+ Teff and NK cells. The ratio of Treg/Teff cells achieved was as high as 0.4 in mice and 1.2 in monkeys. Both CD4+ and CD8+ Tregs were expanded with preferential increases in memory over naïve subsets. A substantial increase in Treg-suppressive capacity over T effector cells was corroborated by enhanced expression of functional and inhibitory markers, including CD25, Foxp3, PD-1, CTLA-4, Tim3 and ICOS. In DTH and TDAR models, CUG252 strongly inhibited antigen-driven inflammation, B cell maturation, and antibody production. The sustained PK/PD profile supports monthly dosing or better in humans. CUG252 was well-tolerated and no changes in body weight, body temperature, clinical pathology or signs of vascular leakage were observed. Moreover, CUG252 demonstrated superior manufacturability.

Conclusion: CUG252 demonstrates an emerging best-in-class profile among IL-2 variants. It displayed exquisite Treg-selectivity while retaining potency comparable to wild-type IL-2. It showed strong anti-inflammatory and anti-antibody production efficacy with significantly improved therapeutic index and manufacturability. Its favorable drug-like property and robust preclinical efficacy warrant further evaluation in patients with a variety of inflammation and autoimmune diseases.

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Pathological calcification in rheumatic diseases

OP0317 ACCURACY OF THE OMERACT DEFINITIONS FOR IDENTIFICATION OF CALCIUM PYROPHOSPHATE CRYSTALS WITH ULTRASOUND: FINAL RESULTS OF THE OMERACT US IN CPPD SUB-TASK FORCE STUDY

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Background: The OMERACT Ultrasound (US) in calcium pyrophosphate deposition disease (CPPD) sub-task force has been working on the use of US in CPPD since 2014 first creating definitions for CPPD identification and then assessing the reliability[1].

Objectives: Objective of this study is to assess the diagnostic accuracy (truth) of US in CPPD.

Methods: Consecutive patients waiting to undergo knee replacement surgery due to osteoarthritis were enrolled in 12 centres from 6 countries. Each patient underwent US examination of the knee, focusing on the menisci and the hyaline cartilage, the day prior to surgery, scoring each site for presence/absence of CPP as defined previously[1]. After surgery, the menisci and the condyles were retrieved and examined microscopically. Six samples were collected, both from the surface and from the internal part of menisci and cartilage trying to cover a large part of it. All slides were observed under transmitted light microscopy and by compensated polarised microscopy. A dichotomous score was given for the presence/absence of CPP. US and microscopic analysis were performed by different operators, blind to each other's findings.