



ZonMw



Sanquin
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revalidatie / reumatologie



ADalimumab DOse reduction aiming LOW serum concentration to control disease activity, in Rheumatoid Arthritis (ADDORA-LOW)

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Disclosures

- No conflicts of interest.

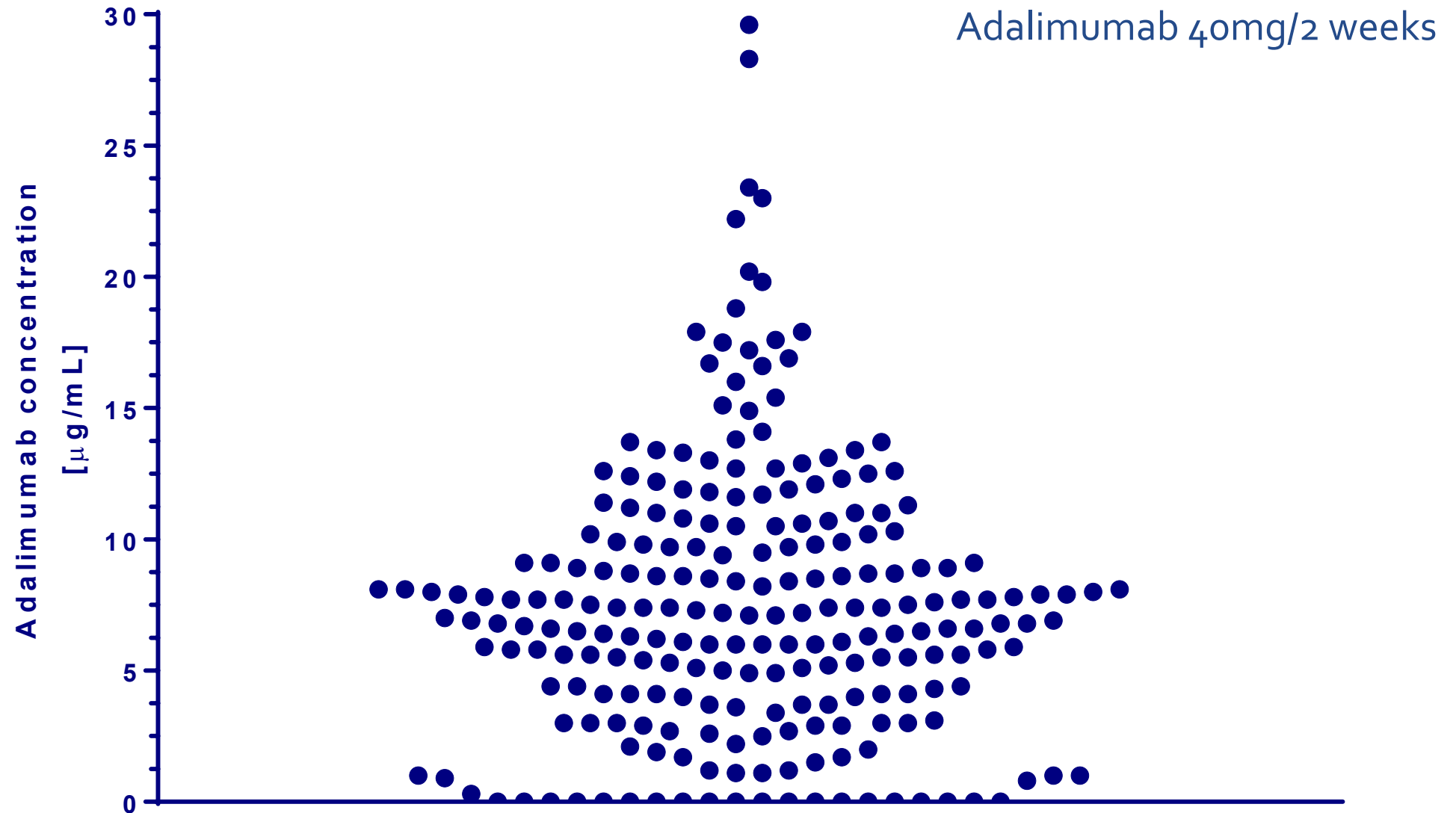
Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

 FREE

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11. After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs 1b (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.



Therapeutic Drug Monitoring (TDM)

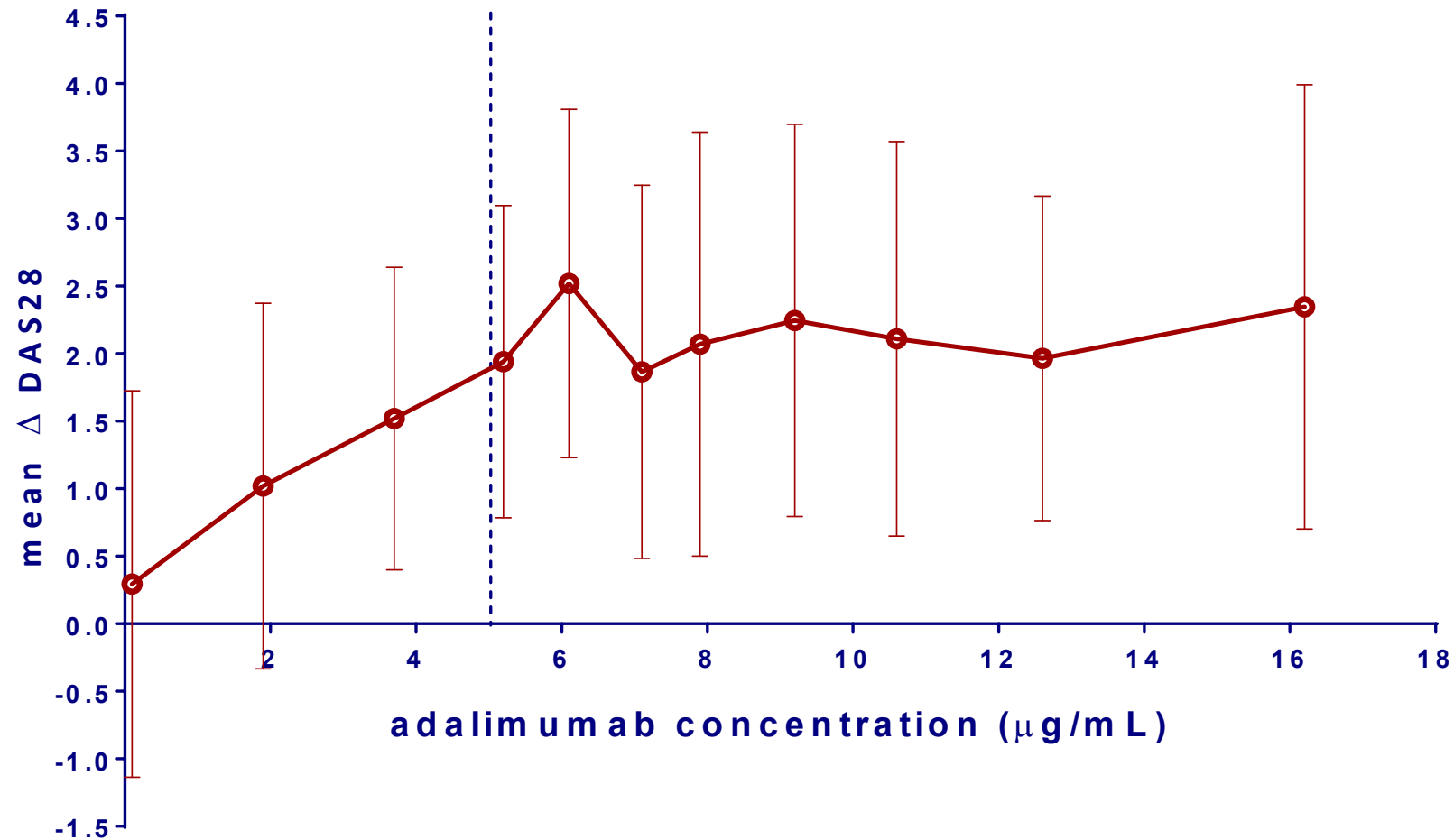


ONE SIZE
FITS ALL



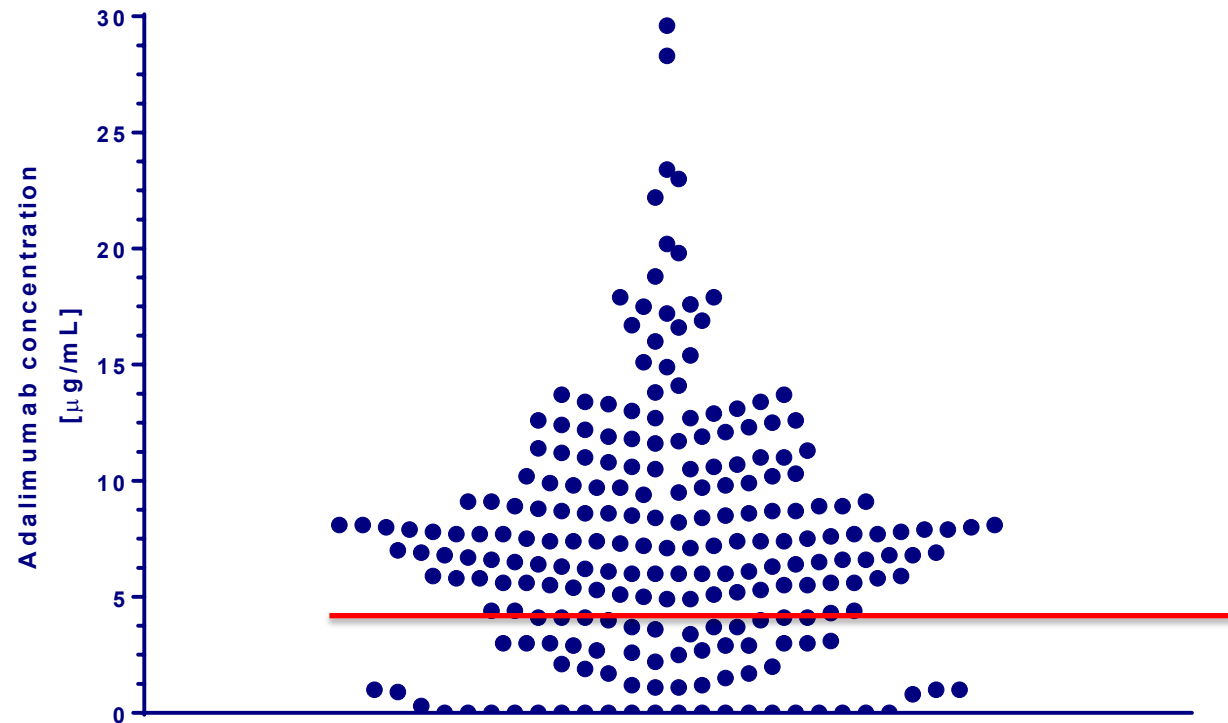
MADE TO
MEASURE

Concentration-effect curve adalimumab ZonMw



Benefits of TDM

- Identify over- & underexposed patients
- Small adjustment of dosing in patients with low serum concentrations
 - Compelling evidence that stopping DMARDs will ultimately lead to flares in most patients(1-3)



1. Emery P, et al., ARD 2015

2. Aguilar-Lozano L, et al., J Rheumatology 2013

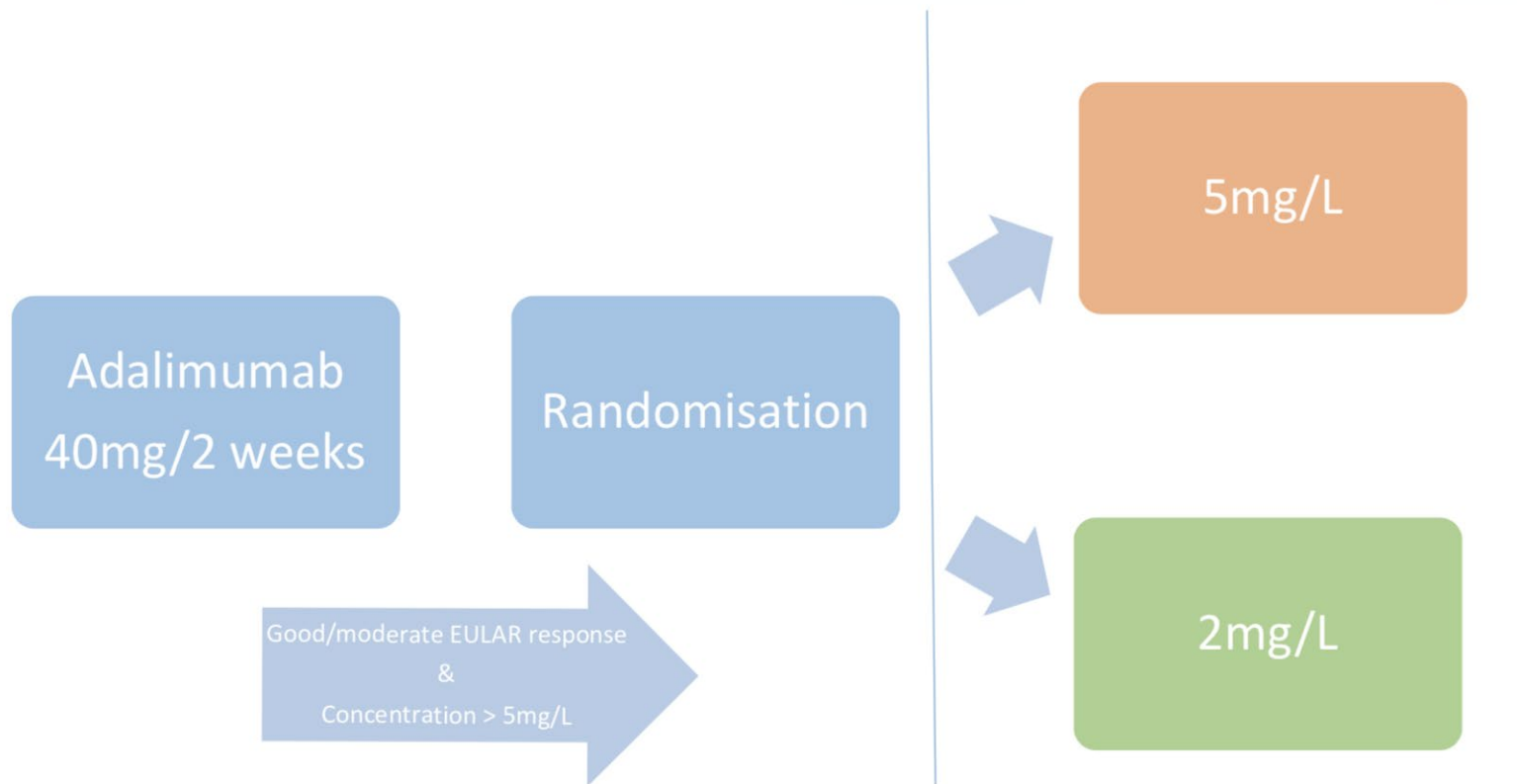
3. Smolen JS, et al., Lancet 2013

Hypothesis

1. Tapering to a **target drug level of 5 mg/L** maintains **disease control** while it **reduces** overall **drug use**
1. Tapering to a lower **target drug level of 2 mg/L** is **non-inferior to** the higher 5mg/L target in controlling **disease activity and en ensuring safety**, while it is **superior in reducing** overall **drug use**.

Study design

Single blind, non-inferiority, randomised clinical trial



Endpoint: Difference in mean time weighted DAS28-CRP over 24 weeks

Follow-up: 24 weeks

Sample size: 62

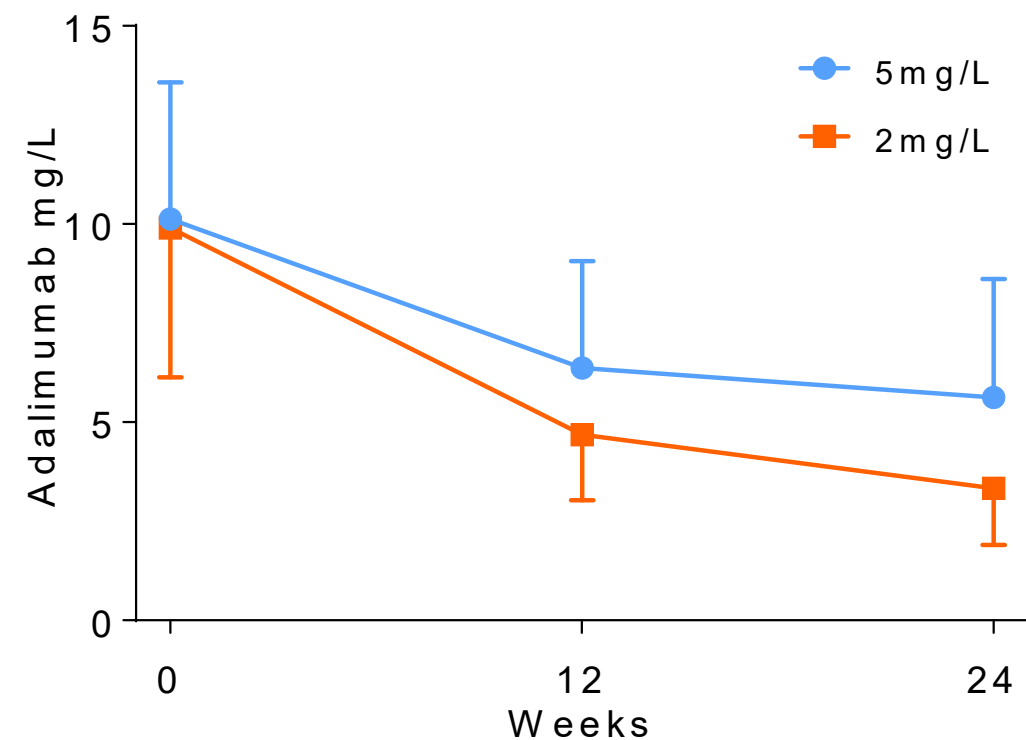
Intervention: dose reduction aiming a drug level of respectively 2 mg/L or 5 mg/L

- PK-PD model of David Ternant (2015)
 - 1-compartment model with linear absorption and elimination
- Monte Carlo modeling to assess the best interval extension

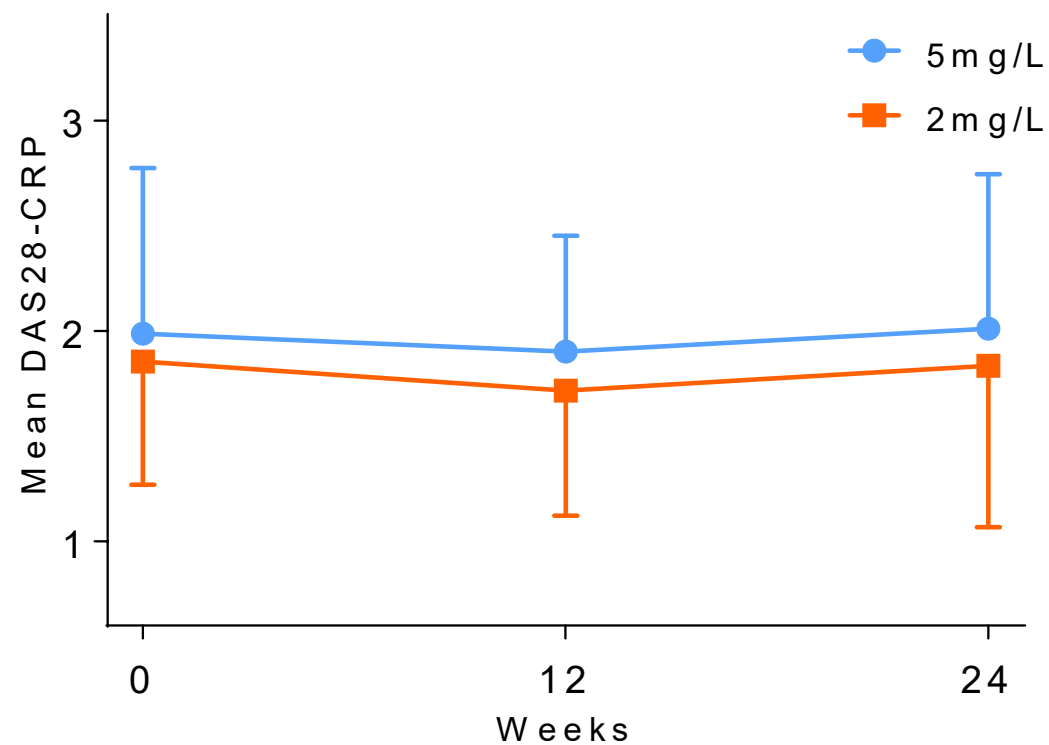
Table 1. Dosing interval algorithm

Drug level at baseline	<3 mg/L	≥3 <5 mg/L	≥5 <6 mg/L	≥6 <8 mg/L	≥8<10 mg/L	≥10 mg/L
Dosing interval (weeks)						
Target [5 mg/L]	2	2	3	3	4	4
Target [2 mg/L]	2	4	4	5	5	6

Adalimumab concentration vs. Disease activity



		N	Mean	SD
ADL.0	5m/L	31	10,12	3,45
	2mg/L	31	9,90	3,77
ADL.12	5m/L	26	6,37	2,70
	2mg/L	24	4,68	1,66
ADL.24	5m/L	26	5,63	2,99
	2mg/L	26	3,33	1,43



DAS28-CRP		N	Mean	SD
Week 0	5m/L	31	1,99	0,79
	2mg/L	29	1,85	0,59
Week 12	5m/L	23	1,90	0,55
	2mg/L	28	1,71	0,59
Week 24	5m/L	27	2,01	0,74
	2mg/L	29	1,83	0,77

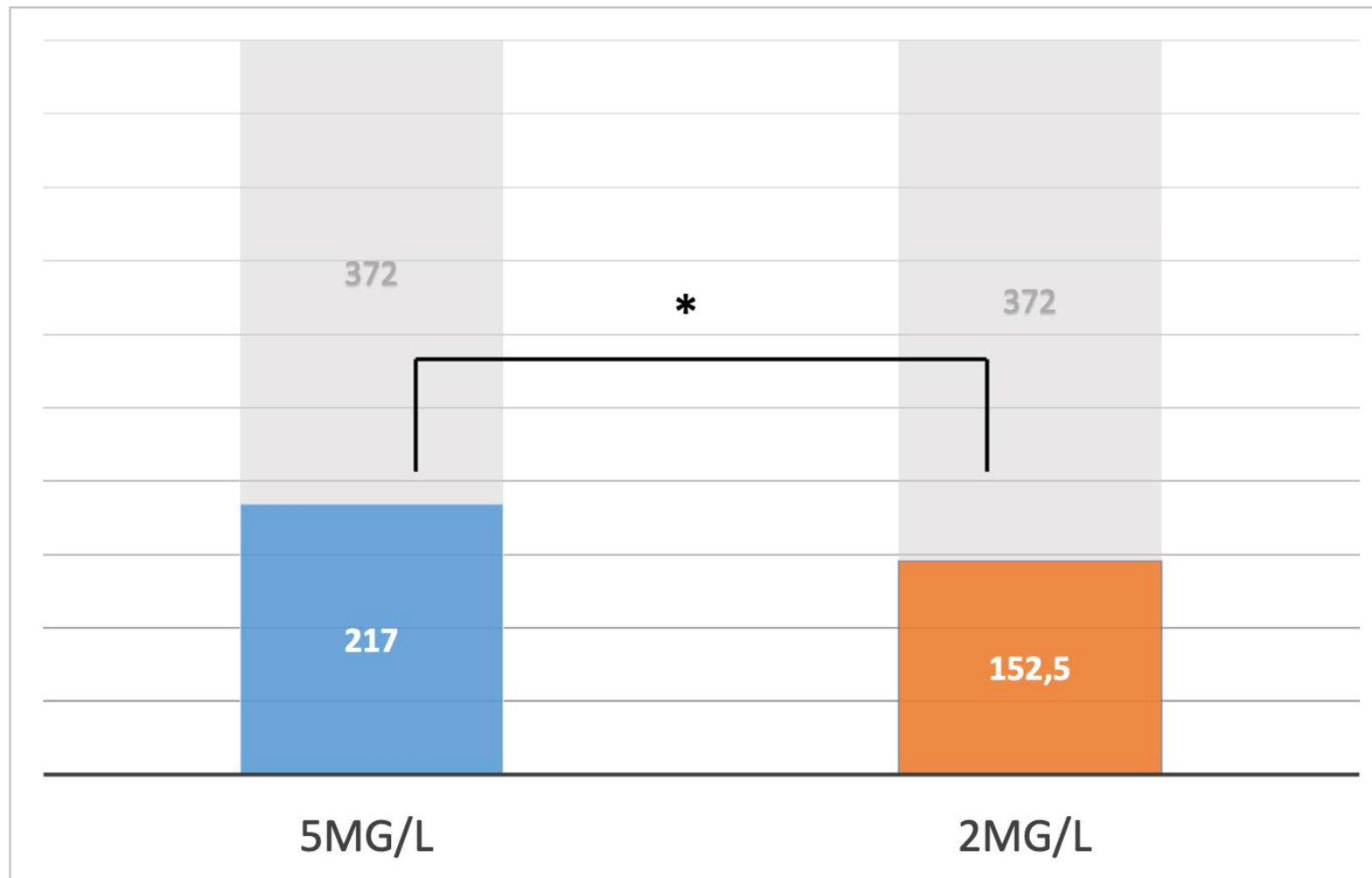
- Primary outcome: Mean Time Weighted DAS28 at week 24
 - In 2mg/L group - 0,23 [95%CI -0.07;0.53] P=0.14.

	5mg/L	2mg/L
MTW_DAS28 (SD)	1.92 (0,65)	1,69 (0,49)

- Flare & dose escalation

	5mg/L	2mg/L	
Flares N (%)	4 (13)	5 (16)	OR 1.30 [95%CI 0.31;5.38] P=0.7
Dose escalation N(%)	4 (13)	2 (7)	OR 0,47 [95CI 0.79;2,75] P= 0.4

Number of injections in 24 weeks



30% difference (2 [95%CI -1,31; -2.85] $P < 0.001$).

- Serum concentration guided dose reduction targeting a drug level of 2mg/L:
 - Non-inferior to 5mg/L in controlling disease activity
 - Safe
 - Substantial reduction in adalimumab use

- Concept of this research can be applied to treatment regimens involving all modern medication
 - More efficient use, broader availability & cost reduction
 - Safer
 - Reducing patient's burden

More rational, progressive and effective strategy

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