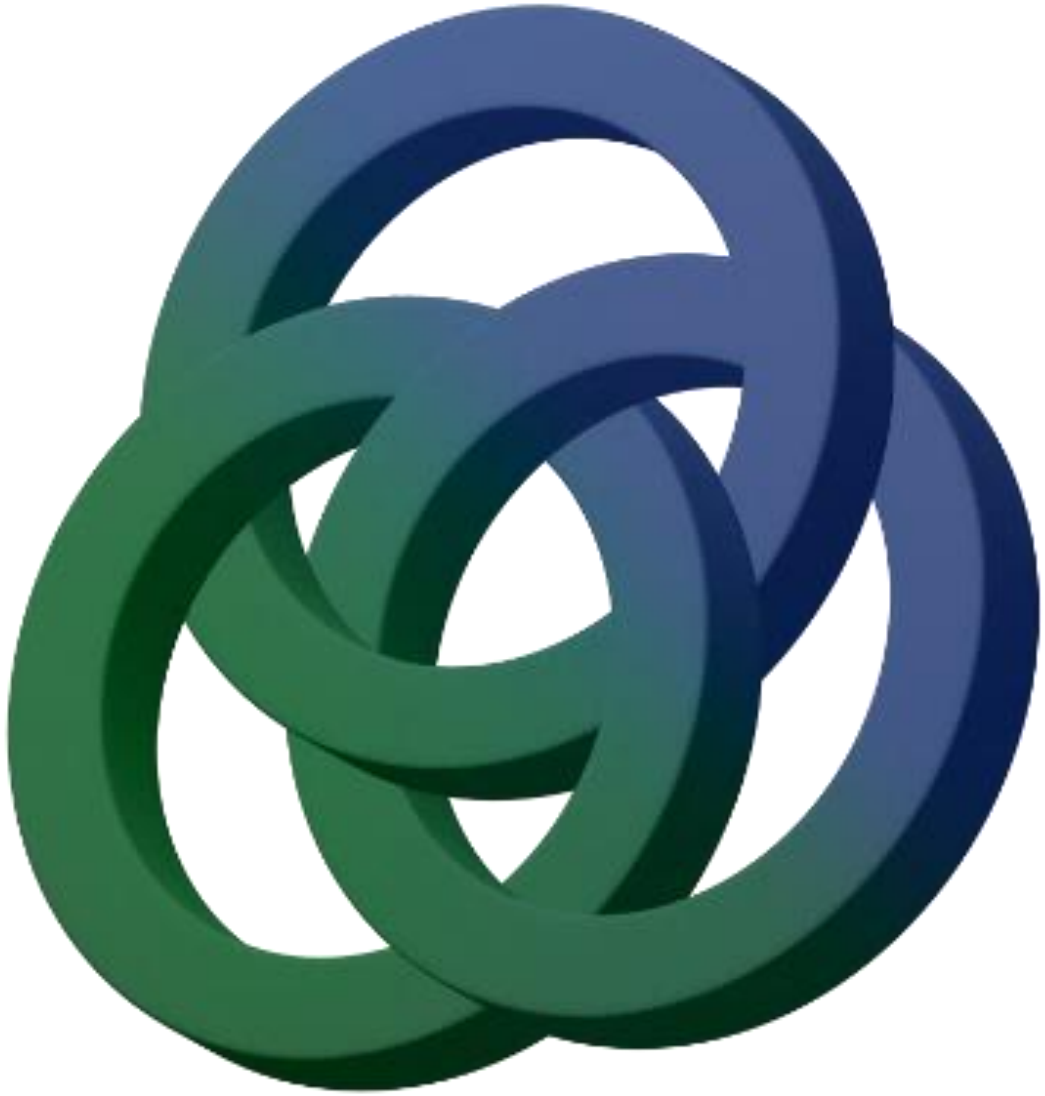

Value of MRI in Drug Development for Immune-Mediated Inflammatory Diseases: The Case for Rheumatoid Arthritis

ISMRM MR in Drug Research Study Group

Full presentation available to ISMRM members at: http://ismrm.adobeconnect.com/pier4nheu0jr/

Brad Wyman, Ph.D.

OThree Consulting, LLC

www.othreeconsulting.com

April 26, 2018

Outline

- Biomarker background
- Imaging in RA
  - Regulatory backdrop
  - X-Ray
  - MRI
    - RAMRIS
    - Beyond RAMRIS
  - RAMRIS Validation Process
- Tofacitinib RA study with MRI
- Conclusion

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Biomarkers Definition

A biomarker or a biological marker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarkers

- In clinical studies biomarkers can be used to assess:
  - Patient selection
  - Safety
  - Efficacy
- An effective biomarker will (one or more):
  - Reduce the time to conduct the study.
  - Reduce the study cost.
  - Provide unique information about the drug's mechanism of action and/or safety.
  - Increase the confidence in the drug go/no-go decision.

Why Biomarkers?

- Clinical endpoints (such as mortality and morbidity), particularly in slowly progressing diseases, may require prohibitively long and expensive trials. Biomarkers can offer a less expensive and faster alternative for study design.
- Biomarkers facilitate trial design and execution by providing information to make a go/no go decision

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Regulatory Environment for RA

- Accepted FDA endpoints for Rheumatoid arthritis (RA) are:
  - Clinical response such as: ACR(20), DAS
  - Physical function: HAQ-DI
  - Structural damage: X-Ray (such as Sharp scores)
- Effective treatments exist for RA
  - Unethical to use placebo > 3 months
  - Structural changes are unlikely to be seen with X-ray at 3 months
- MRI is of *potential interest* to the FDA, but not the EMA.

B. Chowdhury, Eular 2017, N. Nikolov, ACR 2017

FDA Accepted Imaging Endpoints

- Progression free survival or objective response rates (i.e. RECIST) for oncology (MRI, CT)
- Bone mineral density (DEXA) for osteoporosis
- Lesion load and brain atrophy for multiple sclerosis (MRI)
- IMT (US) for atherosclerosis.
- LV ejection fraction, heart failure (US, MRI?).
- X-Ray for joint space narrowing (JSN) in osteoarthritis.
- X-Ray for rheumatoid arthritis(erosions, JSN)
- Total kidney volume for polycystic kidney disease (MRI, US, CT)

Biomarker Qualification Process

- FDA

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm

- EMA

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

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X-Ray

- Visualize bone erosions, joint space narrowing, juxta-articular osteoporosis, cysts, subluxation, malalignment, ankylosis
- Sharp scores are accepted by regulatory agencies for structural claims.
- Well established and validated in longitudinal studies.
- Disadvantages
  - 2D projection of 3D anatomy
  - Insensitive to early bone damage
  - No soft tissue assessment

Modified Sharp-van der Heijde Scoring: Erosion

- 16 joints
- 6-point (0 - 5)
- 160 increments, 160 max score

- 6 joints divided into 12 bones
- 6-point (0 - 5)
- 120 increments, 120 max score

Slide courtesy of Bioclinica

Modified Sharp – van der Heijde Scoring: JSN

- 15 joints
- 5-point (0 - 4)
- 120 increments, 120 max score

- 6 joints
- 5-point (0 - 4)
- 48 increments, 48 max score

Slide courtesy of Bioclinica

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Why MRI in RA Clinical Trials?

- 3D visualization of the entire joint, synovial membrane intra- and extra-articular fluid, cartilage, bone, ligaments, tendons and tendon sheaths.
- Demonstrated correlation between early disease (inflammation and bone marrow edema (BME)) and subsequent bone erosions.

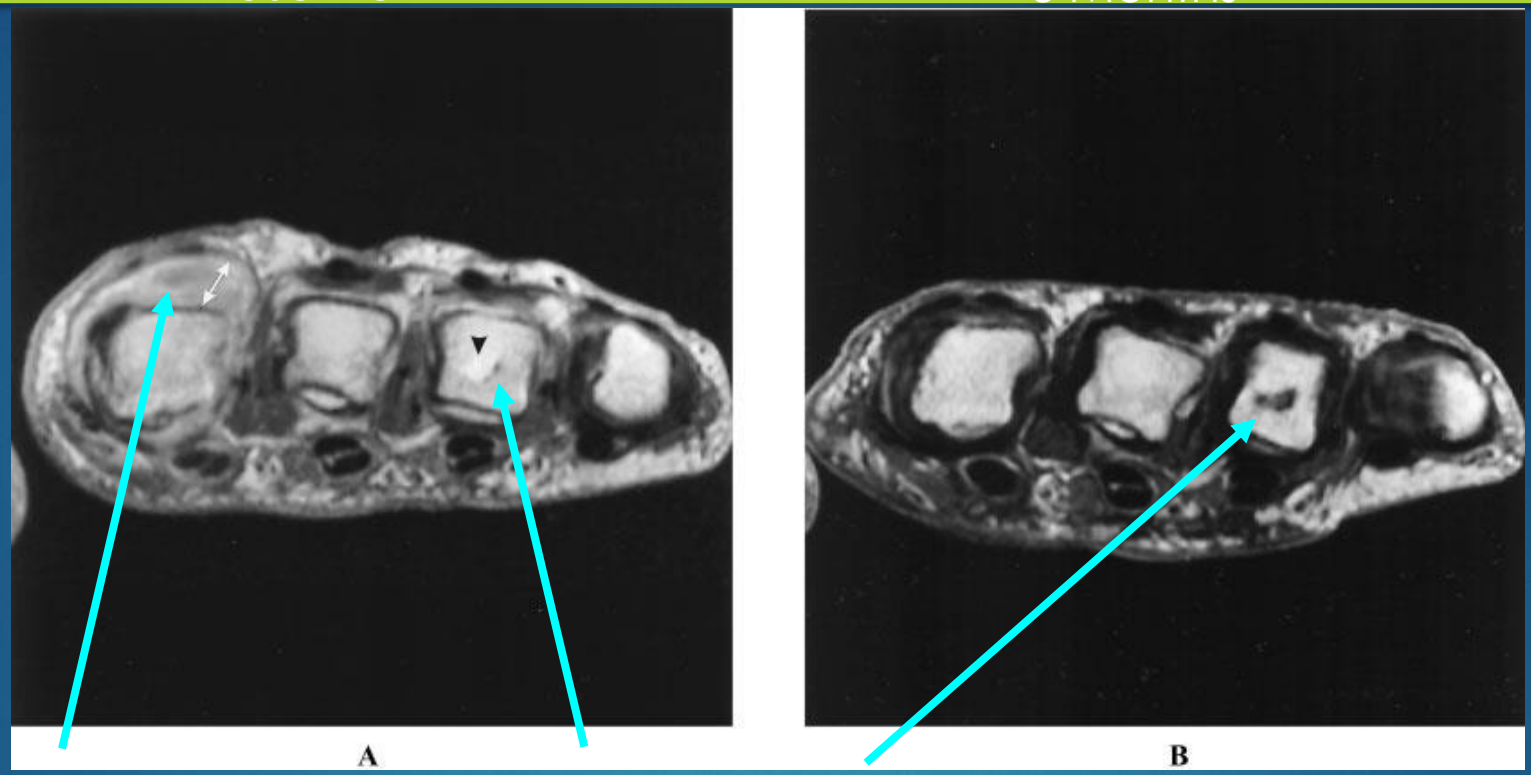
Synovitis → BME → Erosions

- Gain greater insight into treatment effects
- Validated in clinical trials
  - Semi-quantitative methods with established performance (OMERACT – RAMRIS)
  - Demonstrated in a number of longitudinal drug studies
  - More sensitive to change than x-ray

Synovitis

Baseline

3 Months



Synovitis

BME/Erosion

Figure 1. Axial T1-weighted post-gadolinium sequences of the second through fifth metacarpophalangeal (MCP) joints. **A**, Before methotrexate and intraarticular corticosteroid (MTX IAST) therapy. Marked MCP joint synovitis and tenosynovitis are visible, as demonstrated by high signal intensity. **Arrow** indicates the dimension measured for maximum synovial thickness. **Arrowhead** shows an erosion that becomes clearly visible in **B** after suppression of synovitis. **B,** After MTX IAST therapy. (A defect in the cortex, fulfilling the definition of an erosion, was visible on the equivalent coronal film.)

Conaghan, *A&R* 2003.

BME and Erosions

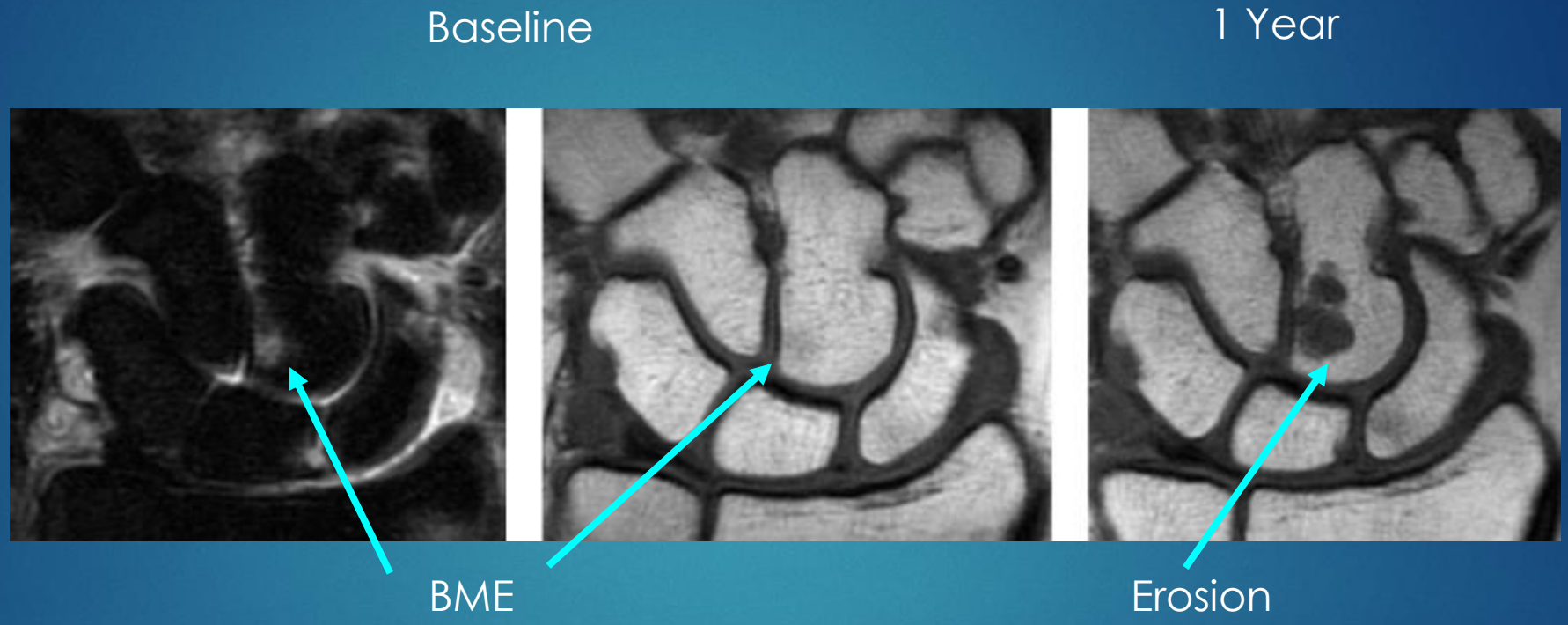


Figure 2 Magnetic resonance imaging (MRI) of the wrist, at baseline (A, B) and 1-year follow-up (C). (A) Baseline coronal STIR image showing bone marrow in the capitate (thick arrow) and the lunate and trapezoid (thin arrows). (B) Baseline T1-weighted image without MRI erosion in the capitate (arrow). (C) T1-weighted image at 1-year follow-up, showing erosive progression in the capitate (arrow). Erosive progression was also seen in the trapezoid and the lunate, even though not optimally displayed in the presented slices.

Haavardsholm, *ARD* 2008

OMERACT-RAMRIS Background

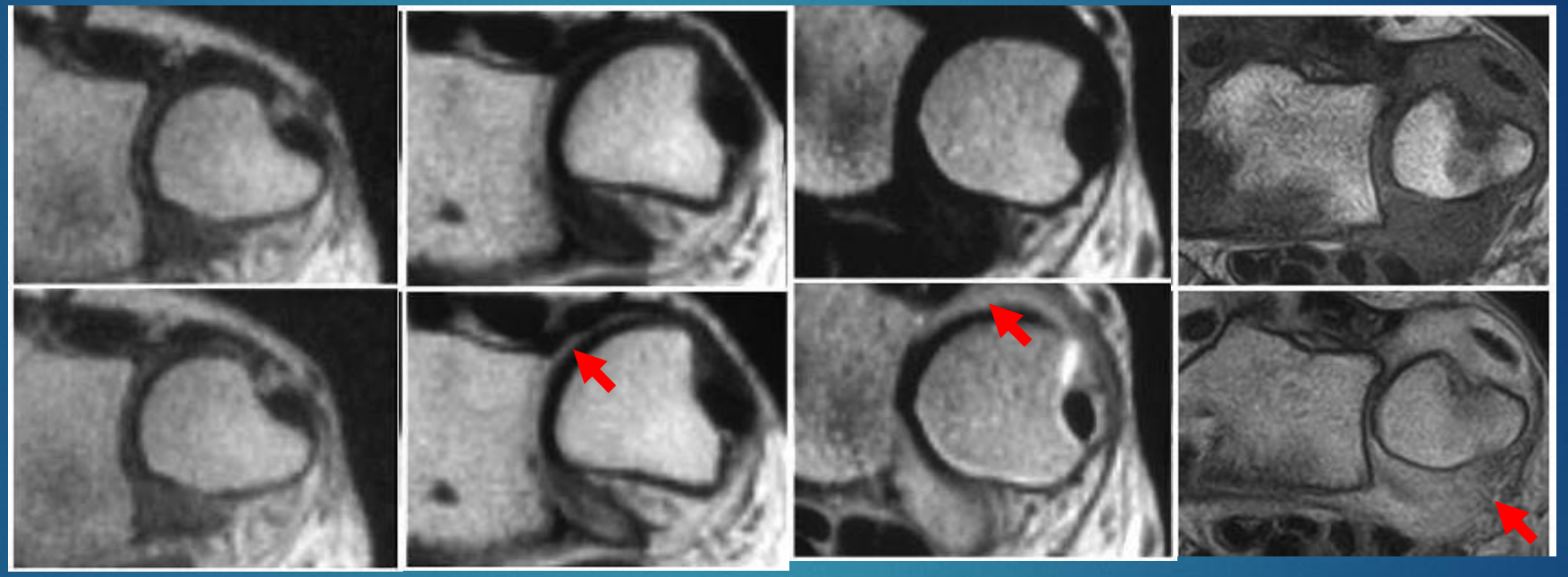
EULAR – OMERACT RAMRIS Scoring

- Outcome Measures in Rheumatology Clinical Trials (OMERACT)
- RA MRI Scoring System (RAMRIS)
- Semi-quantitative MRI method for evaluating the severity of RA appropriate for use in clinical trials.
- 3 components
  - Synovitis
  - Bone marrow edema
  - Erosions

OMERACT – Synovitis Scoring

- Synovitis score 0-3 according to portion of enhancing joint synovium i.e:
  - 0 = no synovitis
  - 1 = mild = 1 - 33% enhancement volume
  - 2 = moderate = 34 - 66% enhancement volume
  - 3 = severe = 67 - 100% enhancement volume
- Scored for the following joints:
  - MCP 3-5
  - Distal radio-ulnar
  - Radio-carpal
  - Intercarpal-CMCJ
- Max score: 9 wrist, 9 MCP.

Synovitis Score – Distal Radioulnar Joint



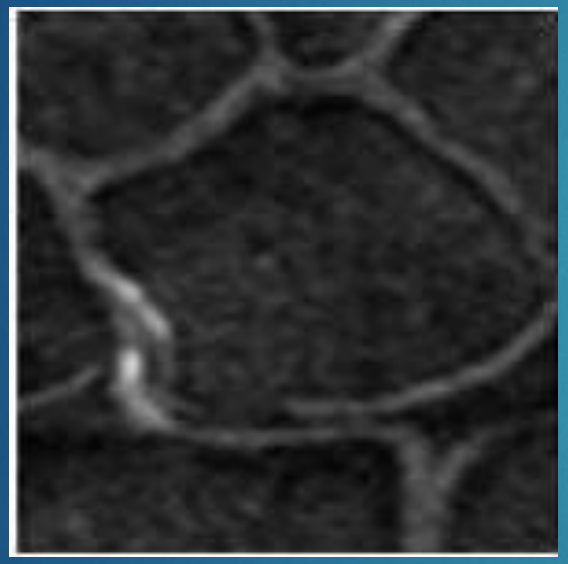
OMERACT Score

Ejbejerg, ARD, 2005

OMERACT – Bone Edema Scoring

- Bone edema score (0-3) according to portion of bone involved. i.e:
  - 0 = no edema
  - 1 = 1-33%
  - 2 = 34-66%
  - 3 = 67-100%
- Scored at:
  - Proximal and distal MCP joints 2-5
  - Base of the metacarpal 1-5
  - Trapezium, trapezoid, capitate, hamate, scaphoid, lunate, triquetrum, pisiform, distal radius, distal ulna
- Max score: 45 wrist 24 MCP

Bone Edema - Lunate



0

1

2

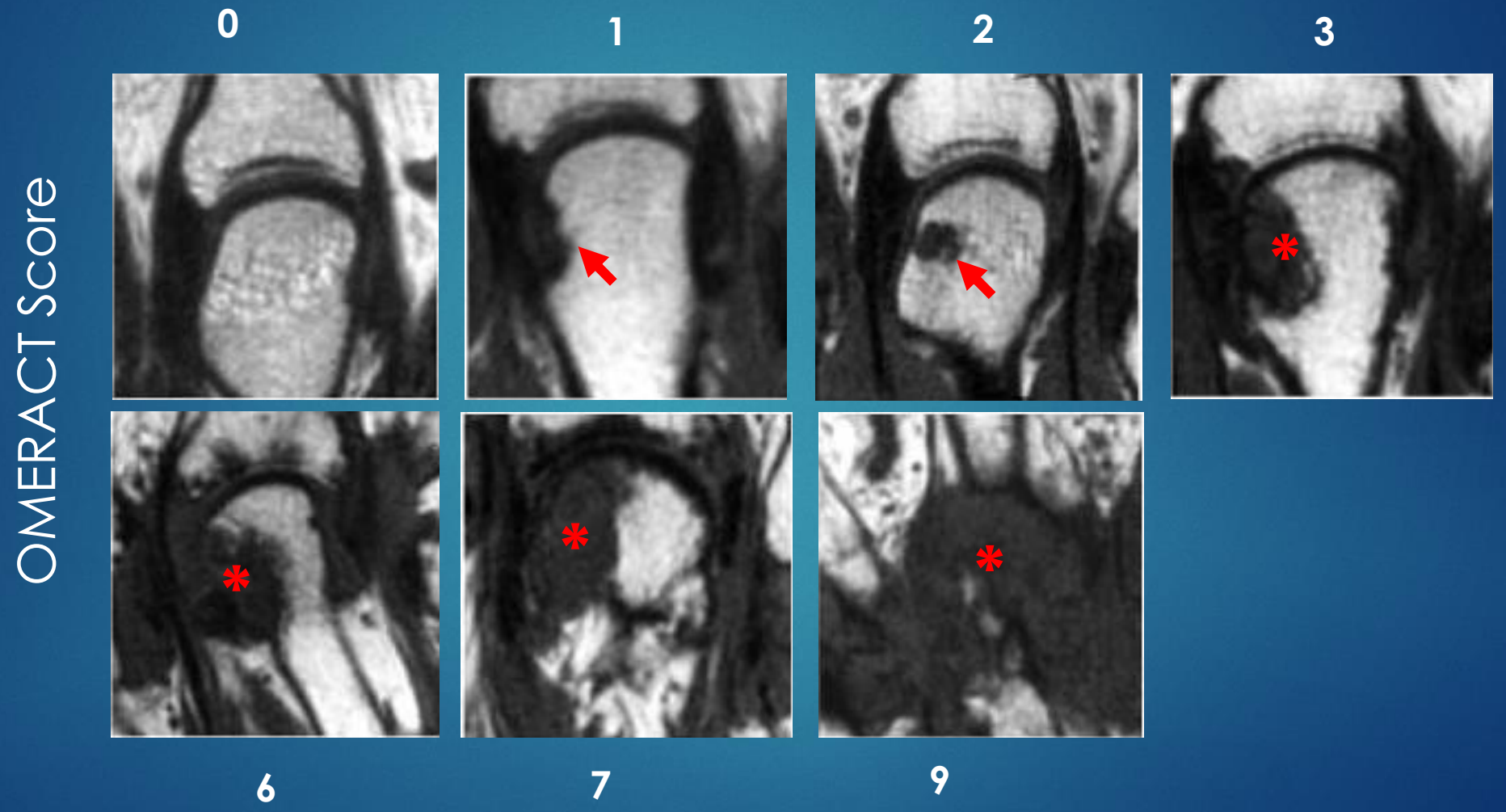
OMERACT Score

Ejbejerg, ARD, 2005

OMERACT – Bone Erosion

- Bone erosion score 0-10 according to portion of bone involved. i.e:
  - 0 = no erosion,
  - 1 = 1-10%,
  - 2 = 11-20% etc.
- Scored at:
  - Proximal and distal MCP joints 2-5
  - Base of the metacarpal 1-5
  - Trapezium, trapezoid, capitate, hamate, scaphoid, lunate, triquetrum, pisiform, distal radius, distal ulna
- Max score: 150 wrist, 80 MCP

Bone Erosion – Metacarpal Head



Conaghan, ARD, 2005

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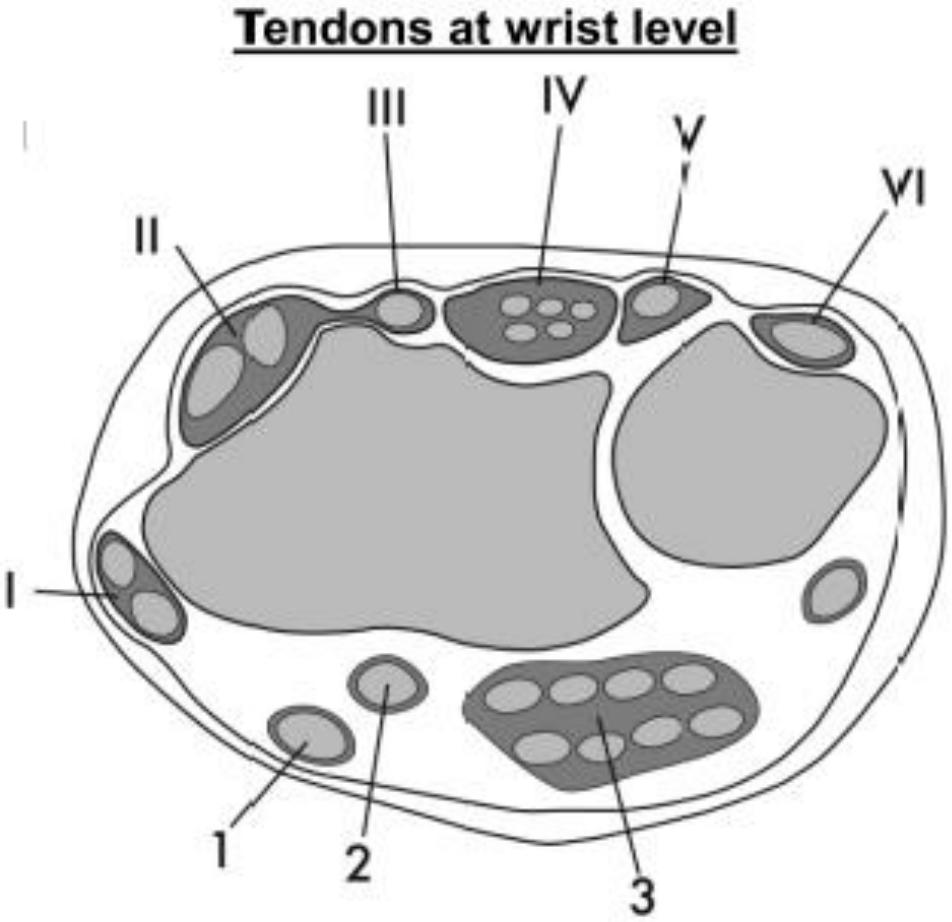
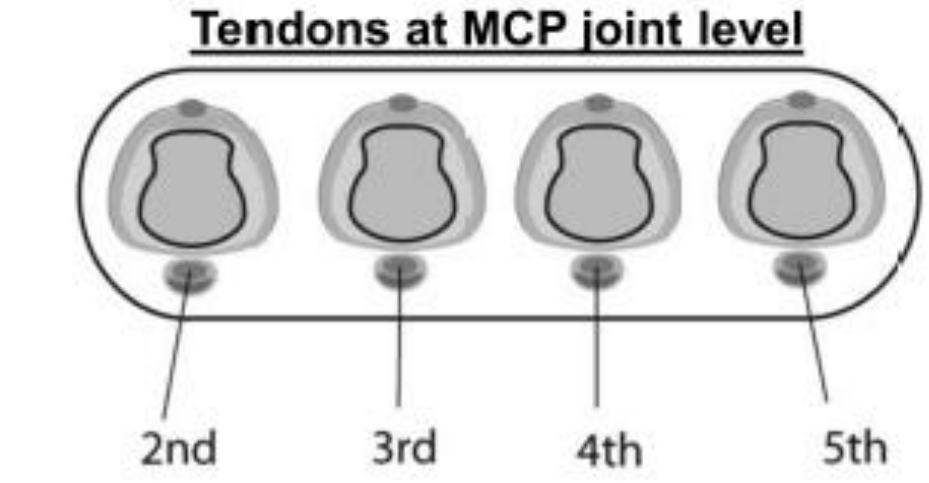


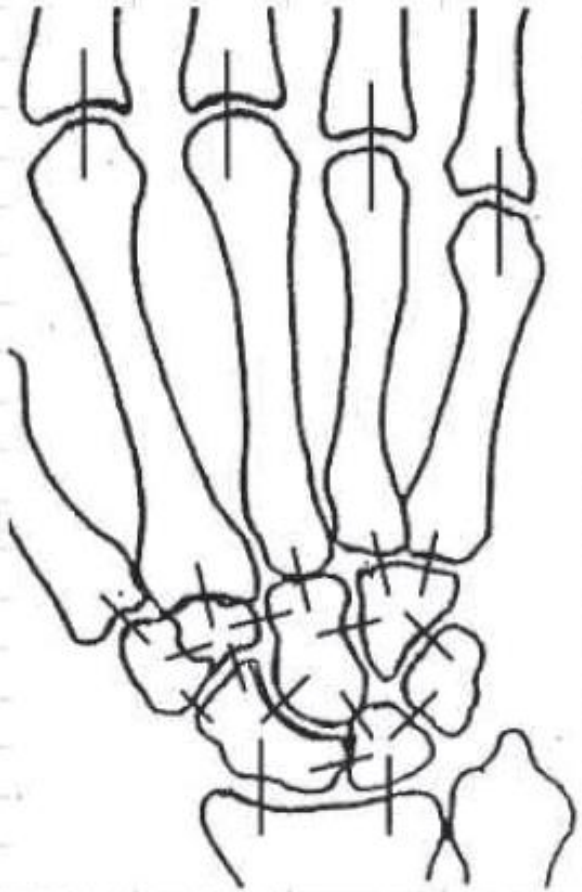


RAMRIS - Tenosynovitis

- Tenosynovitis score 0-3:
  - 0 = no enhacement,
  - 1 = < 1.5 mm effusion
  - 2 = ≥ 1.5 < 3 mm effusion
  - 3 = ≥ 3 mm effusion
- Scored at:
  - Wrist extensor tendons I-VI
  - Wrist flexor tendons FCR,Radial FPL, Ulnar bursa
  - MCP flexor 2-5th finger

Glinatsi, J. Rheumatology 2017

RAMRIS - JSN



MCP	MCP2	MCP3	MCP4	MCP5
Score				

CMC	CMC1	CMC2	CMC3	CMC4	CMC5
Score					
2.row	TRM-TRD	TRD-CAP	CAP-HAM		
Score					
1.-2.row	TRM-SCA	TRD-SCA	CAP-SCA	CAP-LUN	HAM-TRI
Score					
1.row	SCA-LUN	LUN-TRI			
Score					
Rad-Carp	RAD-SCA	RAD-LUN			
Score					

Definition of JSN

Reduced joint space width compared to normal, as assessed in a slice perpendicular to the joint surface

Scoring system (total range: 0-84)

JSN is scored 0-4 at each marked site

0: No narrowing

1: Focal or mild (<33%) narrowing

2: Moderate (34% - 66%) narrowing

3: Moderate to severe (67% - 99%) narrowing

4: Ankylosis

Reader rules

Use coronal images

Score at narrowest point

On T1-weighted image: score "white (bone marrow fat) to white"

If surface is eroded: Ignore erosions and measure "width if there had been no erosion"

If joint with subluxation: Score despite deformities

Østergaard, J Rheum, 2011

RAMRIQ

- RAMRIQ = Quantitative RAMRIS
  - Synovitis
  - Erosions
  - Bone marrow edema
  - Joint space width (narrowing)
  - Tenosynovitis
- Fully automated, quantitative
- *Goal – decrease the variability and increase the dynamic range of measures resulting in greater sensitivity to change.*

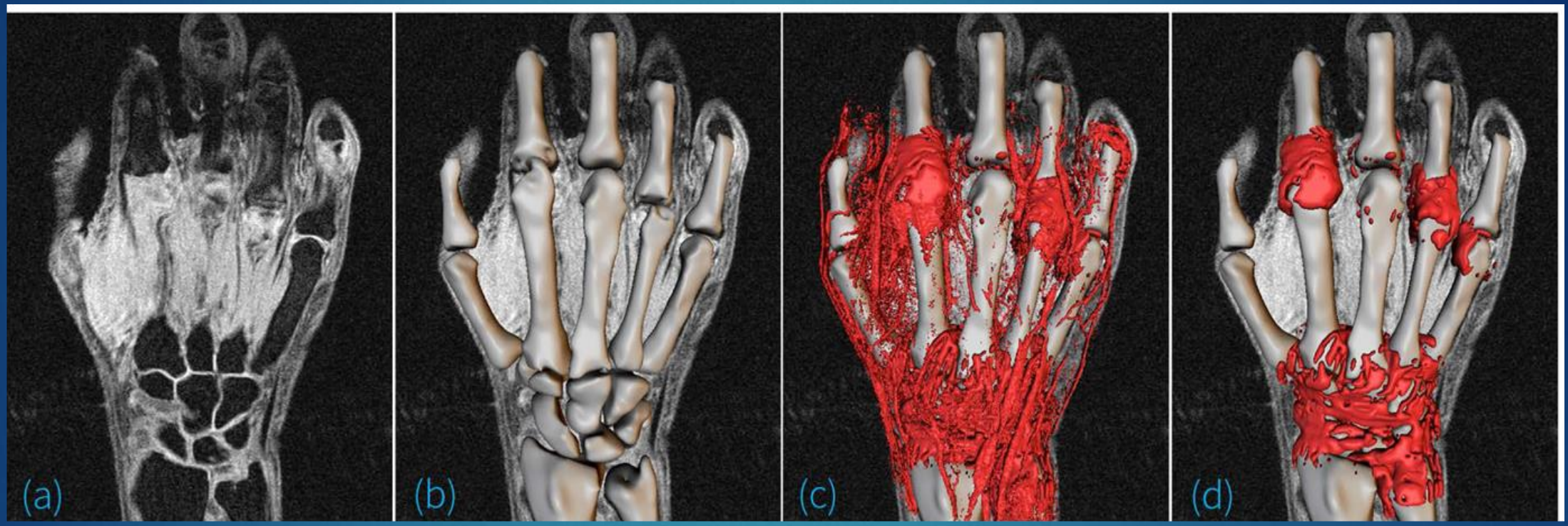
Methods: RAMRIQ

- The basis of all measures is the accurate identification of the hand bones using 3D statistical shape models
- Method works in 3D
  - Not affected by patient's hand position in coil
- Excellent accuracy of ~0.2 mm (around third of one pixel), compared with expert mark-up
- Uses commonly available MRI sequences of RAMRIS
  - Designed to be readily available at imaging centres
- Fully automatic
  - Not susceptible to differences between readers
- Fully quantified
  - Scalar results allow use of more powerful statistical methods compared with categorical semi-quantitative measures

Slide courtesy of Stryker/Imorphics

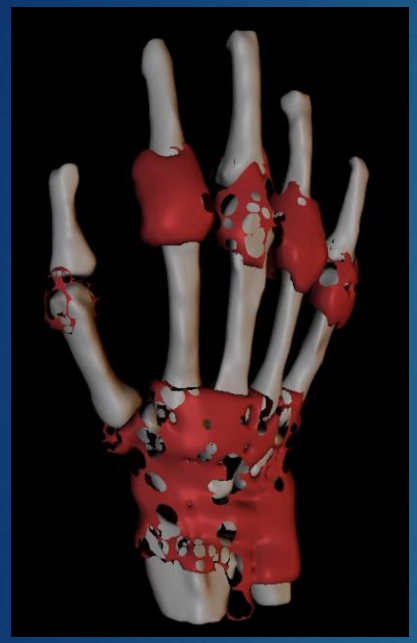
Conaghan, ACR 2016, Presentation 3090

Measurement of synovitis



Slide courtesy of Stryker/Imorphics

Methods: RAMRIQ measures

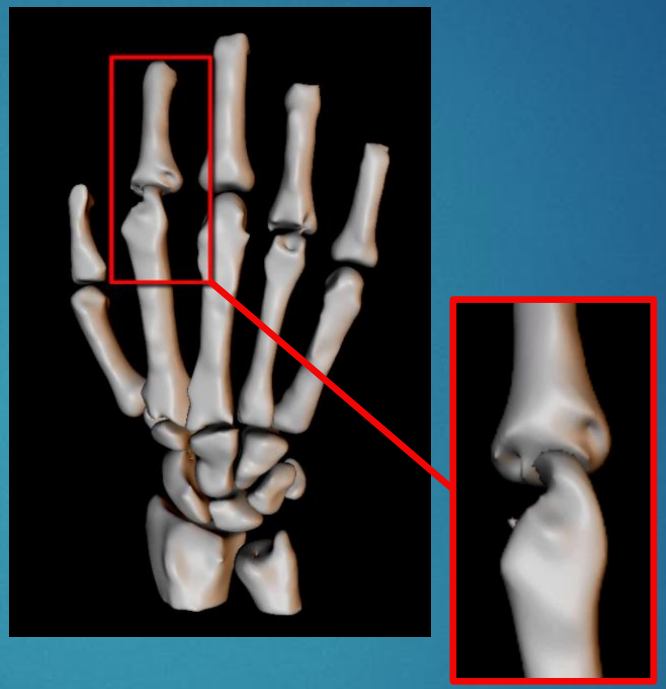


Synovitis

Volume (mm^3)

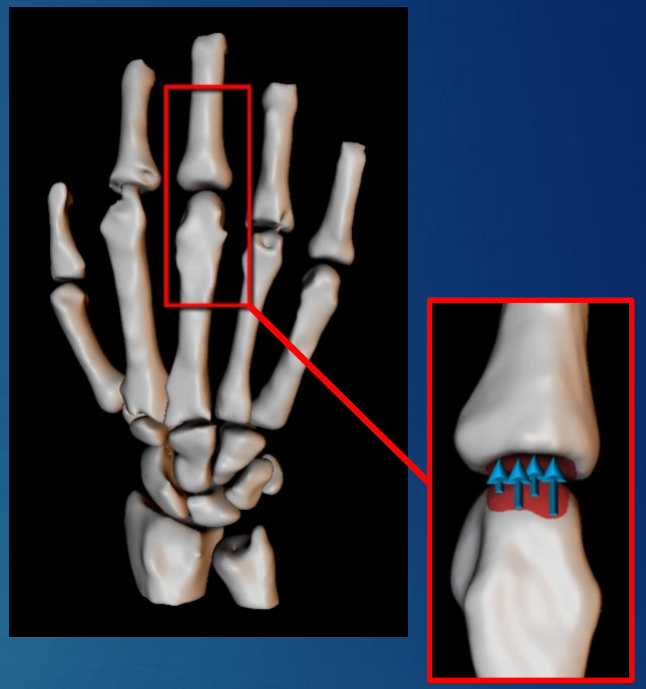
Oedema

Volume (mm^3)



Erosion

Volume (mm^3)



Joint space width

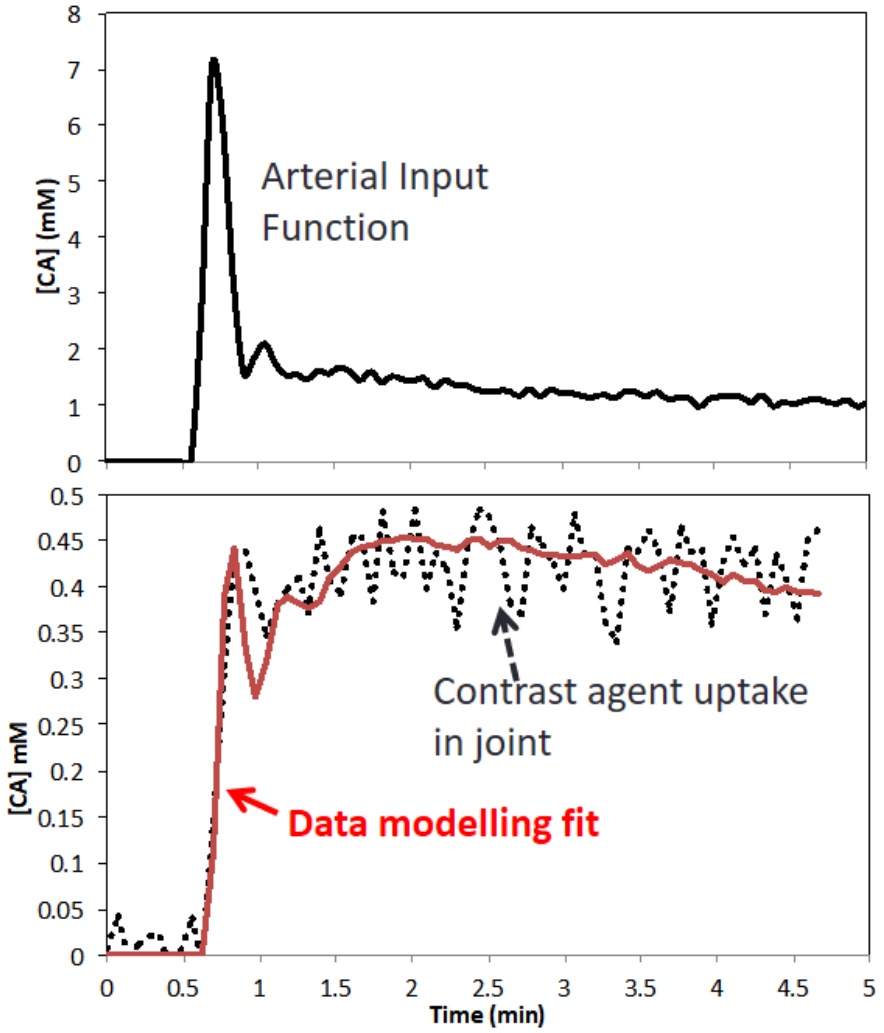
Distance (mm)

Conaghan, ACR 2016, Presentation 3090

Slide courtesy of Stryker/Imorphics

DCE-MRI Method

- Use intravascular injection of contrast agent as a *tracer*
- Monitor concentration over time
- Model the contrast agent kinetics to extract parameters such as blood flow, capillary permeability, max enhancement

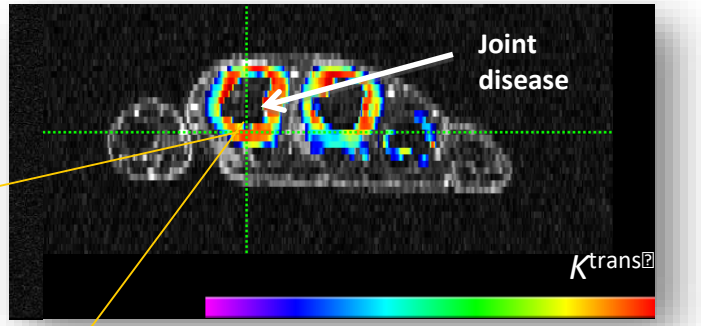


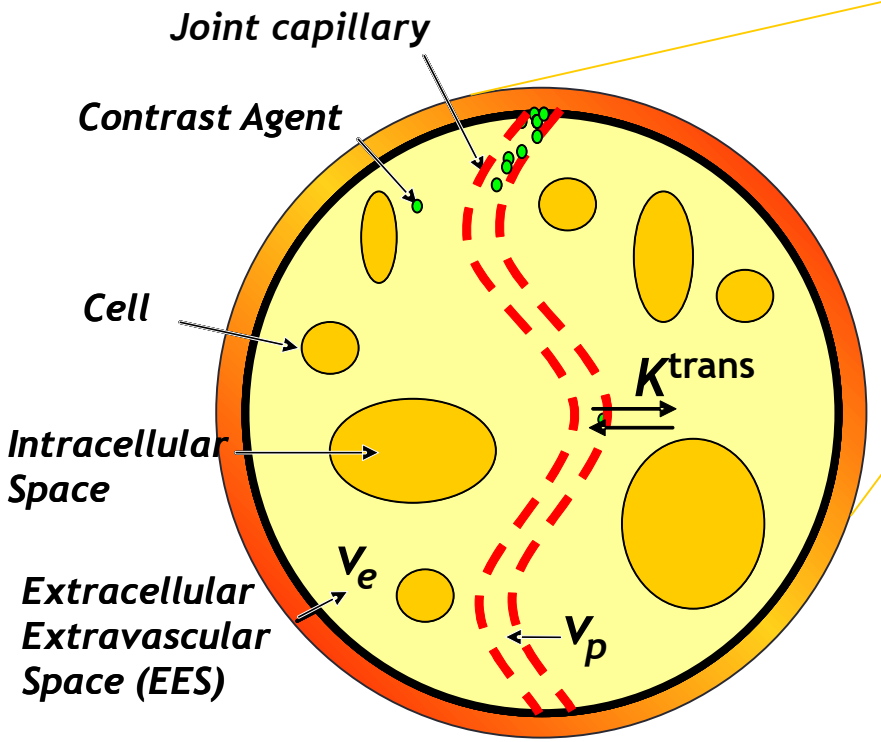
bioxydyn

Contrast agent kinetics and modelling

Routine modelling (extended Tofts/Key)

- Small molecular weight extracellular tracer
- Diffusive transport from arterial supply
- Well-mixed compartments





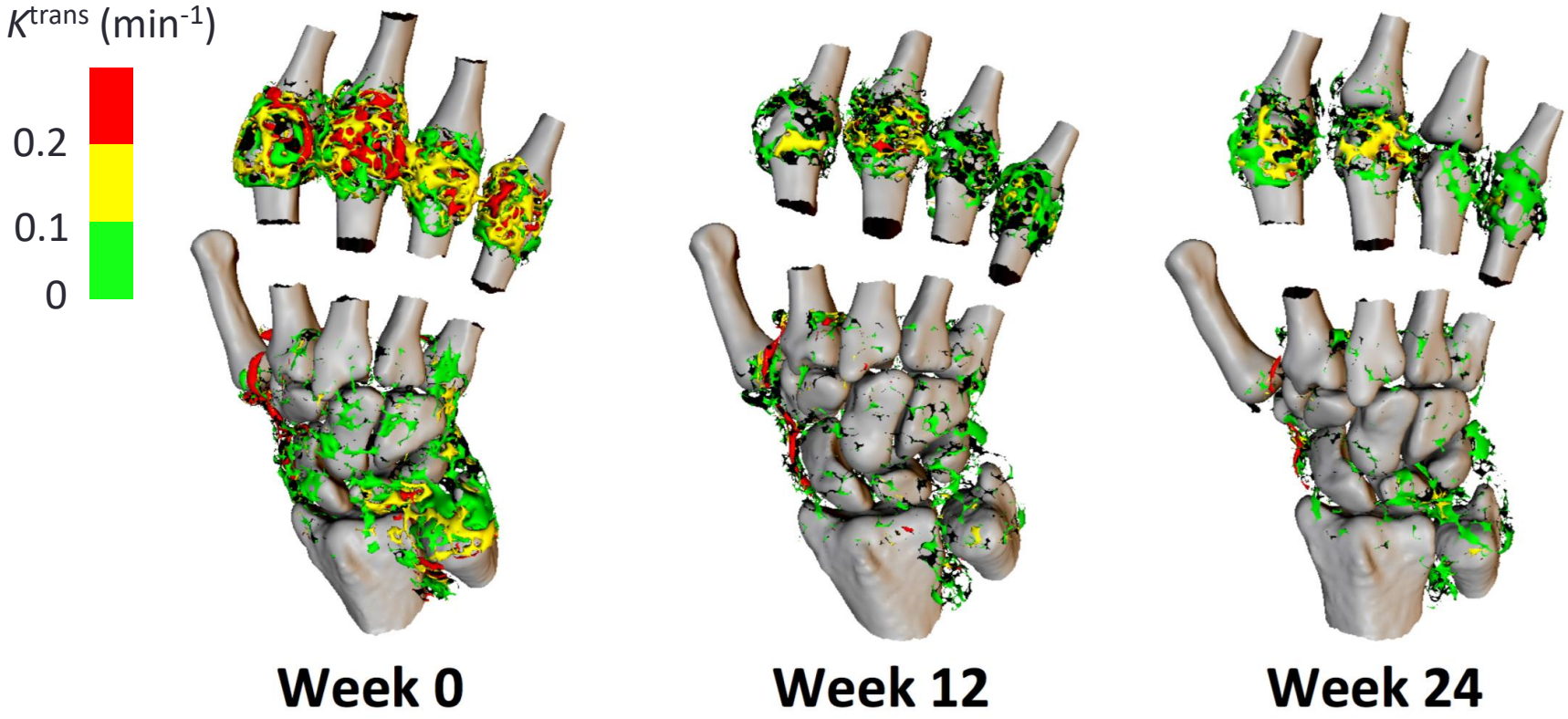
$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(t') \exp\left(\frac{-K^{trans}(t')}{v_e}\right) dt'$$

- Vascular volume (v_p)
- EES (v_e)
- Transfer coefficient (K^{trans}) joint synovial endothelial permeability

bioxydyn

Imaging biomarkers example
DCE-MRI in rheumatoid arthritis

Synovitis measured by DCE-MRI (k^{trans}), decreased from baseline to week 12 and week 24 post-treatment



Roberts *et al* EULAR 2015

bioxydyn

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A Brief History of RAMRIS

- The OMERACT MRI Working Group is formed (Peterfy, J. Rheum 2003). Work started in 1999.
- Acquisition, definitions and scoring system defined (Østergaard, J. Rheum 2003, McQueen, J. Rheum 2003)
- Multicenter reliability is published (Lassere, J. Rheum 2003).
- EULAR-OMERARC RA MRI Reference Image Atlases published (Østergaard, Ann Rehum Dis 2005, Ejbjerg, Ann Rheum Dis 2005, Conaghan, Ann Rheum Dis 2005, Bird, Ann Rheum Dis. 2005.)
- Reliability and sensitivity to change (Haavardsholm, Arthritis Rheum, 2005)
- Comparison of 1.5T to 3.0T (Wieners, Eur Radiol 2007)
- Extension to Tenosynovitis (Haavardsholm, Ann Rheum Dis. 2007)
- Validation against CT and Radiography (Døhn, Ann Rheum Dis. 2007)
- Longitudinal Study (Haavardsholm, Ann Rheum Dis. 2008)
- Randomized controlled trial (CIMESTRA) (Hetland, Ann Rheum Dis. 2009)
- Etc…

Validation of RAMRIS as an RA Endpoint

1) Standardization of measures.
2) Buy-in from larger community.
3) Development of training materials.
4) Evaluation across imaging platforms (scanners/coils).
5) Characterization of test-retest variability.
6) Cross-sectional, longitudinal, multicenter validation.
7) Randomized controlled studies.
8) Modest iteration and refinement.

Significant ground work was required for success.

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EXTENDED REPORT

Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques

Philip G Conaghan,[1] Mikkel Østergaard,[2] Michael A Bowes,[3] Chunying Wu,[4] Thomas Fuerst,[4] Désirée van der Heijde,[5] Fedra Irazoque-Palazuelos,[6] Oscar Soto-Raices,[7] Pawel Hrycaj,[8] Zhiyong Xie,[9] Richard Zhang,[9] Bradley T Wyman,[9] John D Bradley,[9] Koshika Soma,[9] Bethanie Wilkinson[9]

Tofacitinib MRI Study

Conaghan, et. al, Ann Rheum Dis 2016

doi:10.1136/annrheumdis-2015-208267

Methods

- An exploratory, phase 2, randomized, double-blind, parallel-group study.
- 109 Subjects randomized
  - Early and active RA (≤ 2 years since diagnosis)
  - ESR > 28 mm/h or CRP > 7 mg/L
  - Methotrexate (MTX) naïve
- Treatment, randomized1:1:1
  - Tofacitinib 10 mg BID with MTX
  - Tofacitinib 10 mg BID monotherapy
  - MTX monotherapy

Methods

- Assessments
  - ACR and DAS
  - MRI (BL, 1M, 3M, 6M, 12M)
    - RAMRIS
    - RAMRIQ
    - DCE-MRI
  - X-ray (BL, 6M, 12M)
    - van der Heijde modified total Sharp scores (mTSS)
  - Safety

Co-Primary Endpoints

- Change from baseline in RAMRIS wrist and MCP joints of:
  - Bone marrow edema (BME) at month 6
  - Synovitis at month 3

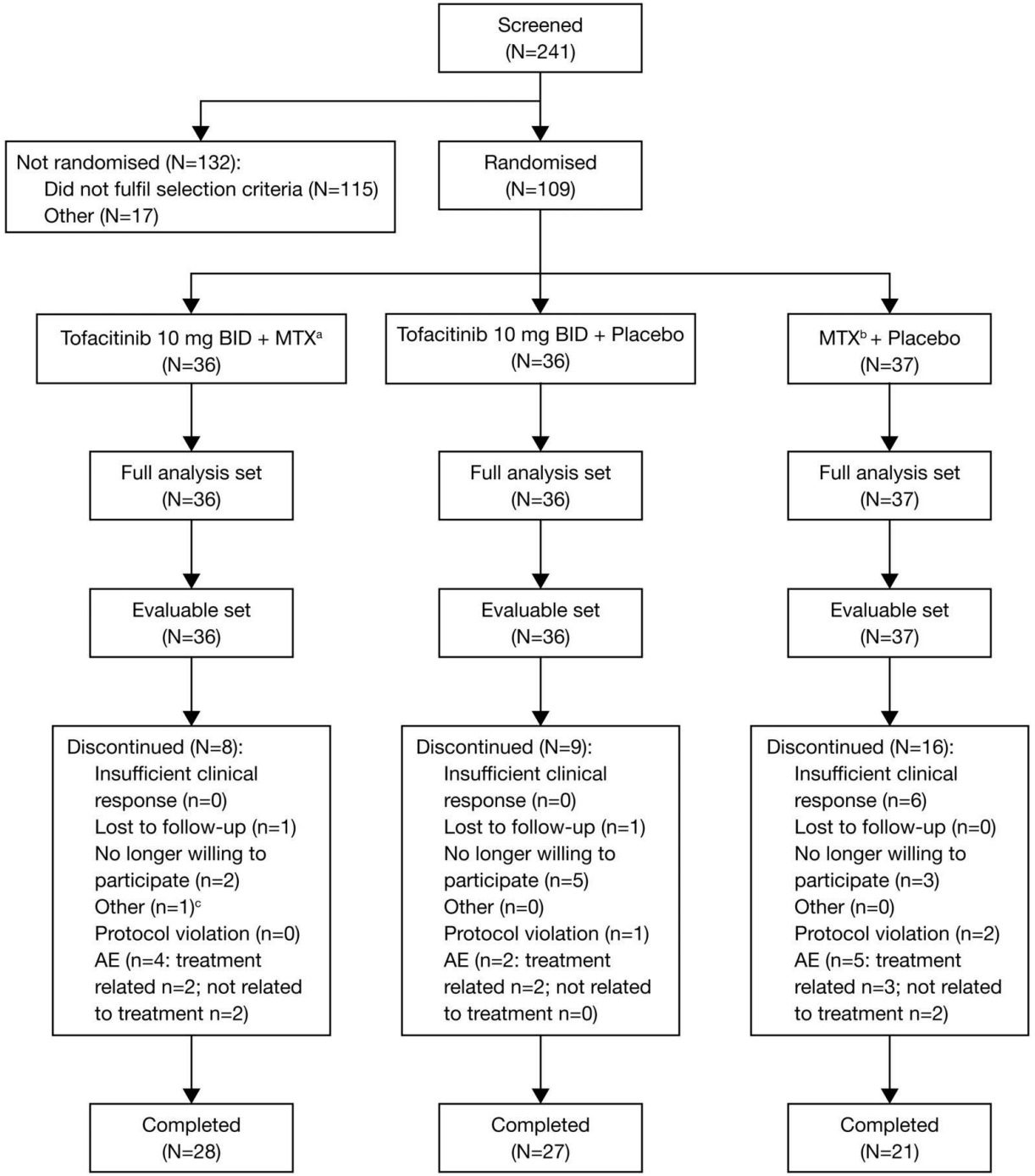
Secondary Endpoints

- Change from baseline in RAMRIS wrist and MCP erosion, BME, and synovitis scores at all other timepoints (months 1, 3, 6 and 12).
- Change from baseline in van der Heijde mTSS, JSN, and erosion scores (months 6 and 12).

Exploratory Endpoints

- Semi-quantitative measurement of:
  - Tenosynovitis
  - Joint space narrowing
- Quantitative (RAMRIQ) measurement of:
  - Erosion volume
  - Synovitis volume
  - BME volume
  - Tenosynovitis
  - Joint space narrowing
- DCE-MRI uptake kinetics in the wrist

Patient disposition

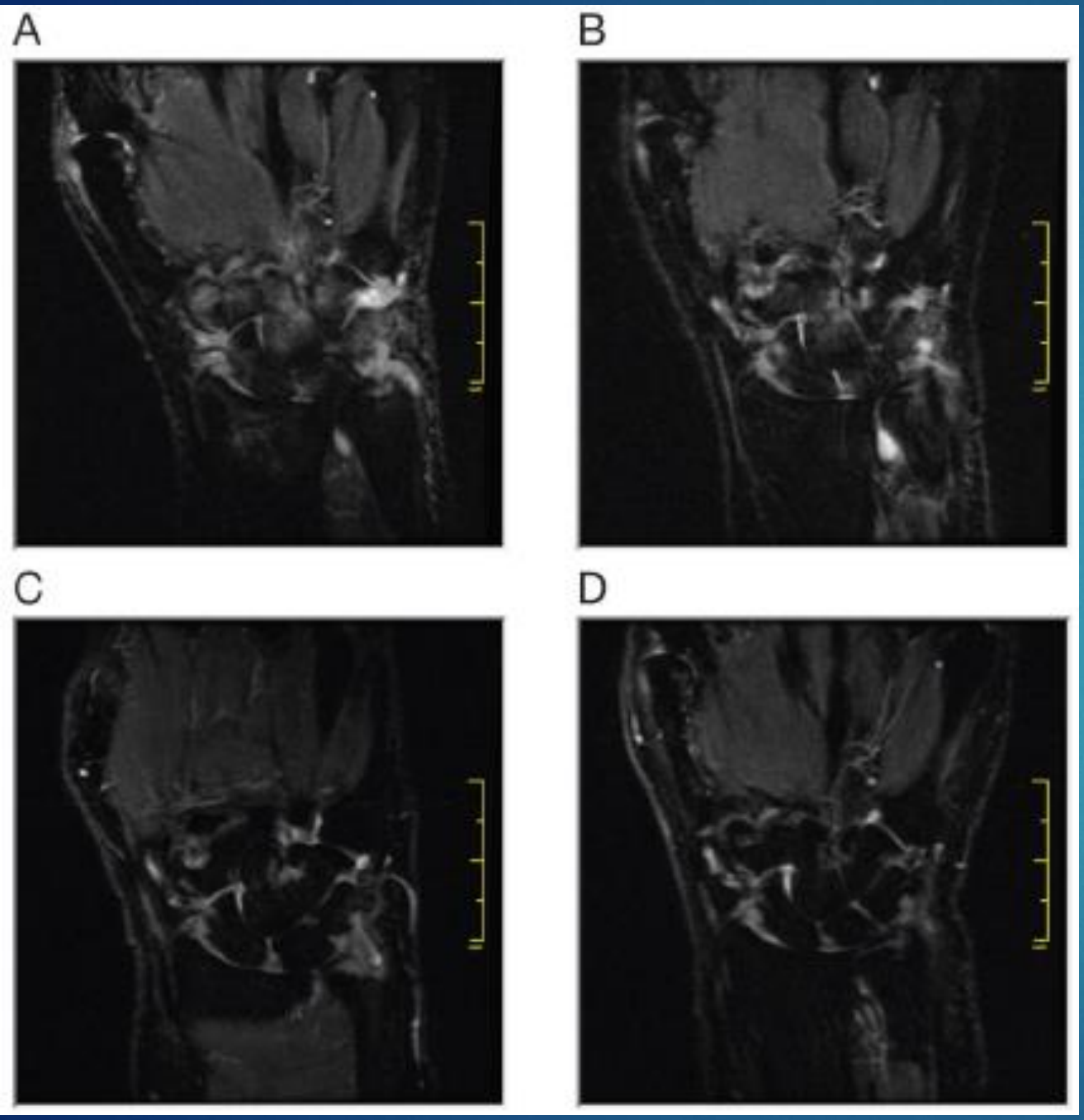


Philip G Conaghan et al. Ann Rheum Dis 2016;75:1024-1033

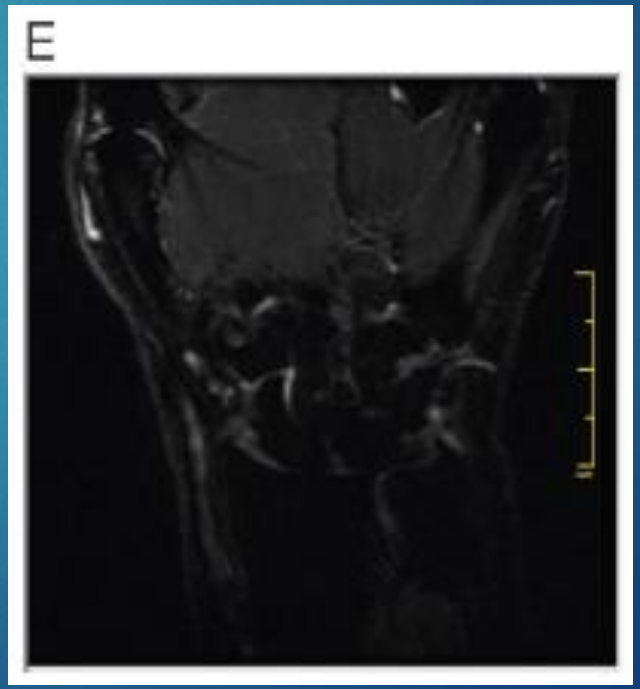
ARD

Table 1 Summary of patient demographics and baseline characteristics

Parameter	Tofacitinib 10 mg twice daily + MTX (N=36)	Tofacitinib 10 mg twice daily monotherapy (N=36)	MTX monotherapy (N=37)
Age, mean (SD)	47.8 (12.3)	50.8 (12.8)	47.8 (11.6)
Females, %	86.1	83.3	78.4
Mean duration of disease, years (range)	0.8 (0.1–2.2)	0.8 (0.1–8.5)	0.6 (0.1–1.9)
Positive for rheumatoid factor, n/N (%)	26/34 (76.5)	27/35 (77.1)	27/37 (73.0)
Anti-CCP positive, n/N (%)	27/34 (79.4)	27/35 (77.1)	30/37 (81.8)
Swollen joint count, mean (range)	13.4 (0.0–32.0)	15.3 (4.0–46.0)	14.4 (6.0–39.0)
Tender joint count, mean (range)	20.6 (0.0–57.0)	20.9 (4.0–53.0)	20.5 (9.0–52.0)
DAS28-4(ESR), mean (SD)*	6.3 (0.9)	6.5 (0.8)	6.4 (0.8)
HAQ-DI score, mean (SD)*	1.5 (0.8)	1.5 (0.6)	1.5 (0.7)
RAMRIS, mean (SD)†			
BME	1.9 (3.7)	2.6 (3.7)	2.2 (5.1)
Synovitis	5.8 (3.8)	5.7 (3.5)	5.3 (3.9)
Bone erosions	9.4 (10.8)	7.5 (7.6)	12.2 (14.9)
RAMRIQ, mean (SD)*			
BME	1.4 (2.8)	1.1 (2.7)	1.4 (2.7)
Synovitis	7750.4 (5432.8)	7971.8 (5510.1)	6980.7 (6304.8)
Bone erosions	1.6 (0.9)	1.6 (0.8)	1.9 (1.3)
DCE MRI N_{Vox}, mean (SD)‡	3013.6 (3605.6)	2767.6 (2140.2)	3079.8 (3704.9)
Radiographic evaluations, mean (SD)†			
van der Heijde mTSS	13.0 (21.7)	12.6 (26.0)	13.7 (26.0)
JSN component score	6.9 (13.3)	5.7 (15.0)	6.1 (12.7)
Erosion component score	6.1 (9.3)	6.9 (11.8)	7.6 (14.3)
Prior MTX, n (%)§	0 (0.0)	2 (5.6)	4 (10.8)
Prior/concomitant systemic corticosteroids, n (%)	20 (55.6)	16 (44.4)	21 (56.8)



Representative images for BME in a patient randomized to tofacitinib monotherapy at A) Baseline, B) Month 1, C) Month 3, D) Month 6, and E) Month 12.



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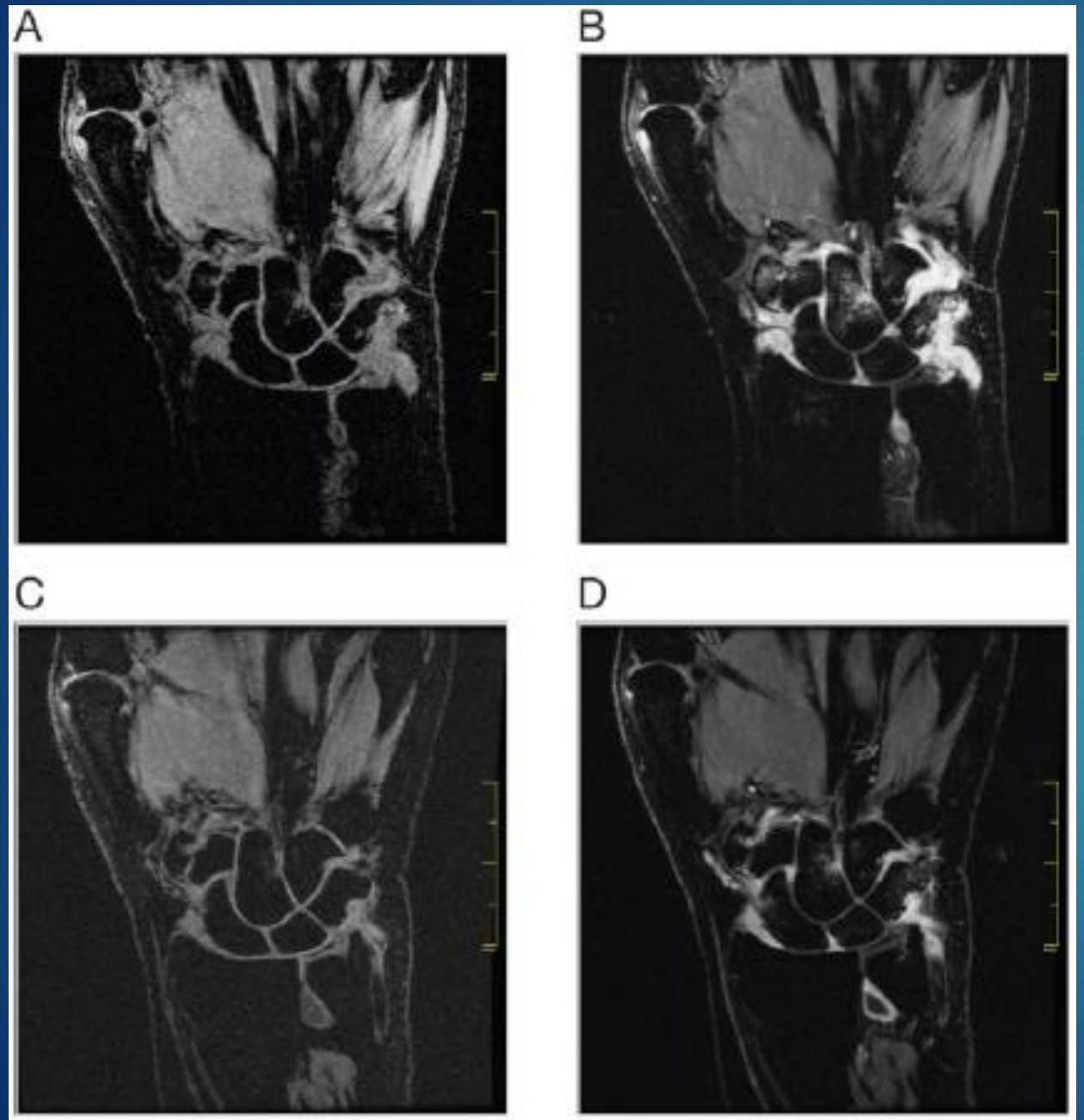
Pre-contrast

Post-contrast

Baseline

1 Month



Representative images for synovitis in a patient randomized to tofacitinib monotherapy at A) baseline pre-contrast, B) baseline post-contrast, C) Month 1 pre-contrast, D) Month 1 post-contrast

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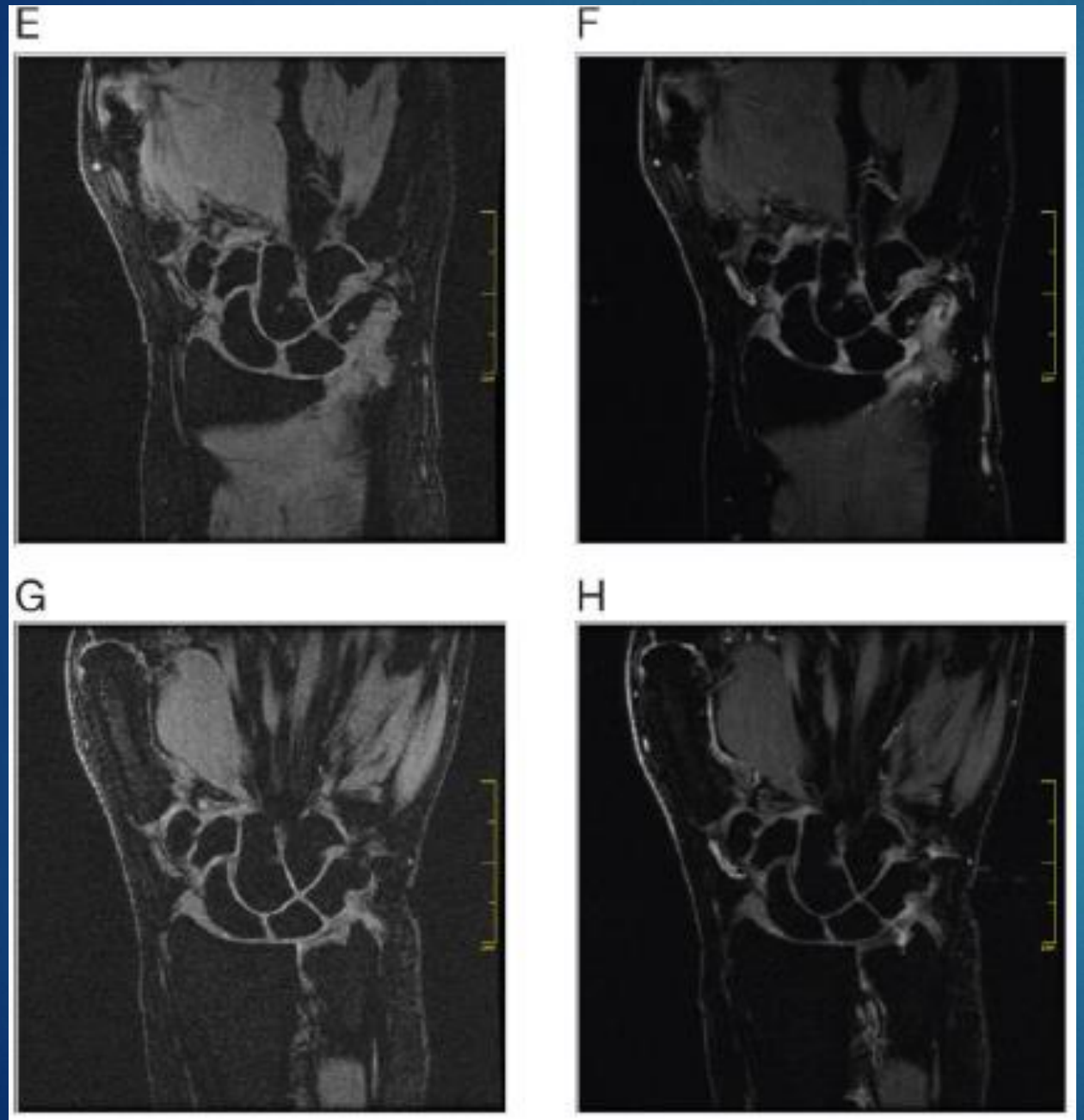
Pre-contrast

Post-contrast

3 Month

6 Month



Representative images for synovitis in a patient randomised to tofacitinib monotherapy E) Month 3 pre-contrast, F) Month 3 post-contrast, G) Month 6 pre-contrast, H) Month 6 post-contrast

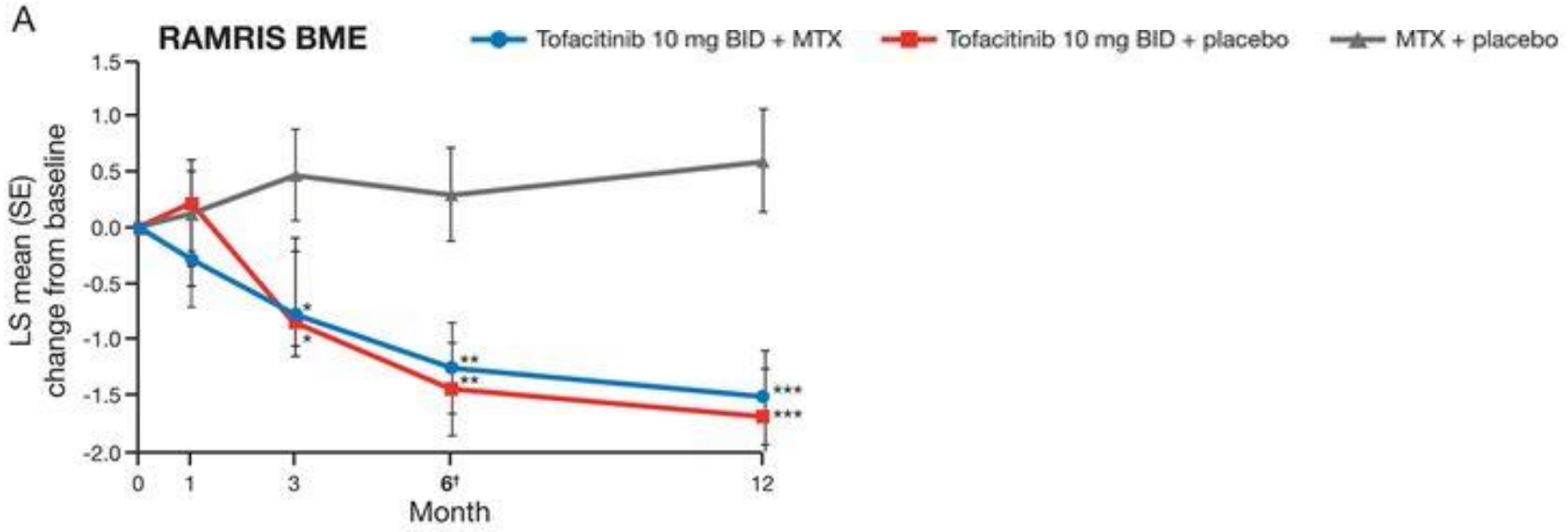
Conaghan, Supplement, ARD 2016

Table 2 Radiographic and clinical endpoints (evaluable set, LOCF)

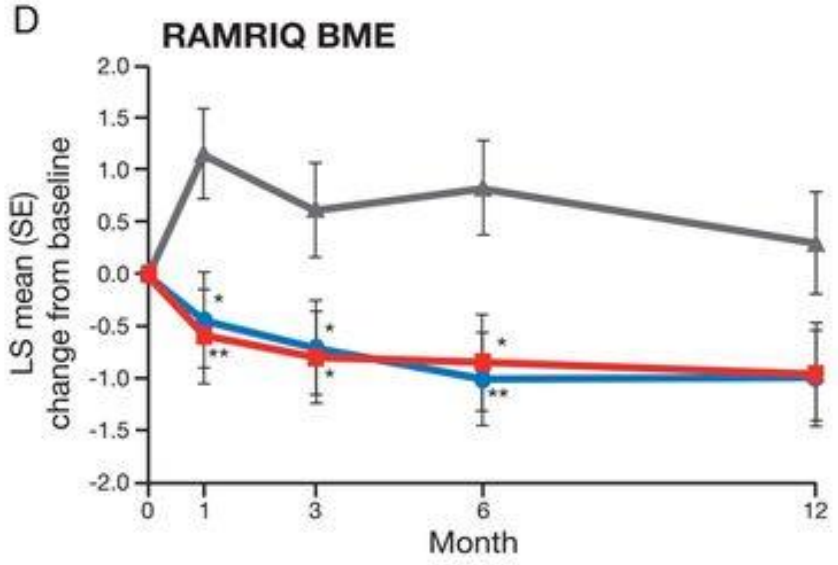
	Tofacitinib 10 mg twice daily + MTX	Tofacitinib 10 mg twice daily monotherapy	MTX monotherapy
LS mean change from baseline (SE)			
van der Heijde mTSS			
Month 6†	0.44 (0.50)	−0.14 (0.51)	0.93 (0.52)
Month 12‡	0.85 (0.51)	−0.15 (0.52)*	1.36 (0.54)
JSN component score			
Month 6†	0.29 (0.34)	−0.06 (0.35)	0.35 (0.36)
Month 12‡	0.43 (0.35)	−0.12 (0.36)	0.71 (0.37)
Erosion component score			
Month 6†	0.16 (0.24)	−0.10 (0.25)	0.58 (0.25)
Month 12‡	0.42 (0.25)	−0.05 (0.26)	0.65 (0.27)
Responders, % (SE)			
ACR20	N=35	N=36	N=37
Month 3	77.1 (7.1)	66.7 (7.9)	56.8 (8.1)
Month 6	77.1 (7.1)*	72.2 (7.5)	54.1 (8.2)
Month 12	82.9 (6.4)	66.7 (7.9)	56.8 (8.1)
ACR50	N=35	N=36	N=37
Month 3	48.6 (8.4)	55.6 (8.3)*	29.7 (7.5)
Month 6	57.1 (8.4)**	52.8 (8.3)*	27.0 (7.3)
Month 12	65.7 (8.0)**	50.0 (8.3)	35.1 (7.8)
ACR70	N=35	N=36	N=37
Month 3	25.7 (7.4)	27.8 (7.5)	13.5 (5.6)
Month 6	34.3 (8.0)	30.6 (7.7)	24.3 (7.1)
Month 12	28.6 (7.6)	33.3 (7.9)	24.3 (7.1)

Table 2 Radiographic and clinical endpoints (evaluable set, LOCF)

	Tofacitinib 10 mg twice daily + MTX	Tofacitinib 10 mg twice daily monotherapy	MTX monotherapy
LS mean change from baseline (SE)			
DAS28-4(ESR) <2.6	N=34	N=36	N=37
Month 3	23.5 (7.3)	2.8 (2.7)	13.5 (5.6)
Month 6	29.4 (7.8)	13.9 (5.8)	13.5 (5.6)
Month 12	35.3 (8.2)*	19.4 (6.6)	13.5 (5.6)
DAS28-4(ESR) ≤3.2	N=34	N=36	N=37
Month 3	32.4 (8.0)	30.6 (7.7)	16.2 (6.1)
Month 6	41.2 (8.4)	27.8 (7.5)	21.6 (6.8)
Month 12	58.8 (8.4)***	30.6 (7.7)	18.9 (6.4)
HAQ-DI improvement ≥0.22§	N=34	N=36	N=37
Month 3	73.5 (7.6)	75.0 (7.2)	81.1 (6.4)
Month 6	76.5 (7.3)	75.0 (7.2)	70.3 (7.5)
Month 12	73.5 (7.6)	72.2 (7.5)	73.0 (7.3)



Tofacitinib 10 mg BID + MTX	N=	28	30	33	29
Tofacitinib 10 mg BID + placebo	N=	31	32	29	26
MTX + placebo	N=	35	31	28	21



Tofacitinib 10 mg BID + MTX	N=	28	30	33	29
Tofacitinib 10 mg BID + placebo	N=	30	32	28	25
MTX + placebo	N=	34	28	28	20

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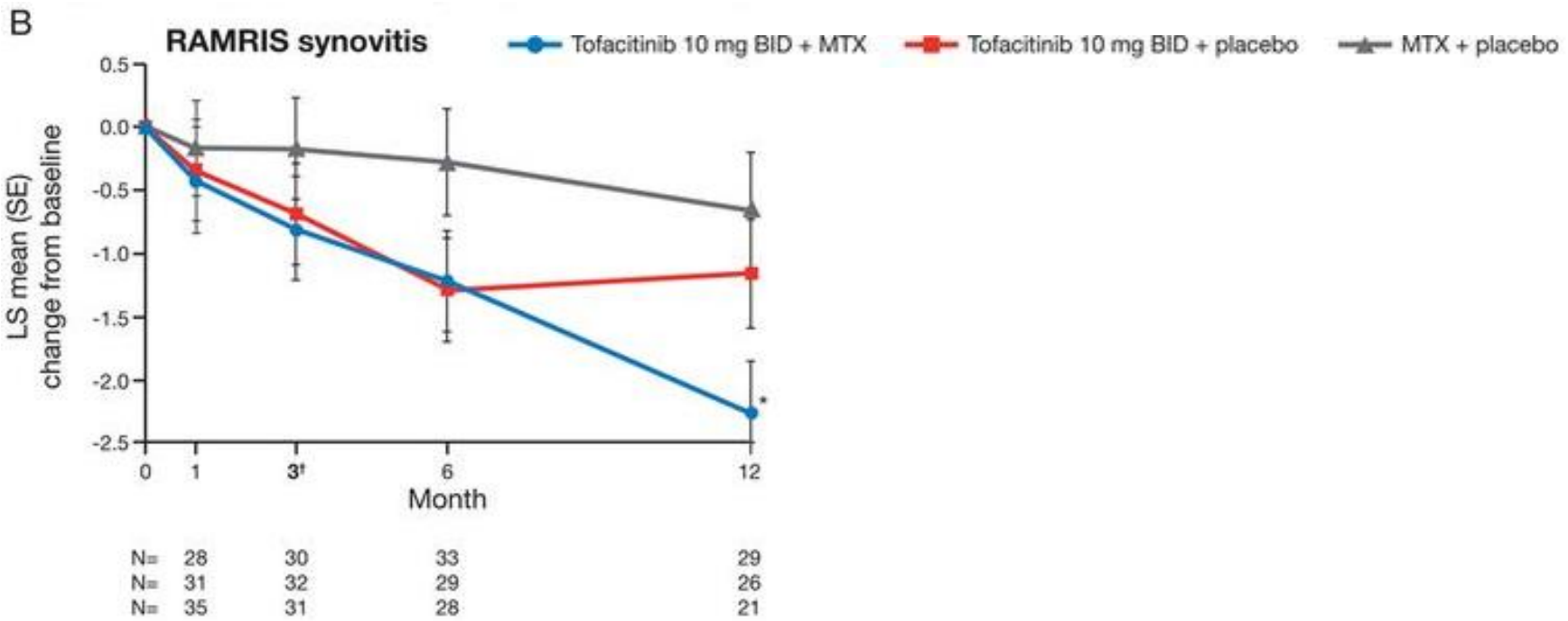

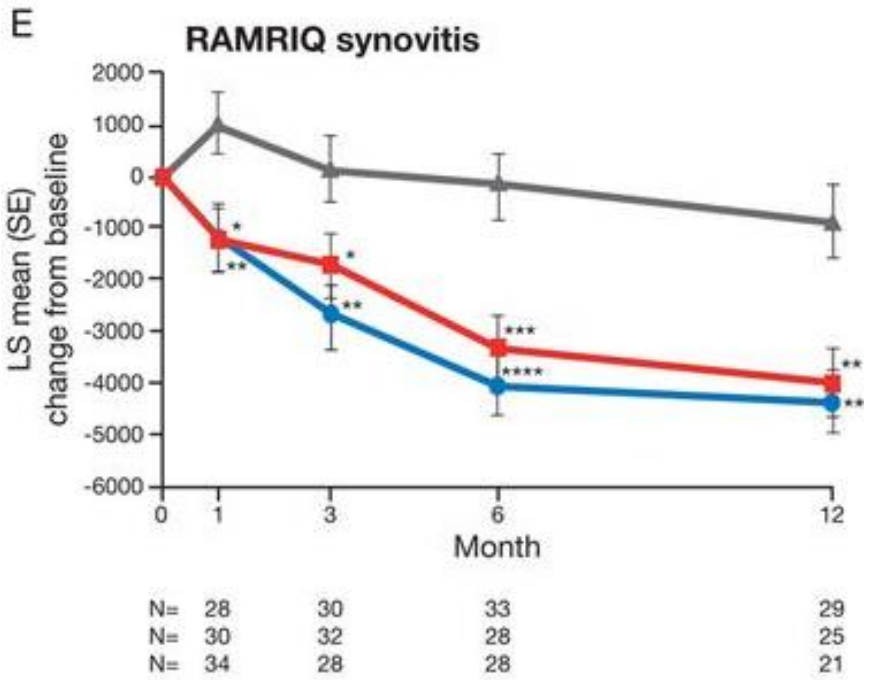

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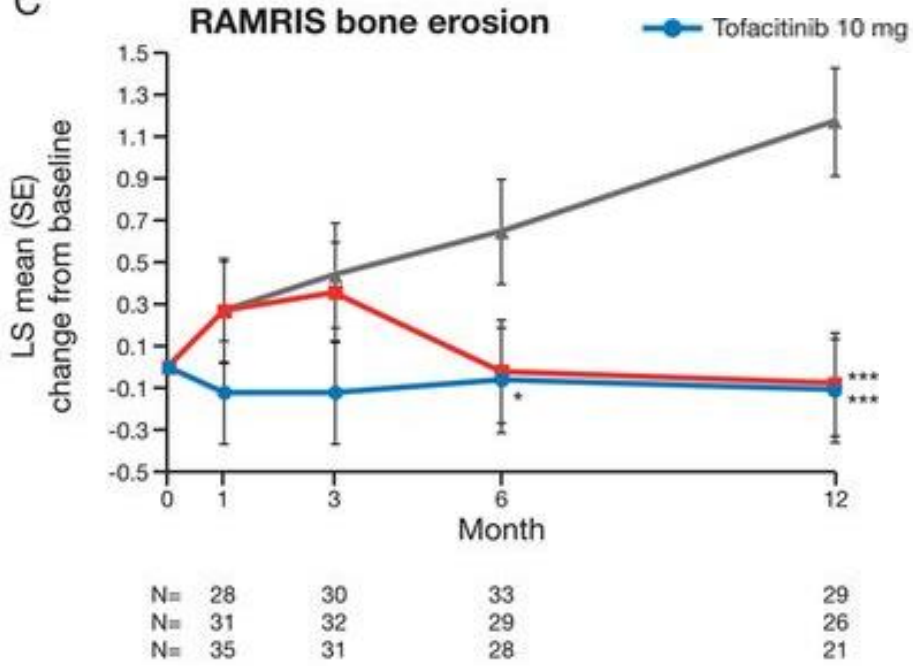
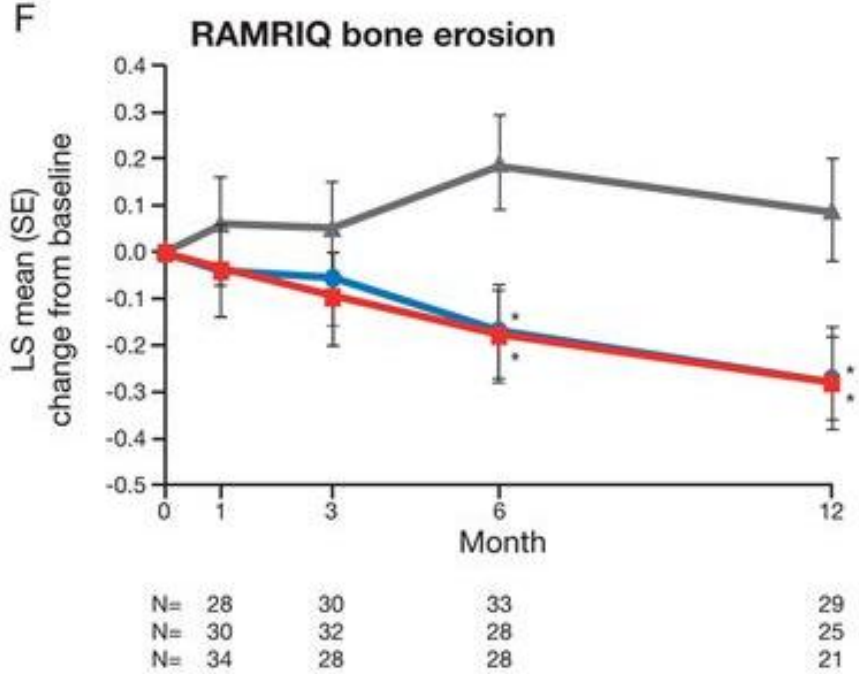
C



F



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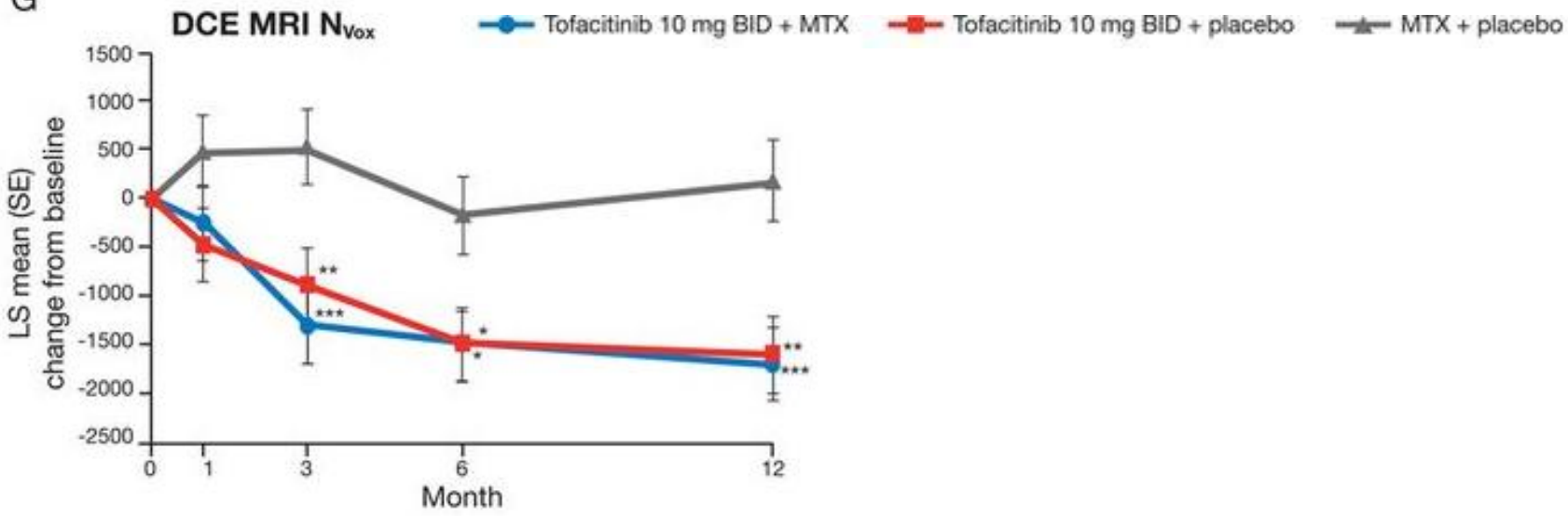

Tofacitinib 10 mg BID + MTX	N=	24	27	31	27
Tofacitinib 10 mg BID + placebo	N=	27	28	26	23
MTX + placebo	N=	28	25	23	19

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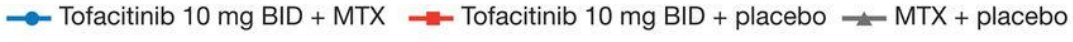
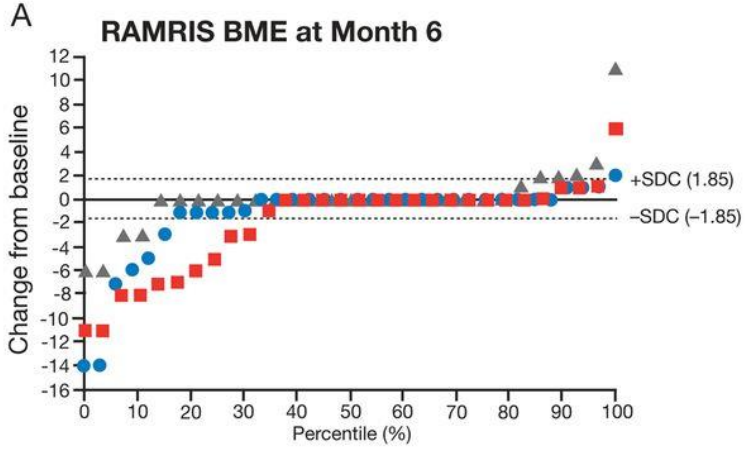
Cumulative probability plots for rheumatoid arthritis MRI score (RAMRIS) endpoints and van der Heijde modification of the total Sharp score (mTSS).

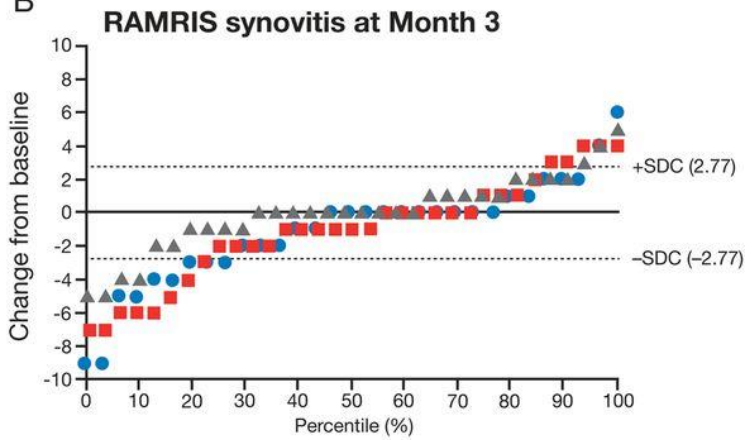


A



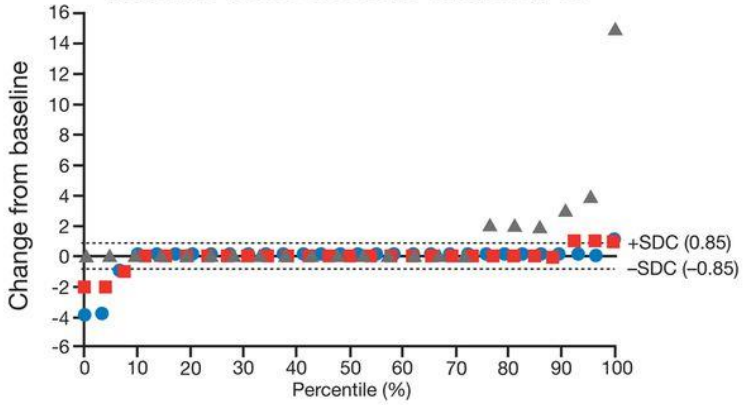
	Regression of BME, n (%) (improvement < –SDC)	Progression of BME, n (%) (deterioration >SDC)
Tofacitinib + MTX (N=33)	5 (15.2)	1 (3.0)
Tofacitinib + placebo (N=29)	9 (31.0)	1 (3.5)
MTX + placebo (N=28)	3 (10.7)	5 (17.9)

B



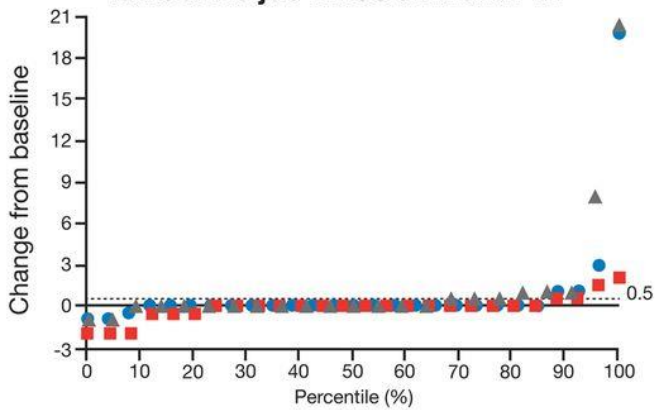
	Regression of synovitis, n (%) (improvement < –SDC)	Progression of synovitis, n (%) (deterioration >SDC)
Tofacitinib + MTX (N=30)	8 (26.7)	2 (6.7)
Tofacitinib + placebo (N=32)	7 (21.9)	5 (15.6)
MTX + placebo (N=31)	3 (9.7)	3 (9.7)

C



	No deterioration of erosions (%) (change < – SDC)	Deterioration of erosions (%) (change >SDC)
Tofacitinib + MTX (N=29)	2 (6.9)	1 (3.5)
Tofacitinib + placebo (N=26)	2 (7.7)	3 (11.5)
MTX + placebo (N=21)	0 (0.0)	6 (28.6)

D



	No progression in mTSS, n (%) (change ≤0.5)
Tofacitinib + MTX (N=26)	22 (84.6)
Tofacitinib + placebo (N=25)	23 (92.0)
MTX + placebo (N=22)	17 (77.3)

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Key Points

- Tofacitinib was effective at reducing synovitis, BME and erosions compared to methotrexate only therapy.
- MRI was effective in demonstrating longitudinal treatment changes in synovitis, BME, and erosions.
- Some treatment changes were significant compared to an active treatment group in as little as 1 month with small cohorts (~27 patients/group)
- The quantitative methods, RAMRIQ and DCE-MRI, were more sensitive to change than RAMRIS
- MRI was more sensitive to change than X-Ray

Outline

- Biomarker background
- Imaging in RA
  - Regulatory backdrop
  - X-Ray
  - MRI
    - RAMRIS
    - Beyond RAMRIS
  - RAMRIS Validation Process
- Tofacitinib RA study with MRI
- Conclusion

The Future of MRI for RA Studies

- Strong business case for the use of MRI
  - Faster, cheaper structural trials
  - Differentiate from the active treatment arms.
  - Scientific credibility is gained as RAMRIS has become relatively standard in other RA treatment studies.
- Hopefully, regulatory acceptance of RAMRIS for structural claims is forthcoming.
- Further validation and deployment of quantitative methods should promote their acceptance.
- MRI may find expanded use for treatment monitoring.

Conclusion

- Biomarkers are an important tool for the development of drugs for immune-mediated inflammatory diseases.
- RAMRIS was carefully and systematically developed, validated and qualified for clinical drug development.
- Regulatory acceptance is slow but potentially progressing.
- RAMRIS provides a platform for the development of new, potentially more sensitive techniques such as RAMRIQ.

Questions?

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