JAKi: Does clinical practice match clinical trial data?

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Disclosures

- **Organisations:** Chairman of BioReg (Austrian registry for Biologicals, Biosimilars, and tsDMARDS in the treatment of inflammatory rheumatic diseases
- **Clinical trials:** Centocor, Abbott, Amgen, Aesca, TRB, UCB, Roche, MSD, Celltrion,
- **Consultancies:** Schering-Plough, Wyeth, Aesca, Abbott, Amgen, Astropharma, Roche, UCB, Boehringer-Ingelheim, MSD, Pfizer, BMS, GSK, Celgene, Grünenthal, Janssen-Cilag, Eli-Lilly, Novartis, Sandoz, TRB
- **Speakers' bureau**: Aesca, Wyeth, Abbott, Amgen, Roche, MSD, Pfizer, Actiopharm, Boehringer-Ingelheim, BMS, Celgene, Sandoz, Grünenthal, TRB, UCB, Eli-Lilly

JAK inhibitors approved for RA

Baricitinib[1]

4.1. Therapeutic indications

Rheumatoid arthritis

OLUMIANT is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.

Olumiant may be used as monotherapy or in combination with methotrexate (see ´sections 4.4, 4.5 and 5.1 for available data

on different combinations)

Tofacitinib[2]

4.1. Therapeutic indications

Rheumatoid arthritis

XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthrits (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.

XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.5)

1. Olumiant [SmPC]. Utrecht, The Netherlands: Eli Lilly Nederland B.V., 2019; 2. Xeljanz [SmPC]. United Kingdom: Pfizer Limited, 2019

Importance of RWE in RA

- Longer observation period
- Can enable research not possible with RCTs
  - Research into high-risk groups (e.g., older patients, comorbidities)
  - Address data gaps in patients not eligible for RCTs
- Better representation of impact of treatment in routine clinical practice in more diverse patient populations

RCT=randomized controlled trial; RWE=real-world evidence

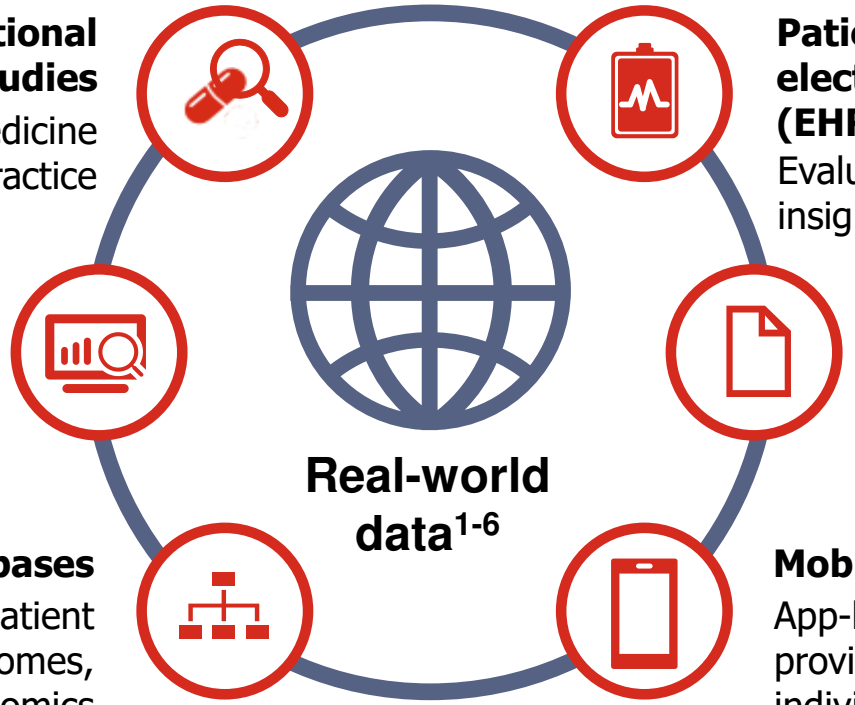
1. Mason KJ, et al. *JAMA Dermatol*. 2018;154:581-588. 2. Monti S, et al. *Rheumatology (Oxford)*. 2018;57(57 Suppl 7):vii54-vii58. 3. Katkade VB, et al. *J Multidiscip Healthc*. 2018;11:295-304. 4. Kim HS, et al. *J Korean Med Sci*. 2018;33:e213.

Sources of real-world data

Non-interventional studies/Observational studies
Data on the use of a specific medicine gathered during routine clinical practice

Patient registries
Evaluation of treatment patterns reflective of everyday clinical decision-making, including all options for a specific condition

Health claims databases
Large electronic datasets related to patient healthcare and well-being, treatment outcomes, and health economics



Patient chart reviews and electronic health records (EHRs)
Evaluation of patient charts and EHRs to gain insights into patient history and management

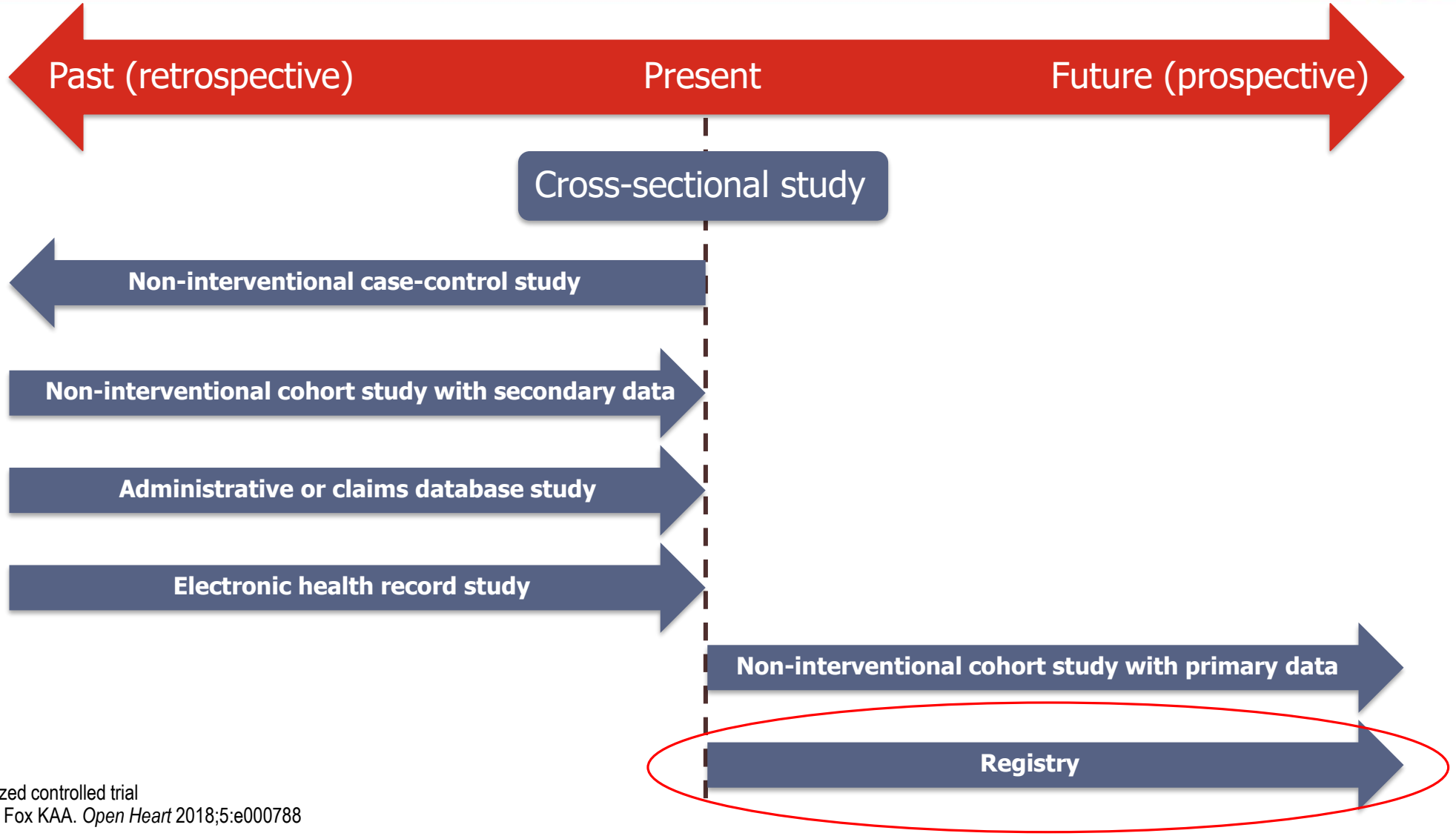
Surveys (patient, HCP, public)
Collect descriptions of health status, wellbeing, and healthcare utilization

Mobile health and wearable tech
App-based patient management providing insights into and trends for individual and population wellness benefits

HCP=healthcare professional

1. Sherman RE et al. *N Engl J Med* 2016;375:2293-2297; https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf; 3. Garrison LP et al. *Value Health* 2007;10:326-335; 4. https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf; 5. Izmailova ES et al. *Clin Pharmacol Ther* 2018;104(1):42-52; 6. Byrom B et al. *Value Health* 2018;21(6):631-639

Types of real-world studies



RCT=randomized controlled trial
Camm AJ and Fox KAA. *Open Heart* 2018;5:e000788

Registry versus RCT

RCT	Registry
Low number of included patients	Potentially high number of patients
Homogenous patient cohort	Heterogeous patient groups
Homogeneity between centers	Heterogeneity between centers
Stringent inclusion and exclusion criteria (co-morbidities excluded)	If possible all patients (including co-morbidities)
controlled efficacy data, safety data extension data	Real world data Long-term safety data

BioReg shows the „secret usual case“

Manfred Herold

RCT=randomized controlled trial

Disclosures:

BioReg is a non-profit organization, supported by pharmaceutical companies. The project can be realized through an unrestricted/restricted educational grant“ .

BioReg cordially thanks

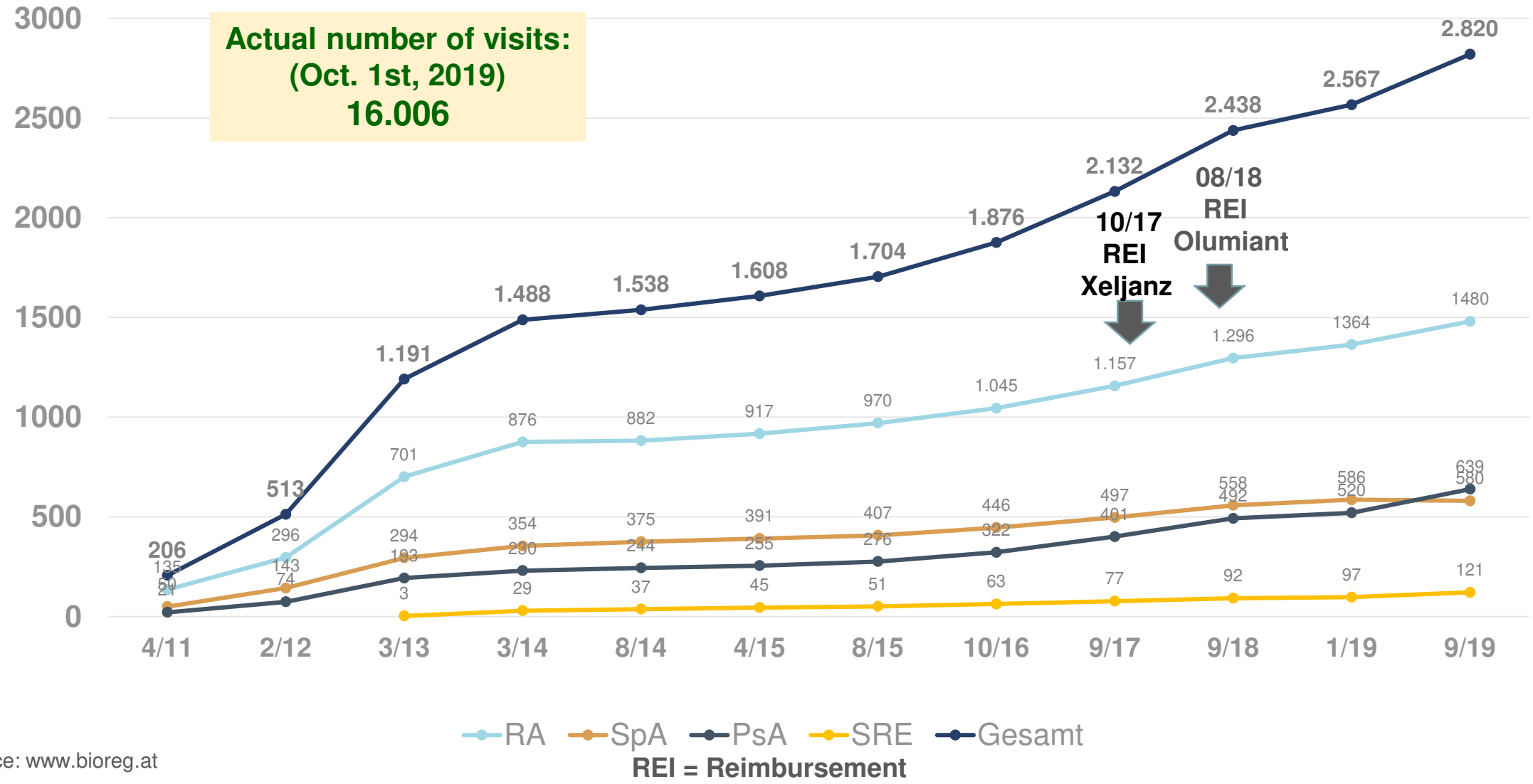
ABBVIE GmbH; AMGEN GmbH, CELGENE GmbH; BIOGEN GmbH, ELI-LILLY GmbH, MERCK SHARP & DOHME GmbH; PFIZER CORPORATION AUSTRIA GmbH, ROCHE AUSTRIA GmbH; SANDOZ Pharma GmbH, UCB Pharma GmbH

Aims and Methods:

- **Quality control**
  Safety profiling
  Economical conclusions
  Drug prescription habits
  Reimbursement issues

- To study the frequency and nature of adverse events as well as long-term consequences
- To investigate long-term efficacy, duration of therapies, and course of diseases
- To elucidate direct and indirect costs

Development BioReg up to 2019



Source: www.bioreg.at

Demographic data

BioReg 2019

Total n = 1.480 RA pat	Baricitinib (n=74)	Tofacitinib (n=48)
Age (yrs.; min,max)	64 (26-84)	64 (35-89)
Female	80,3%	87,5%
RF pos	60,5%	60,4%
Height (cm, min,max)	166 (150-182)	167 (153-183)
Weight (kg, min,max)	74,7 (45-130)	71,4 (43-119)
Duration (yrs; mean± SD)	14,1 (± 9,7)	12,9 (± 9,39)
biologic naive (n, %)	14 (19%)	8 (17%)
≤ 2 biologics (n, %)	42 (57%)	34 (71%)
> 2 biologics (n, %)	18 (24%)	6 (12,%)
Co-Morbidities (n, %)	48 (65%)	35 (73%)
Baseline DAS28-ESR	3,83	3,8
Baseline CDAI	15.66	20,33

PLEASE NOTE: This table is not for comparison purposes

Source: www.bioreg.at

Key Scores Retrieved

BioREG 2019

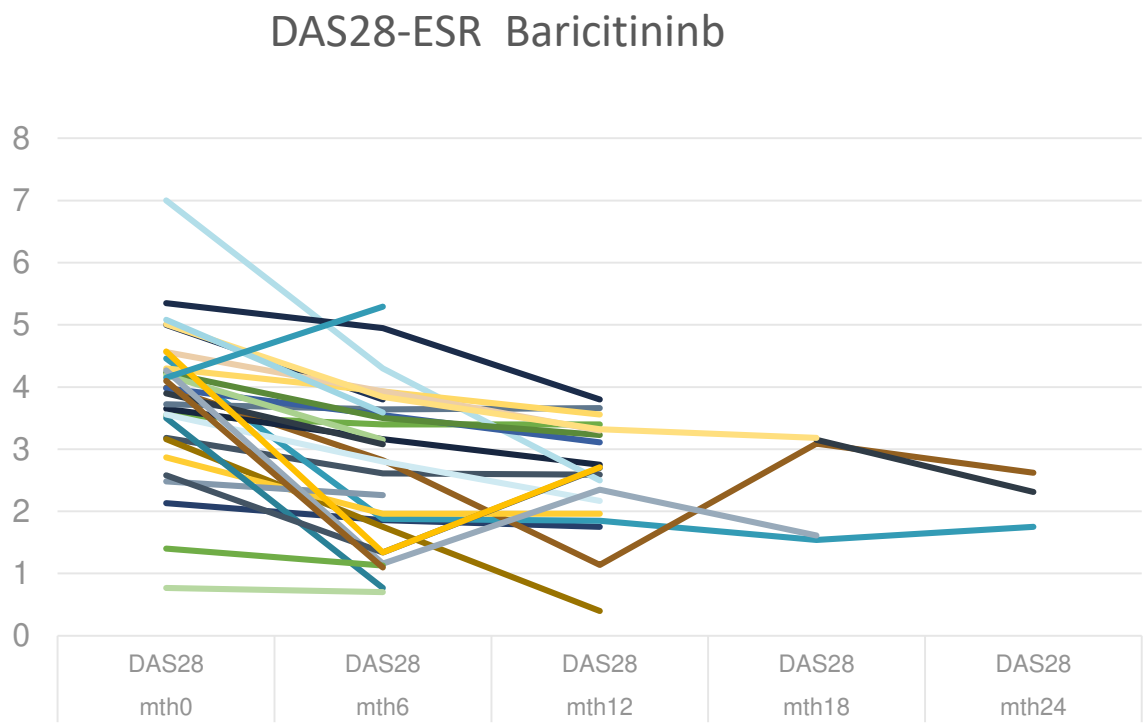
Given the clinical routine situation, the following Scores retrieved from the register are comparable to the corresponding JAKi- clinical study data

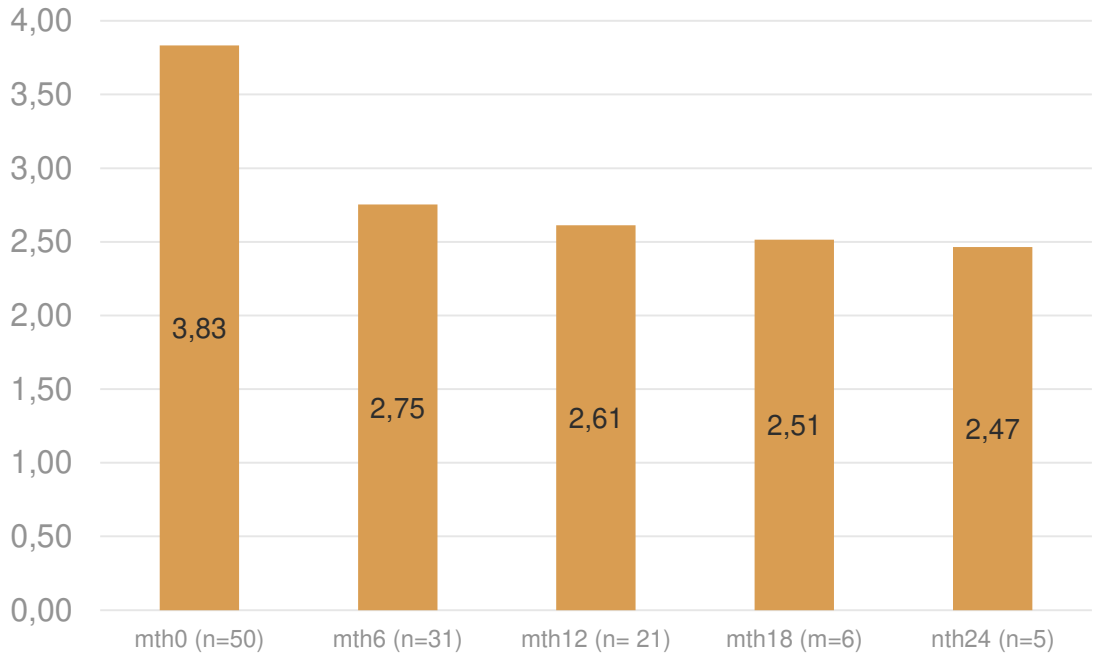
- **DAS28-ESR**
- **CDAI**
- **HAQ-DI**
- **RADAI-5* (not collected in the clinical study program)**

- PRO; five-item questionnaire; result between 0 (best) and 10 (worst)
  Leeb BF et al.: **Patient Centered Rheumatoid Arthritis Activity Assessment by a Modified RADAI. J Rheumatol 2008, Jul;35(7):1294-9. Epub 2008 May 15.**

Source: www.bioreg.at

Baricitinib DAS28-ESR Total Patients

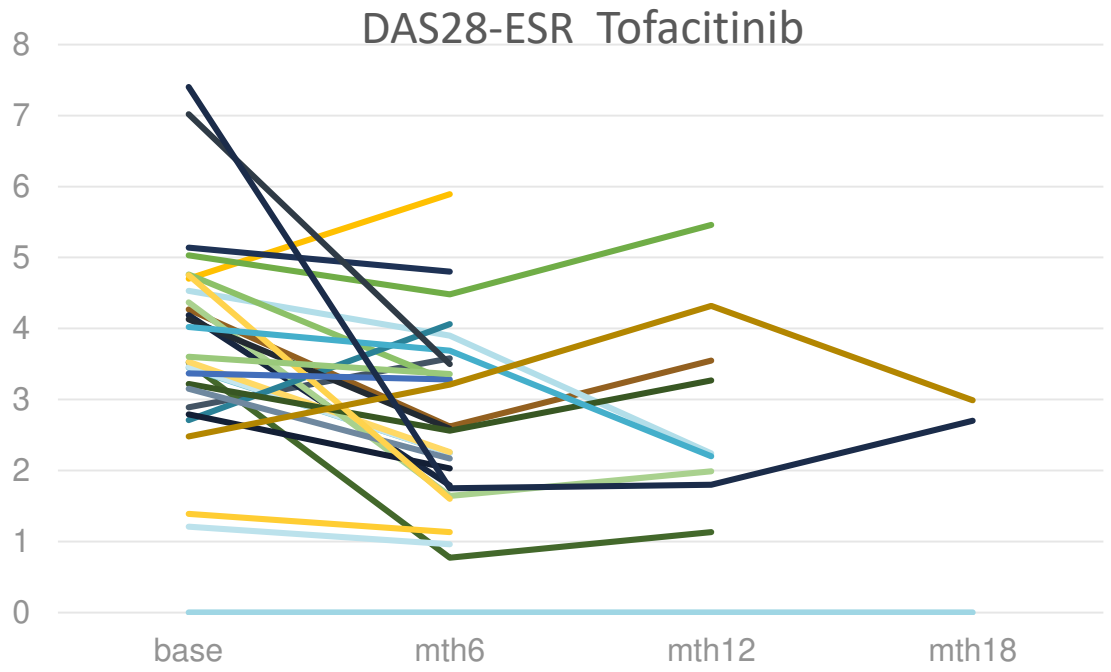


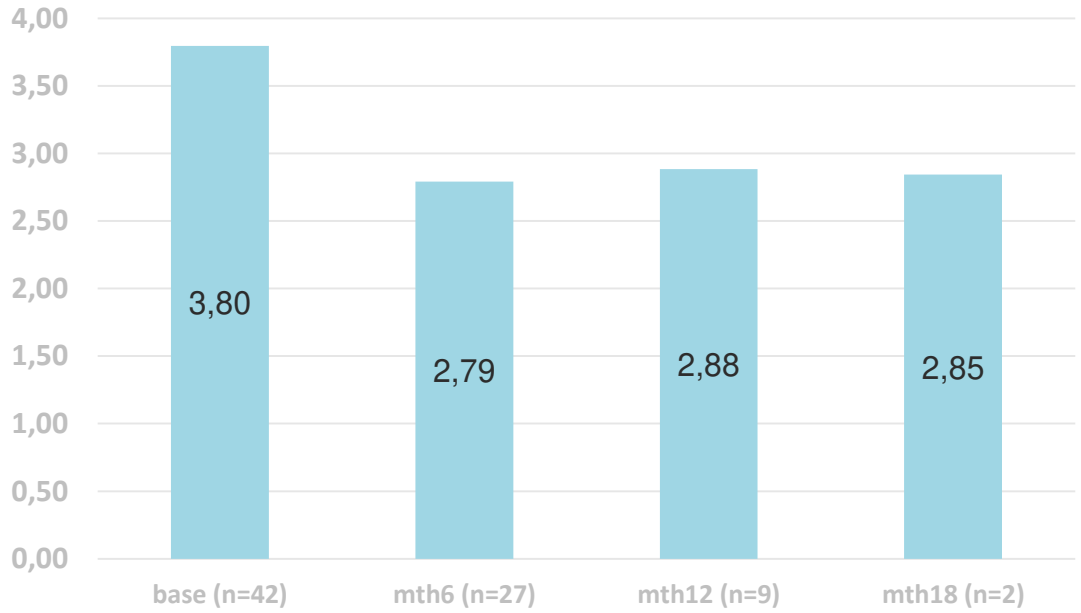


Source: www.bioreg.at

Base/mth 0 = start of JAKi therapy

Tofacitinib DAS28-ESR Total Patients



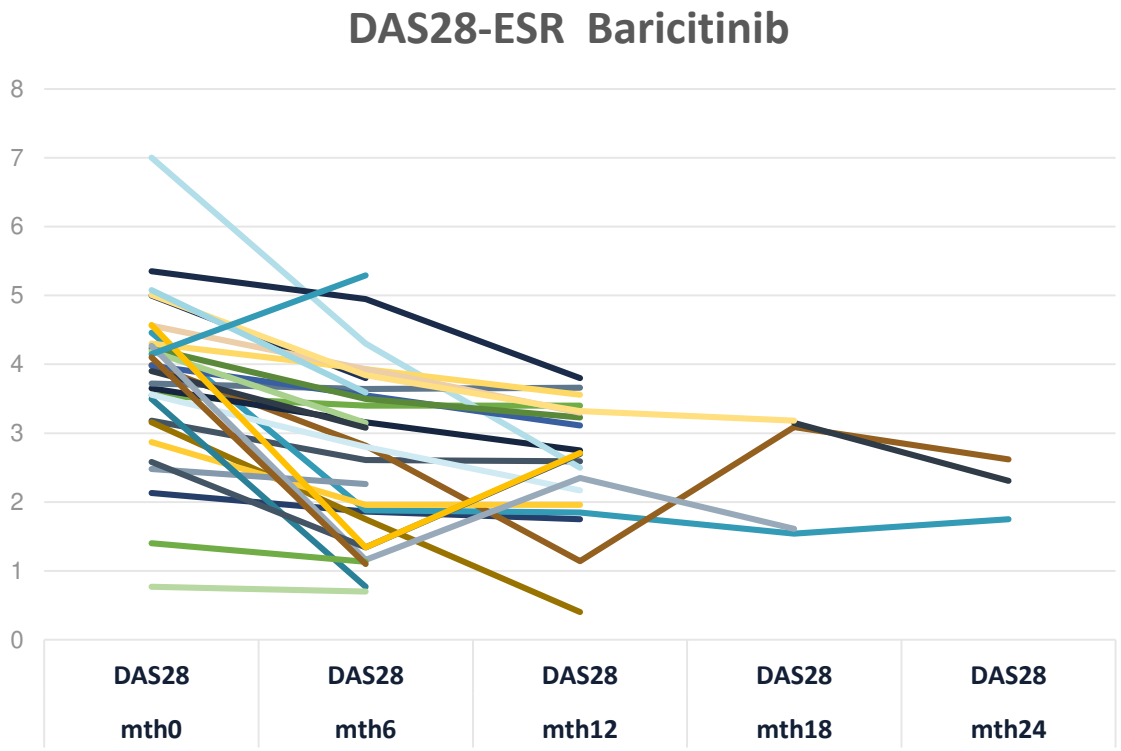


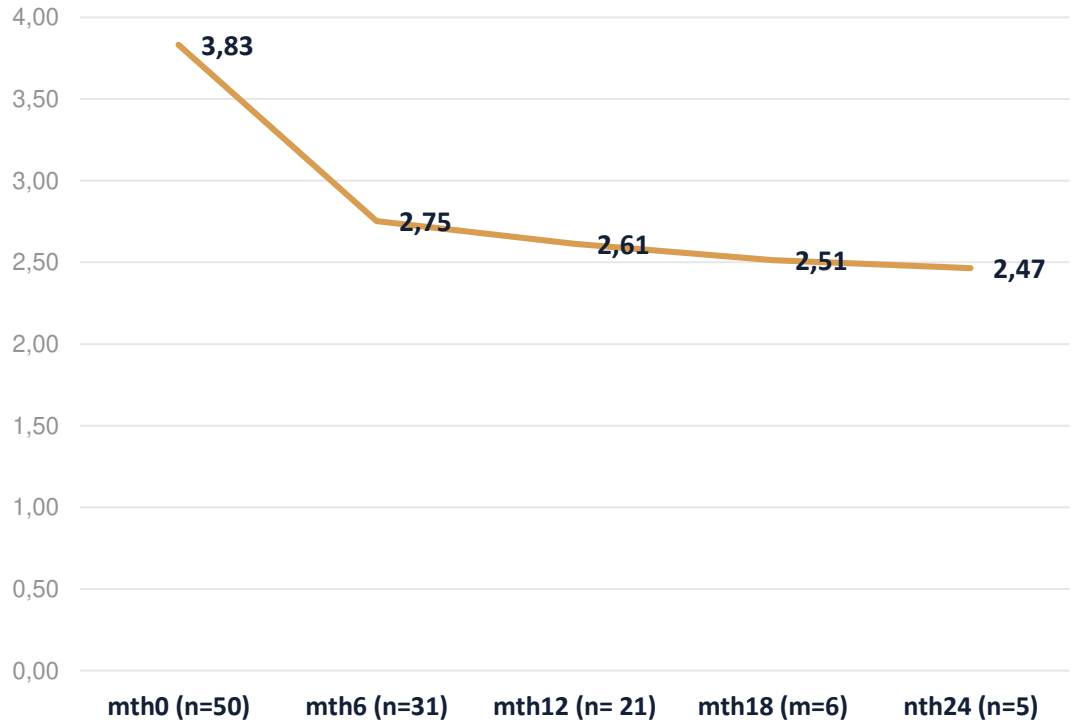
Source: www.bioreg.at

Base/mth 0 = start of JAKi therapy

Baricitinib
DAS28-ESR in patients pre-treated with ≥ 1 bDMARD

BioReg 2019

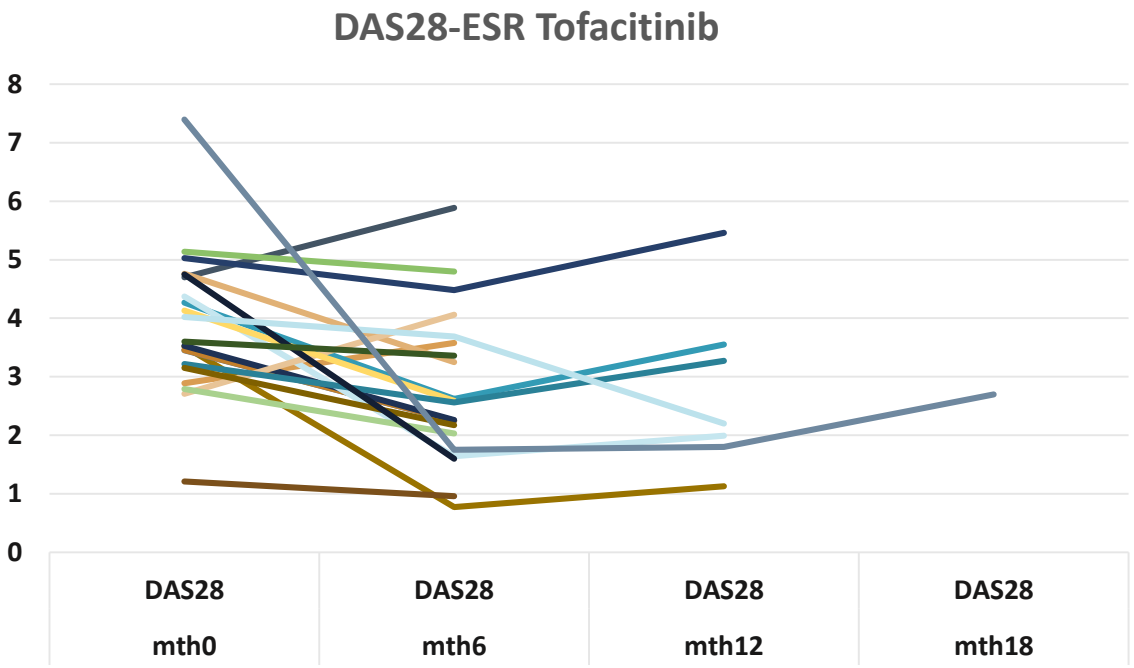


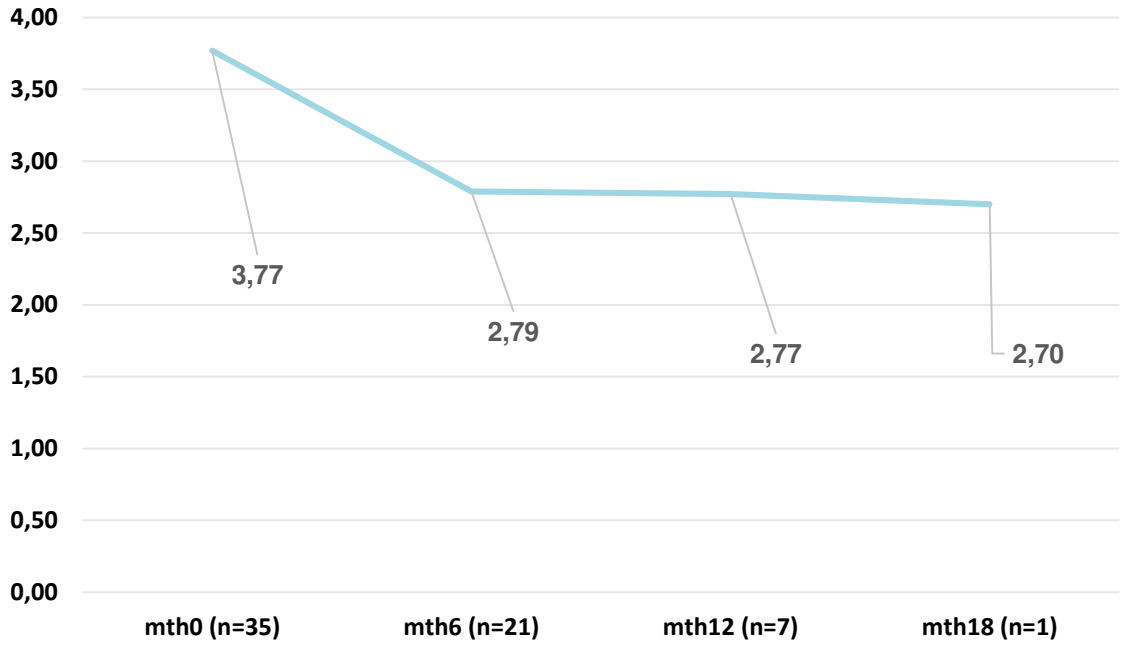


Source: www.bioreg.at

Tofacitinib
DAS28-ESR in patients pre-treated with ≥ 1 bDMARD

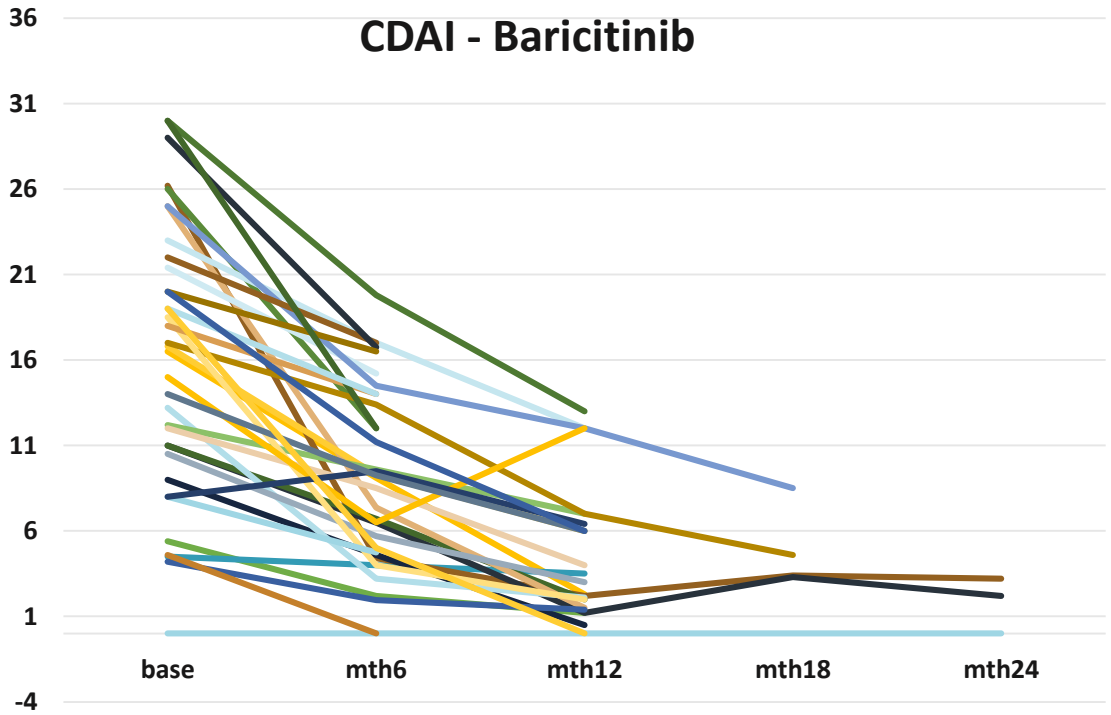
BioReg 2019

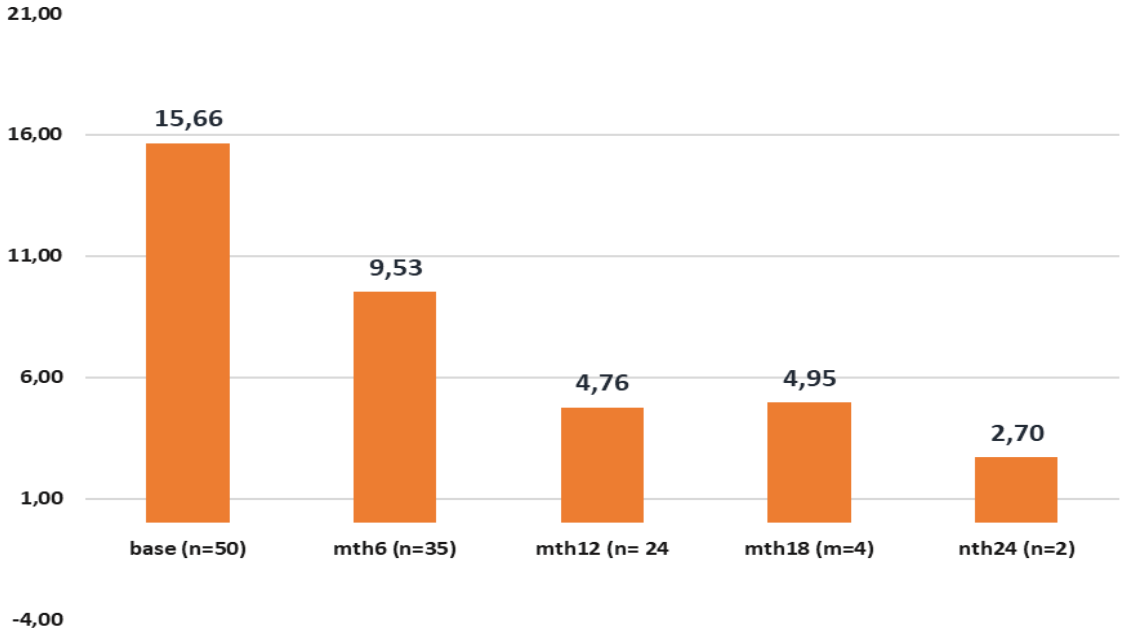




Source: www.bioreg.at

Baricitinib CDAI





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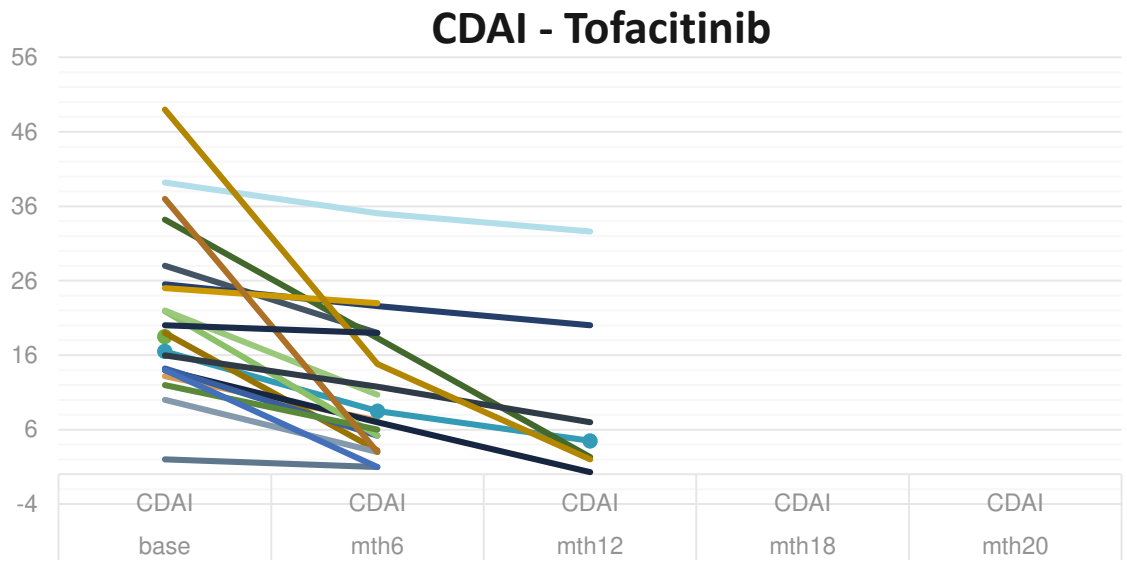
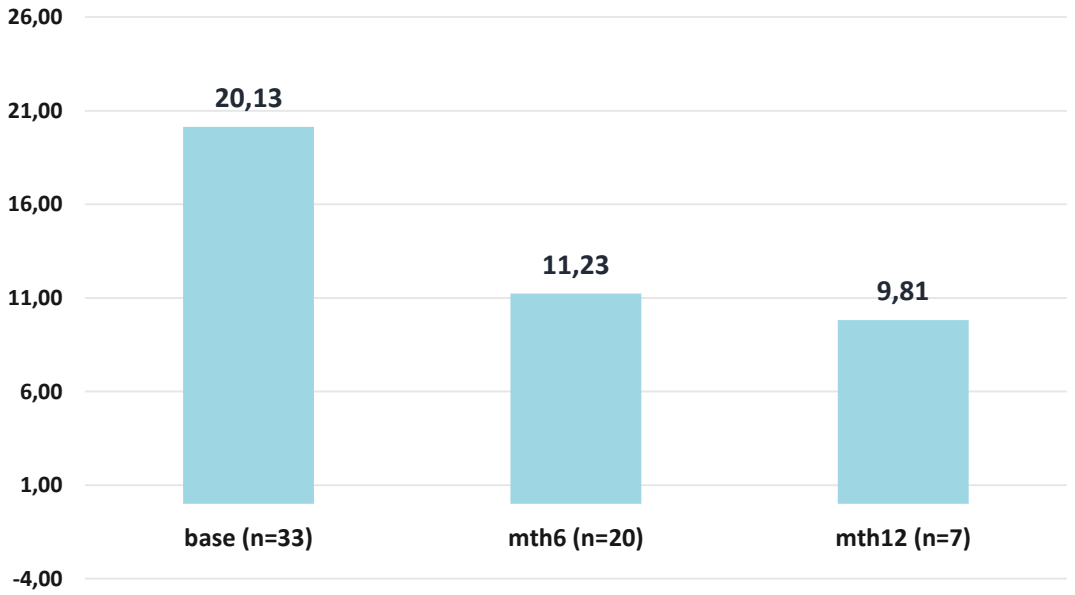
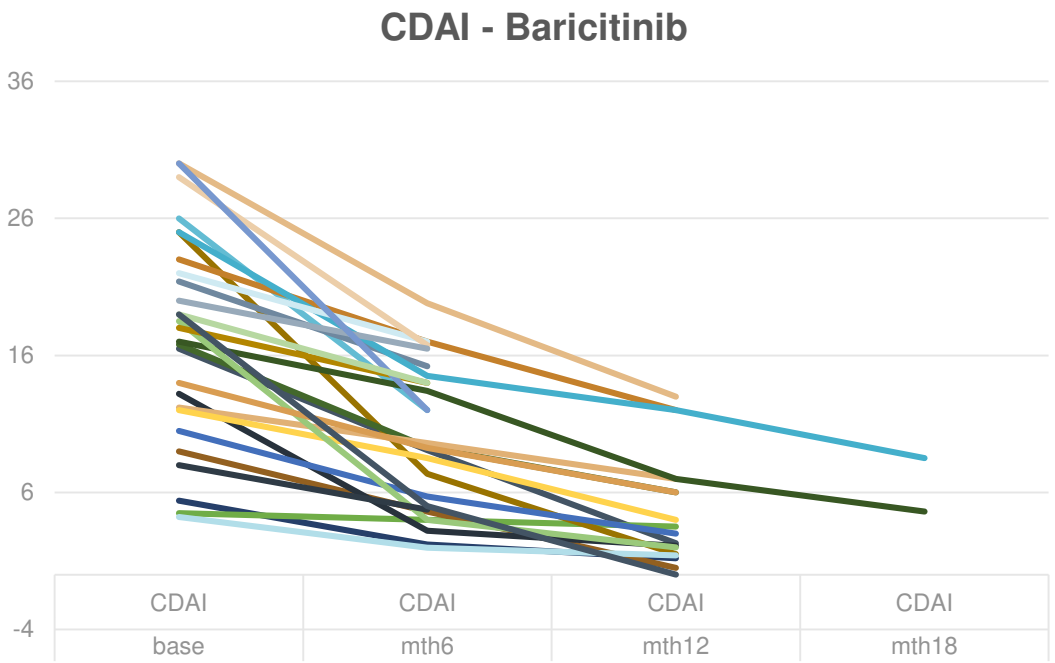
Tofacitinib CDAI

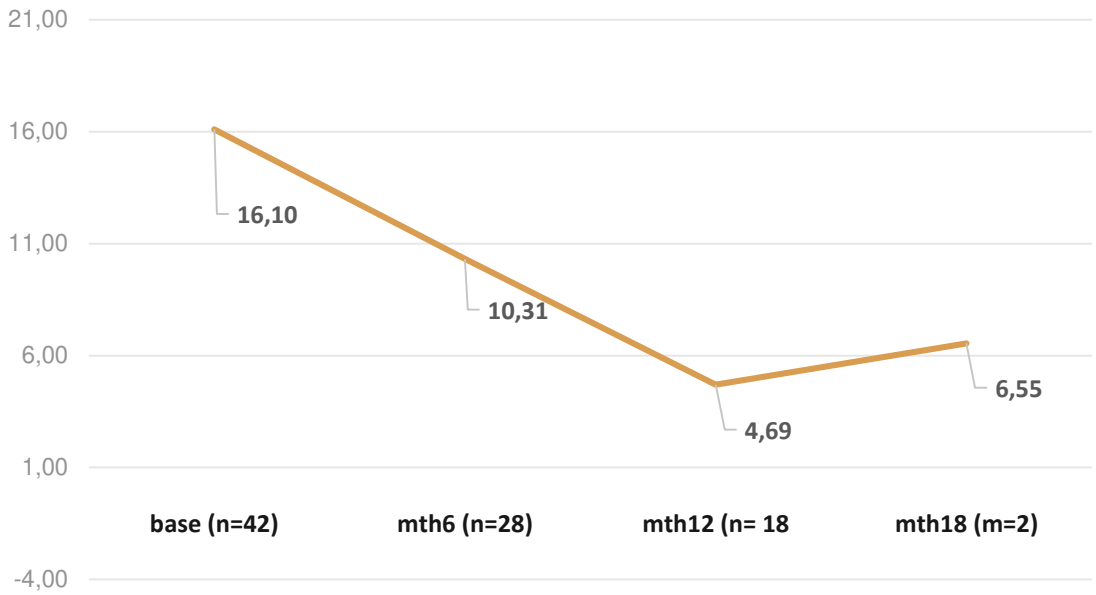




Source: www.bioreg.at

Baricitinib
CDAI in patients pre-treated with ≥ 1 bDMARD





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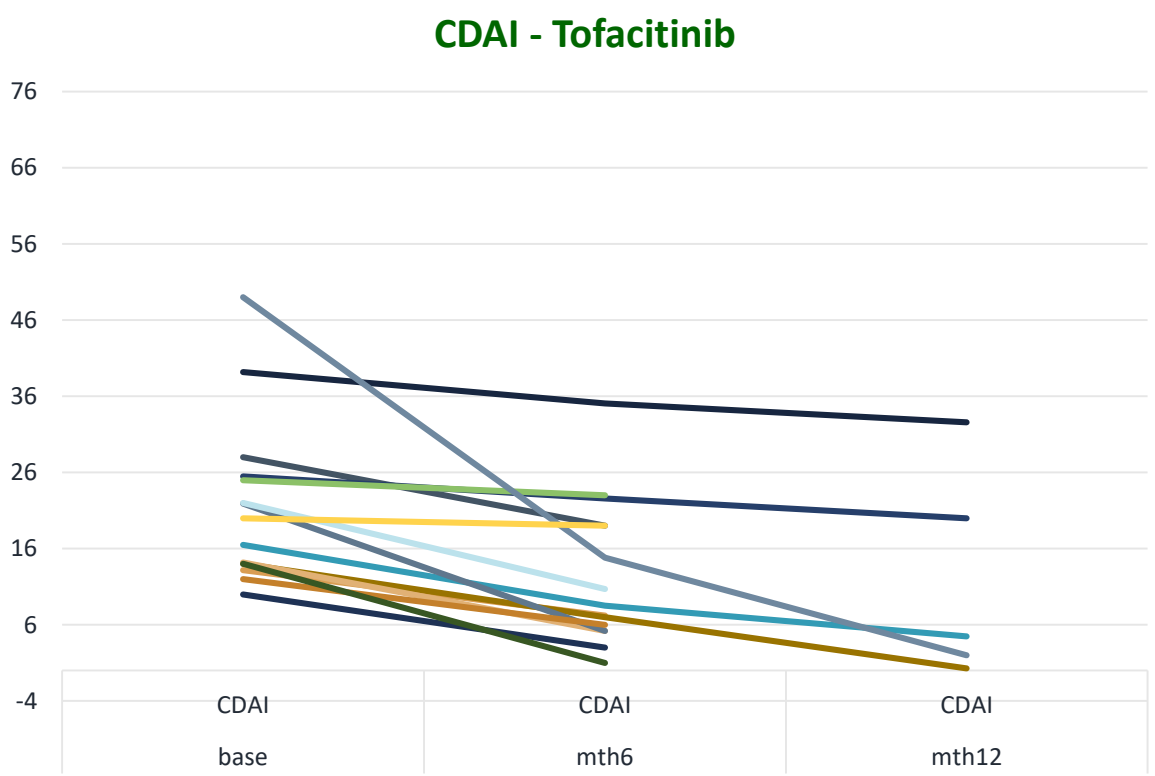
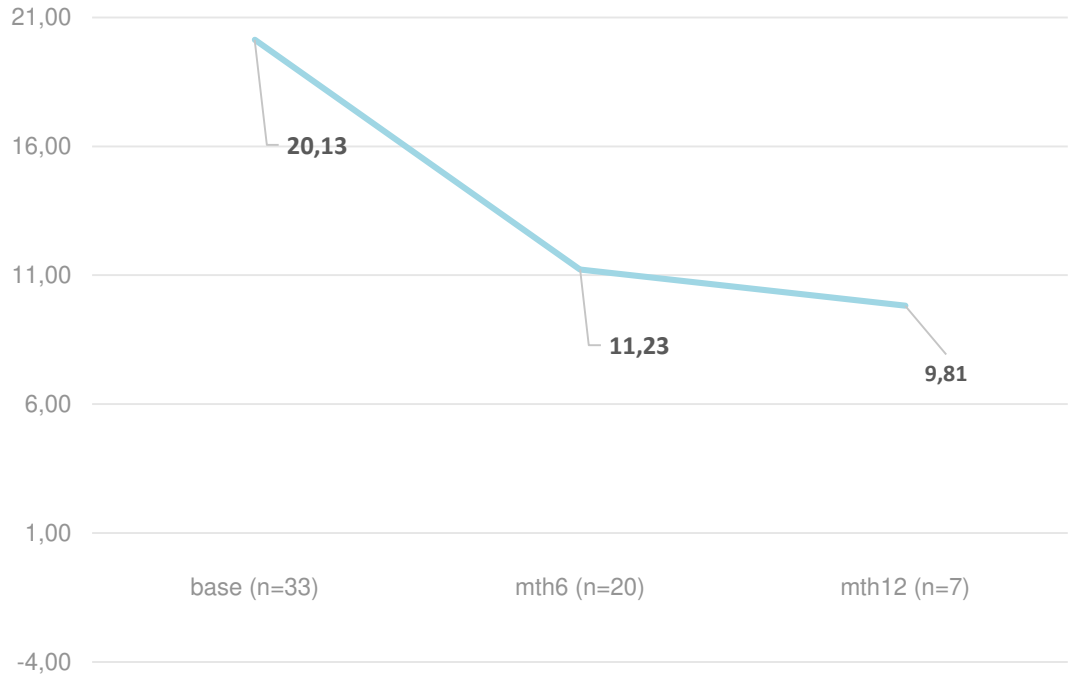
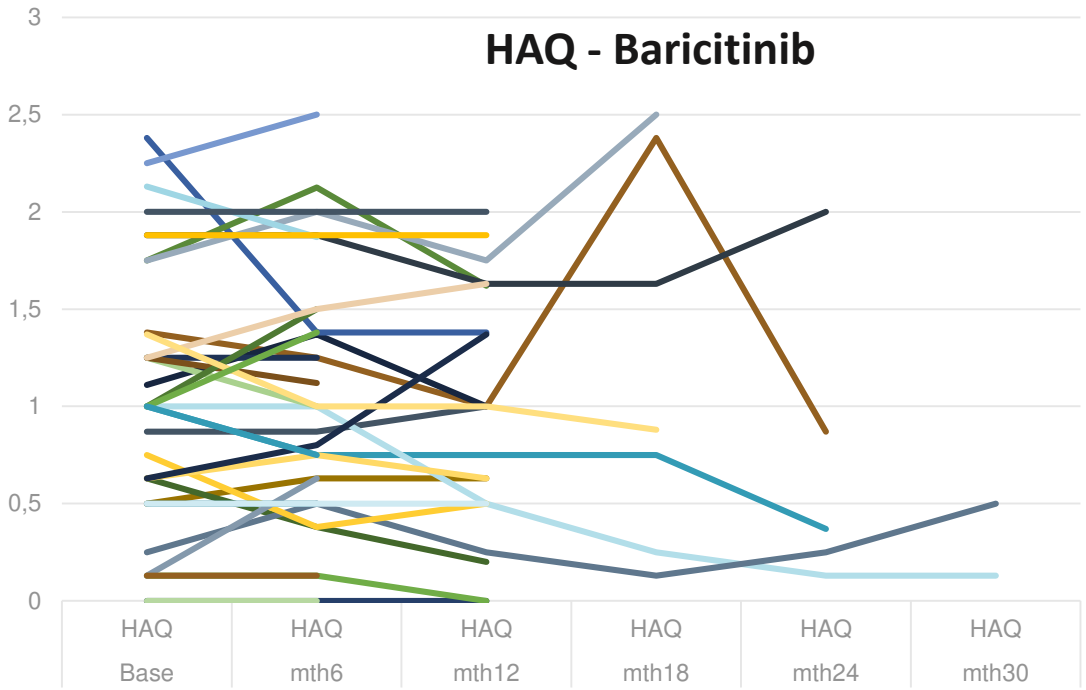
Tofacitinib
CDAI in patients pre-treated with ≥ 1 bDMARD

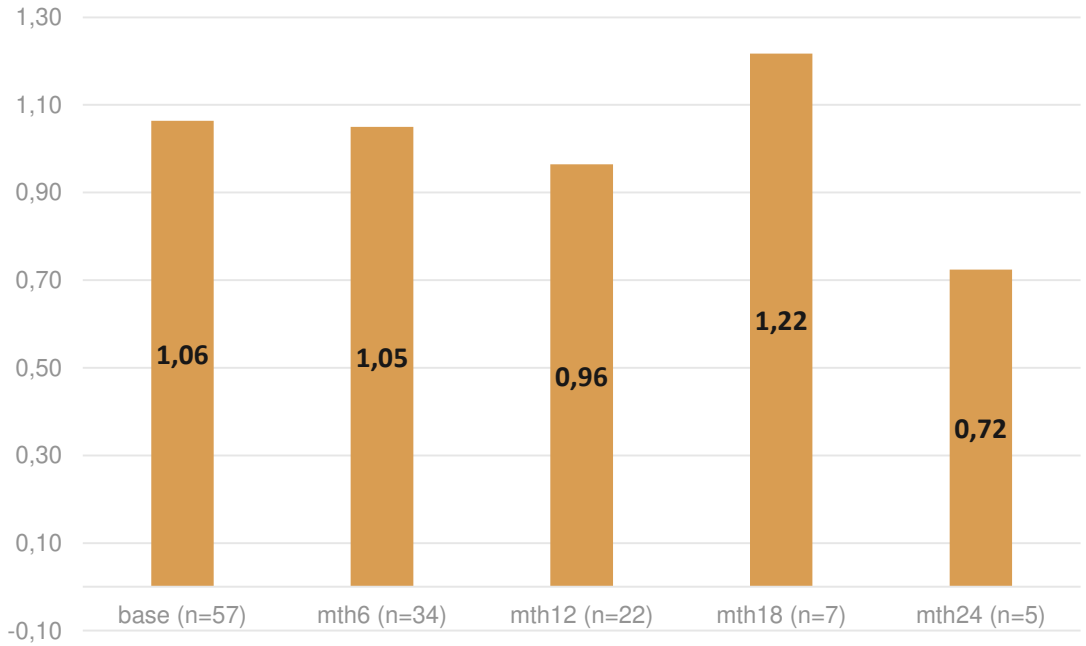




Source: www.bioreg.at

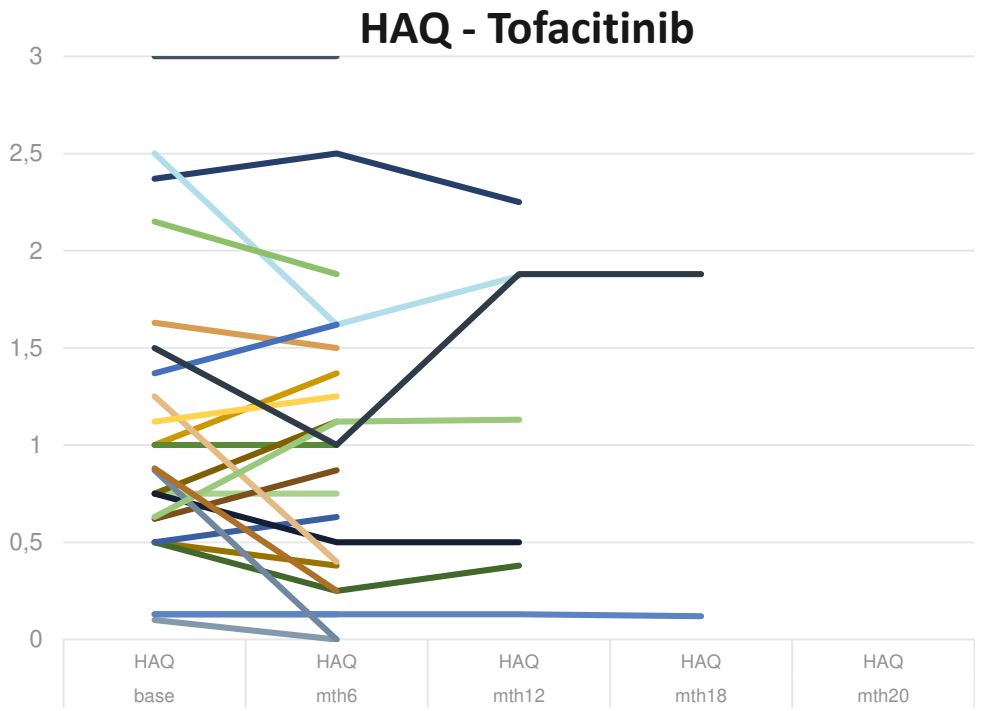
Baricitinib-HAQ
Total Patients

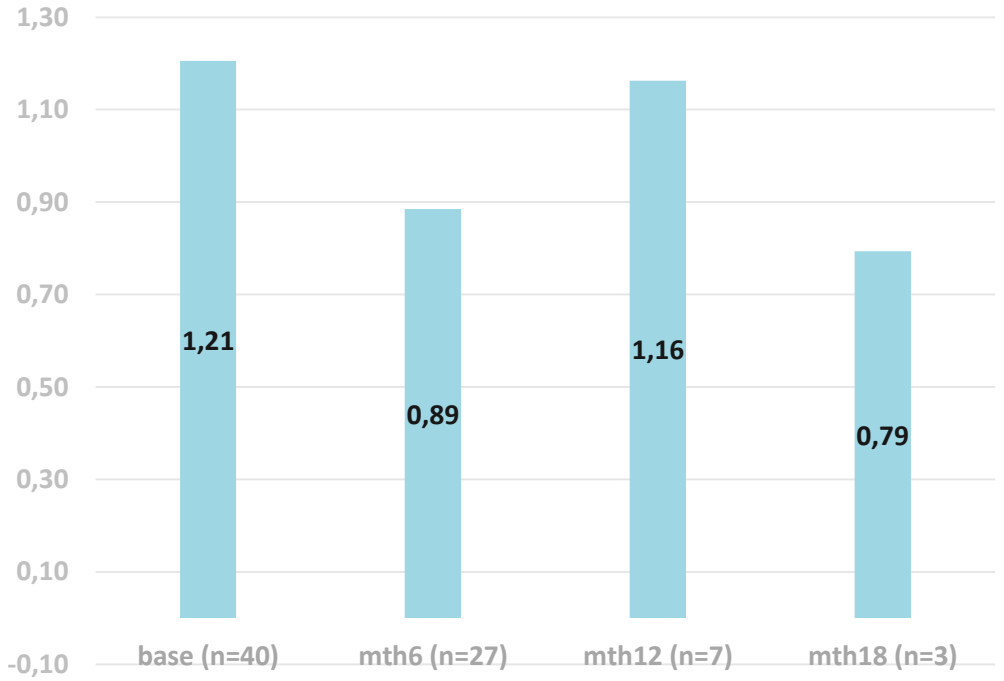




Source: www.bioreg.at

Tofacitinib-HAQ
Total Patients





Source: www.bioreg.at

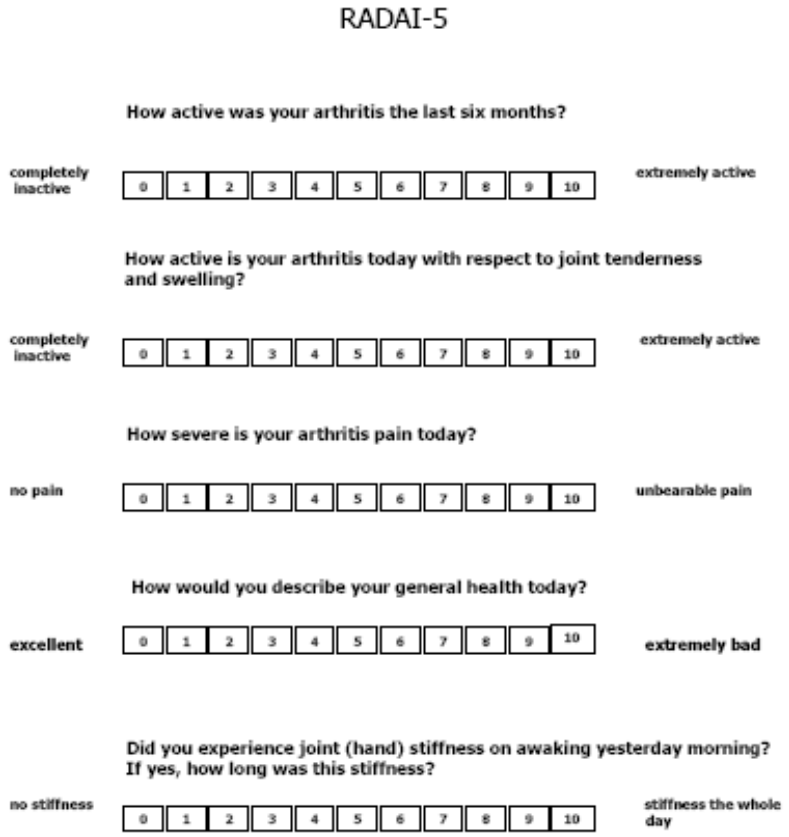
RADAI – 5:

Bio REG 2019

- Developed from the RADAI
  - Patient‘s general health assessment replaces joint counts = Question 4
  - (Q1+Q2+Q3+Q4+Q5)/5
  - ranges from 0 - 10

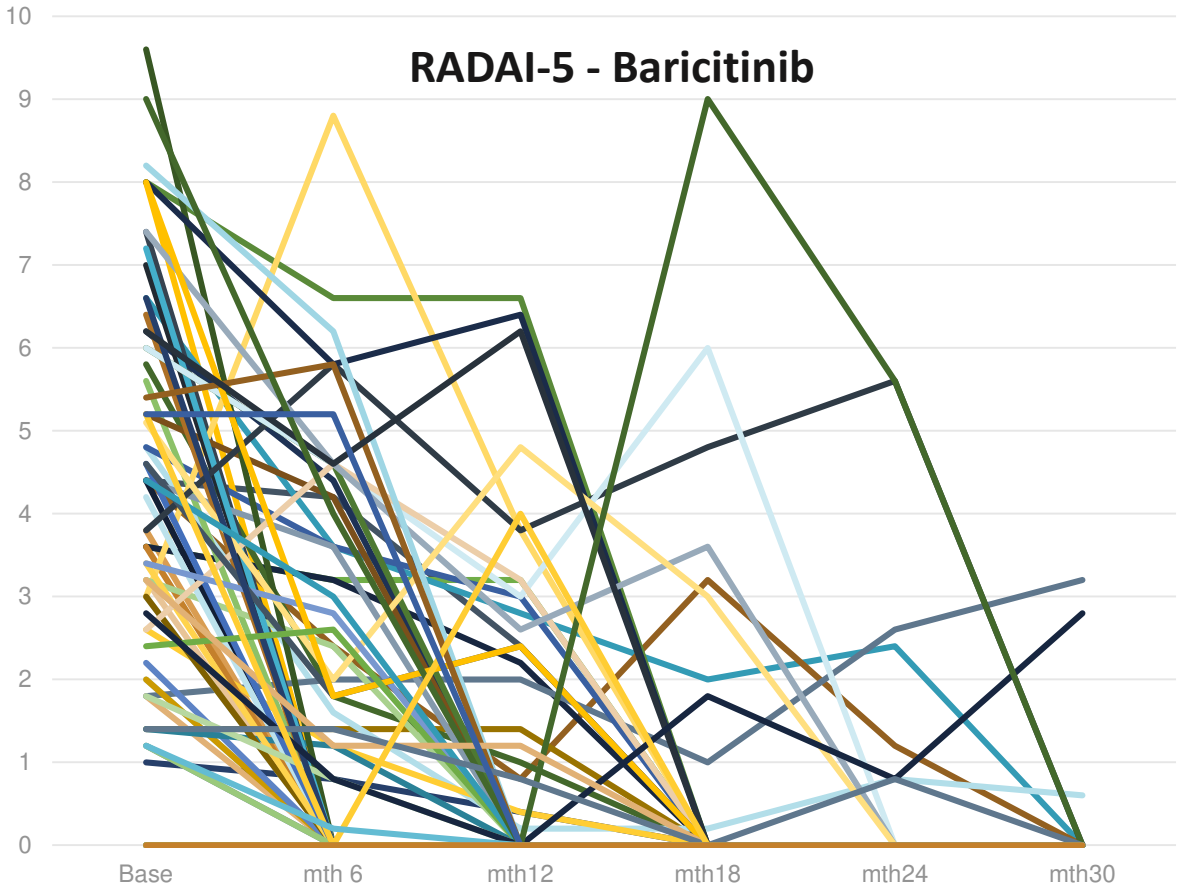
RADAI-5 categories:

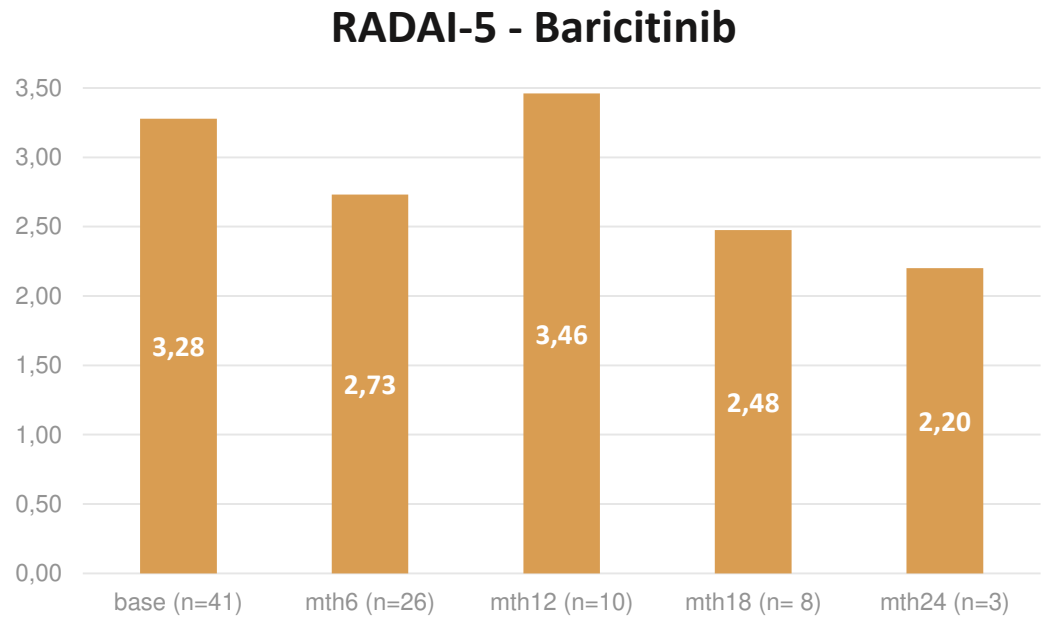
- **Remission 0.0-1.4**
- **Mild 1.6-3.0**
- **Moderate 3.2–5.4**
- **High 5.6-10.0**



Stucki G, Liang MH, Stucki S, Bruhlmann P, Michel BA. Arthritis Rheum 1995; 38:795-798
Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. J Rheumatol. 2008 Jul;35(7):1294-9

Baricitinib-RADAI-5



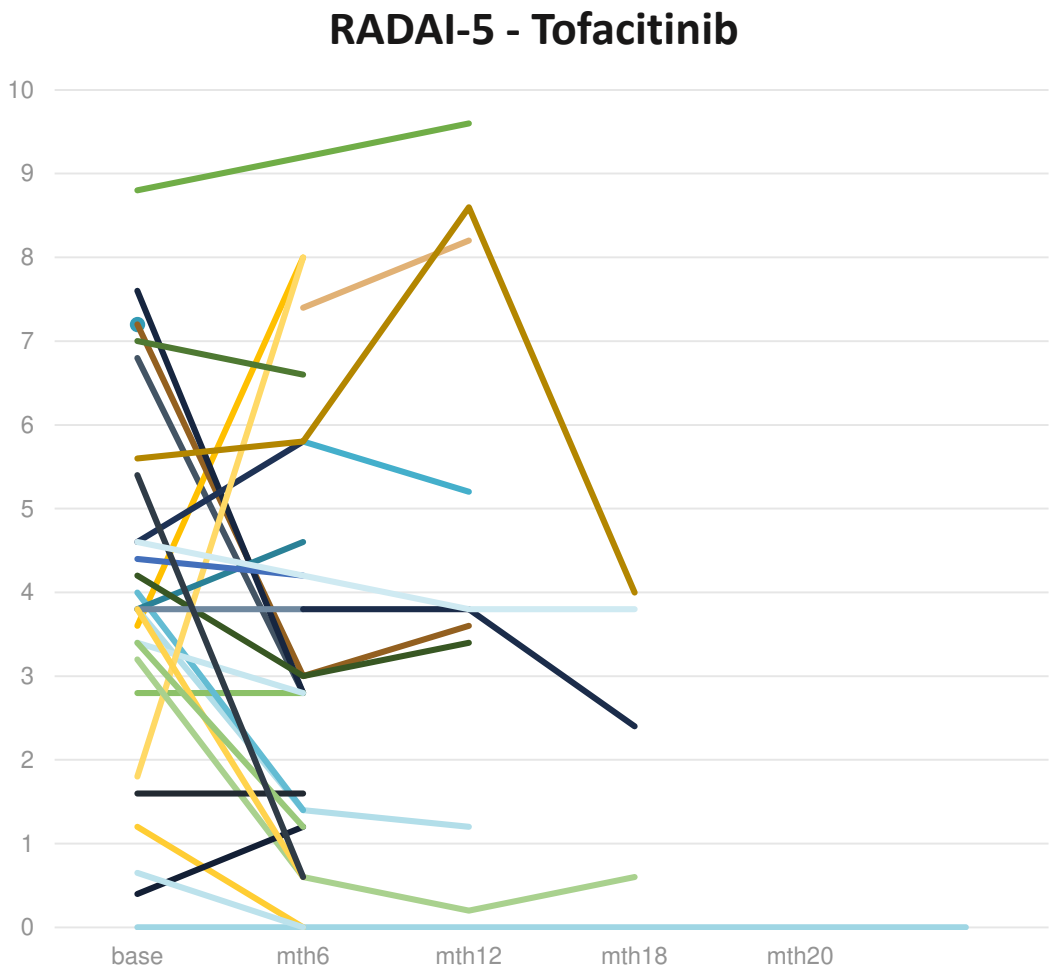


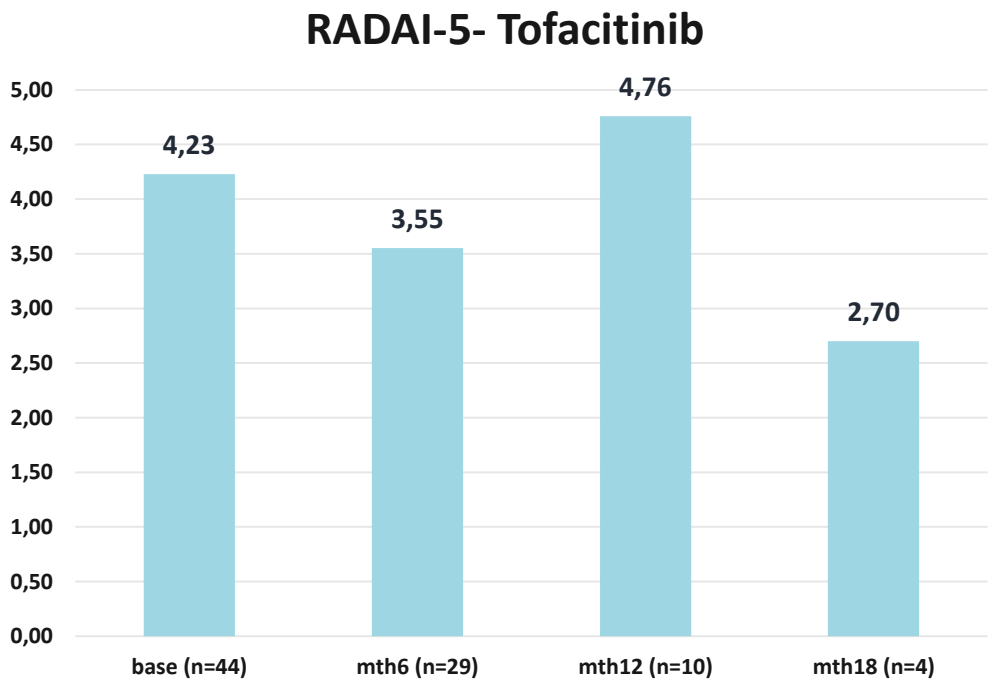
Source: www.bioreg.at

- **PRO; five-item questionnaire; result between 0 (best) and 10 (worst)**

Leeb BF et al.: **Patient Centered Rheumatoid Arthritis Activity Assessment by a Modified RADAI. J Rheumatol 2008, Jul;35(7):1294-9. Epub 2008 May 15.**

Tofacitinib-RADAI-5





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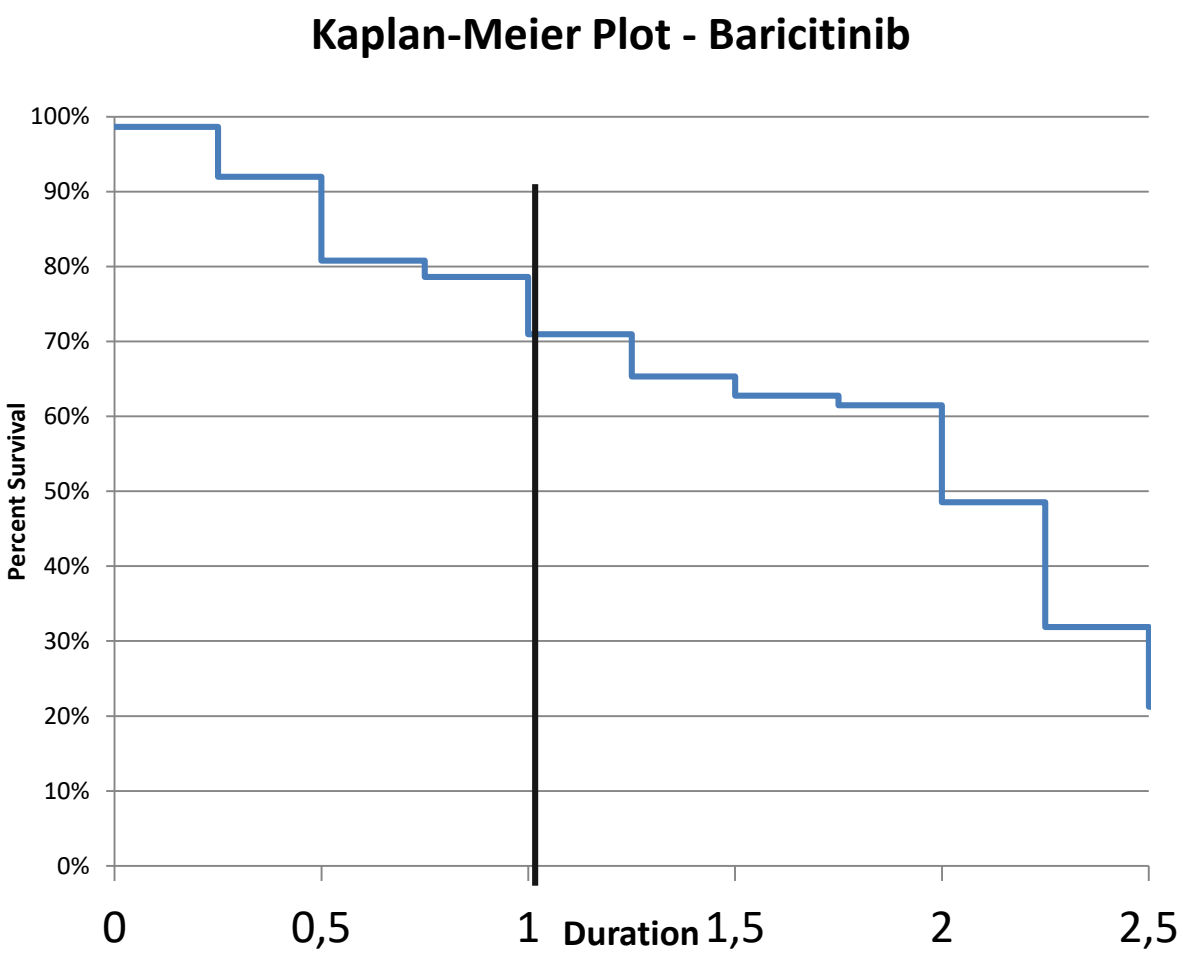
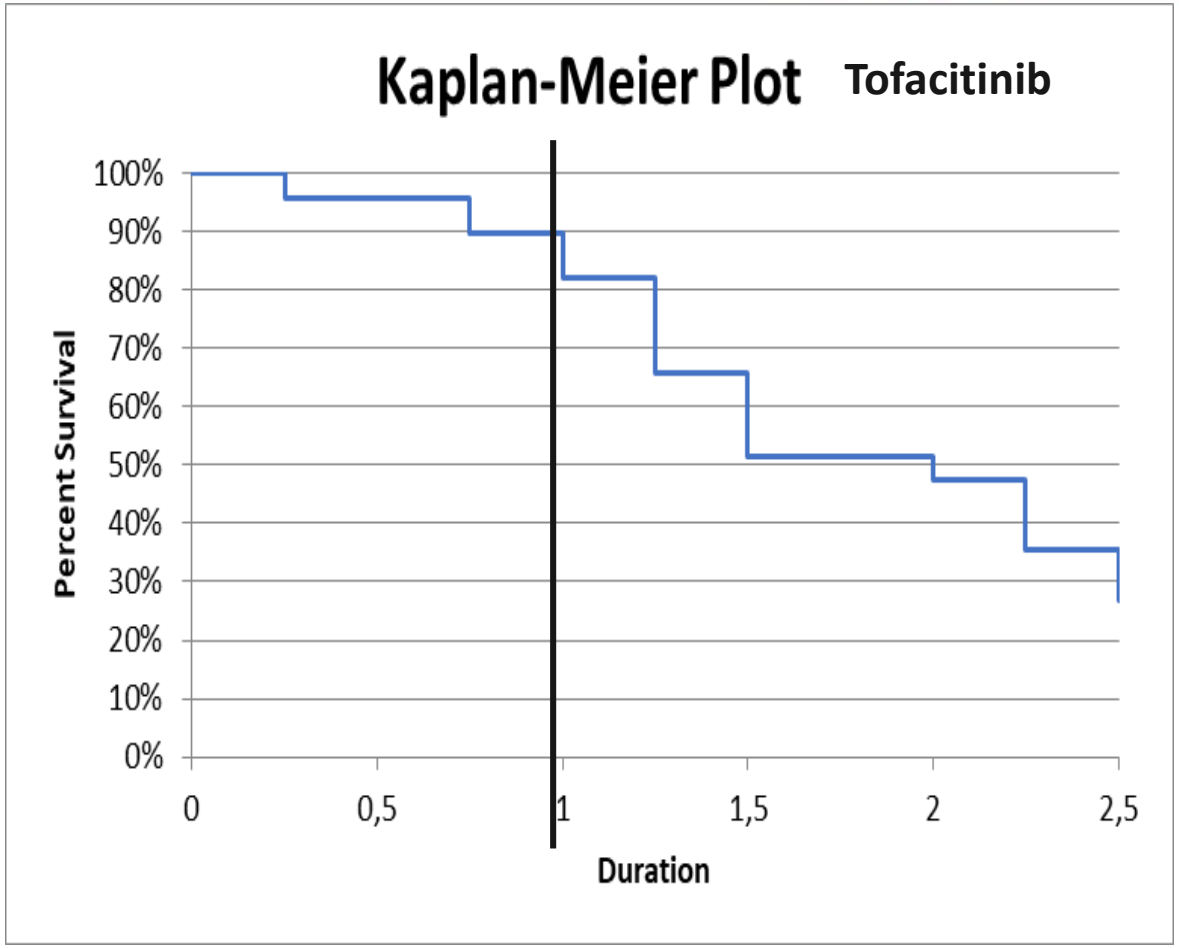
- PRO; five-item questionnaire; result between 0 (best) and 10 (worst)

Leeb BF et al.: Patient Centered Rheumatoid Arthritis Activity Assessment by a Modified RADAI. J Rheumatol 2008, Jul;35(7):1294-9. Epub 2008 May 15.

Duration on Therapy
After 1y ~80% of pat are still on JAKi therapy

BioReg 2019





Source: www.bioreg.at

Insufficient response rate

BioReg 2019

	Olumiant (n=74)	Xeljanz (n=48)
duration of therapy (median, min, max)	1,25 yrs (0,25-2,5)	1,25 yrs (0,25-2,5)
Discontinuation of therapy (n, %)	13 (17,6%)	14 (29,2%)
Insufficient response* (n, %)	24 (32,4%)	21 (43,8%)
Adverse events* (n, %)	16 (21,6%)	12 (25,0%)

PLEASE NOTE: This table is not for comparison purposes

* Not obligatorily leading to discontinuation

Source: www.bioreg.at

Conclusion

- Emerging real-world data will help provide further insights in the use of JAK inhibitors in routine clinical practice, including treatment patterns (naïve vs bDMARD-IR, monotherapy, discontinuations)
- JAK inhibitors have proven efficacy (Baricitinib in addition superiority* to ADA as standard of care) and acceptable safety in randomized controlled trials
- The Austrian experience in bDMARD IR patient population has so far confirmed the efficacy related to Phase III study program of JAK inhibitors.
- JAKi safety profile proved to be acceptable and is being further characterized with more data becoming available
- Illustration of patient trajectories are of special importance when showing data with low number of patients

* in ACR20 and in mean change of DAS28-CRP at week 12, both in combination with MTX

1. Taylor PC et al. *N Engl J Med* 2017;376(7):652-62
bDMARD=biologic disease-modifying antirheumatic drug; IR=inadequate responder; JAK=Janus kinase